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KEYNOTE PRESENTATIONS

K1

Why suppression of HIV replication does not always make everything better

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Journal of the International AIDS Society 2010, **13(Suppl 4):**K1

The advent of combination antiretroviral therapies has altered the clinical course of HIV infection such that successful suppression of HIV replication typically results in sufficient restoration of immune function to protect most patients from the opportunistic complications that have defined AIDS. Yet a substantial proportion of treated HIV infected persons fail to increase circulating CD4 T cell counts to "normal" levels and a failure of CD4 T cell restoration predicts increased an increased risk of life threatening events that include malignant, hepatic and cardiovascular morbidities. Recent work suggests that the drivers of immune deficiency and "non-AIDS" complications of HIV infection may be intimately linked and in both settings, immune activation and inflammation are central. To this end, we have accused both HIV and the translocation of microbial elements from the damaged gut as drivers of both progressive CD4 T cell depletion and an increased tendency to coagulation and thrombosis formation in HIV infection. The Cleveland Immune Failure (CLIF) study was designed to explore the characteristics and potential drivers of disease pathogenesis among HIV infected persons who failed to achieve robust CD4 T cell increases despite successful suppression of HIV replication with combination antiretroviral therapy. In this study, we find evidence that immune activation, inflammation and increased thrombosis persist even in the setting of "complete" control of HIV replication and propose that this is not related to ongoing HIV replication but more likely to translocation of microbial products from the damaged gut.

K2

The public health implications of antiretroviral therapy – 2011 and beyond

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Journal of the International AIDS Society 2010, **13(Suppl 4):**K2

2011 will mark the 30th anniversary of the first description of AIDS, and the 15th year since combination antiretroviral therapy (ART) was introduced. Since its introduction, ART has had profound impact on AIDS incidence and mortality in industrialized countries, and international collaboration, mainly through the Global Fund and the President's Emergency Plan for AIDS Relief, has provided treatment to more than 4 million HIV-infected persons in low and middle income settings.

Despite these advances and much speculation, the full prevention benefits of ART still await clarification. Experience with mother-to-child transmission of HIV gave insight into the critical importance of HIV RNA as the dominant risk factor for HIV transmission, as well as proof of concept that ART reduced transmission rates through lowering viral load. Important studies published in 2010 include evidence that among couples discordantly infected with HIV, a 92% reduction in transmission occurred when the infected index was taking ART (Donnell D, et al. Lancet 2010). The concept has arisen of community viral load as a risk factor for community-wide transmission (Das-Douglas, CROI 2010), and ecologic evidence has been presented of ART scale-up correlating with reduced HIV incidence at the population level (Lima VD, Lancet 2010). These observations suggest more widespread ART among HIV-infected persons ("test and treat") could provide substantial prevention benefit but data on such an approach are awaited, despite several mathematical models examining this.

ART may provide prevention benefit when given as post-exposure prophylaxis and possibly as pre-exposure prophylaxis. The recent widely acclaimed study of a tenofovir-containing gel, associated with 39% protective efficacy against HIV acquisition in women on primary analysis (Karim QA, Science 2010), provides evidence of efficacy of pre-exposure prophylaxis as well as the feasibility of an efficacious microbicide. Results of trials of oral pre-exposure prophylaxis will become available in the near future.

These developments occur in a global context of financial economic downturn, increased attention to the other health-related millennium development goals, and an emerging pandemic of non-communicable diseases. How to use ART most effectively and comprehensively for HIV prevention will challenge decision makers, even as evidence for individual approaches mounts.

K3

ART achievements and challenges in Africa

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Journal of the International AIDS Society 2010, **13(Suppl 4):**K3

Combination antiretroviral therapy (ART) as we know it today has only been practiced in Africa in a significant segment of people living with HIV (PLH) in the past 6 years. We have put behind us the litany of reasons which were given as obstacles in the implementation of ART in Africa. Today the majority of the 5.2 million people on ART are from sub-Saharan Africa. Cohort comparisons between resource-rich and resource-limited

settings have demonstrated similar immunologic and virologic responses to ART. There is however a higher mortality, of more than 4 times in the first 6 months of ART in the developing world. There is therefore need to address this early mortality to fully harness the benefits of ART. Ecological data from a region in South Africa has shown that tuberculosis rates have fallen by 50% in the community in association with the widespread use of ART. The benefits of ART extend to many other spheres including reduction of perinatal infection and improved socio-economic indices in children and adults. There is also strong argument that the increased roll-out of ART will impact maternal mortality, hence contribute to the achievement of MDG5. Potential additional benefits of antiretroviral therapy in prevention are emerging as exemplified by the positive outcome of CAPRISA004; a study that showed a preventive role of tenofovir gel of 39% in women in Durban, South Africa. Other ARV-based microbicide studies and studies of ART as pre-exposure prophylaxis will report soon and may broaden the use and benefits of ART beyond therapeutics. The roll-out of ART in Africa is not without challenges. Currently only 42% of PLH who qualify for treatment are on therapy, moreover it is estimated that 10 million more will require ART when the new WHO guidelines recommendation of ART initiation at a threshold of 350 cells/mm^3 are considered.
Other recommendations including emphasis on diagnosing HIV early, the use of more expensive drugs in first-line therapy, the emphasis on immunologic and virologic diagnosis of failure will require increased resources. The availability of resources is threatened by the world economic crisis and changing funding paradigms. The challenge ahead is to mobilize resources to enable use of ART in an efficient manner and in a way that exploits the expanding role of ART in both HIV therapy and prevention.

ORAL PRESENTATIONS

O1

O111. The changing face of HIV resistance; HIV drug resistance north and south — what's next?

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O1

HIV drug resistance has proved to one of the greatest challenges to effective and durable viral suppression. Selection of drug resistance mutations and widespread cross-resistance between agents of a class are a main obstacle when administering antiretroviral agents in clinical practice. This has been perhaps the greatest barrier to incorporating HIV care in to routine medical management administered by general practitioners. As opposed to many other disease states where the development of effective therapy allowed for simple widespread use as part of general care, HIV drug resistance has mandated cumbersome, resource consuming and demanding medical practice from both clinicians and even more so patients. Extremely demanding lifelong drug taking behavior by patients, high level clinician knowledge and expertise; and expensive monitoring technologies are all required for durable clinical benefit from antiretroviral therapy due to resistance.
But knowledge and understanding of drug resistance has also brought great improvement in HIV care. Technologies to detect and identify resistance as well as rapid and reasonably accurate interpretation have been developed and refined. A far greater understanding of resistance and its consequences by providers and patients have molded our highly effective modern care. Development of improved drugs including those with unique mechanisms has greatly benefited from our growing knowledge.
As we move forward to the next decade of HIV care, we need to revisit how we relate to and address HIV drug resistance. Old assumptions need to be challenged; data needs to be critically evaluated considering our new and improved drugs, and widespread treatment of patients in resource limited settings need to be specifically prioritized as challenges may not be identical. How should our much improved (but expensive) resistance assays be used? To what degree do we need to continue to closely monitor HIV drug resistance and in what settings? Is resistance still a high priority when designing optimal drug combinations for our patients – those naive and those drug-experienced? How can we minimize the barrier resistance presents to more simplified and widespread antiretroviral therapy? These are important issues we must address to guarantee the best care for the most patients in coming years.

O2

O112. International perspectives on adherence and resistance to HIV antiretroviral therapy

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O2

Public health debates about providing HIV antiretroviral therapy to impoverished HIV+ populations are based on the relationship between adherence and risk of drug resistance to HIV antiretroviral therapy. Early justifications for withholding antiretroviral therapy from marginalized domestic populations, such as drug users and the homeless, were mistaken for two reasons. First, levels of adherence in marginalized populations were not much different than the general HIV+ population, and second, early single protease-based antiretroviral therapy lead to drug resistance predominately in highly (80-95%) adherent individuals. In retrospect, HIV antiretroviral drug resistance during the first decade of effective therapy was not driven by poor adherence, but rather by the fact that early regimens were not potent enough to fully suppress the virus in patients who took most, if not all, of their medications. The introduction of more potent ritonavir-boosted protease inhibitor and non-nucleoside reverse transcriptase inhibitor regimens have shifted this relationship towards full viral suppression and cessation of drug resistance at high levels of adherence.
Similar concerns slowed the provision of HIV antiretroviral therapy in resource-limited settings based on the expectations that extreme poverty would lead to poor adherence and the global spread drug resistant virus. Data from most studies indicate that these concerns were overstated. Individuals in resource-limited settings consistently take >90% of their medication, compared to 70% in resource-rich settings. Successful adherence can be explained on the practice of individuals leveraging their social capital to ask friends and family to overcome structural and economic barriers to treatment adherence. Furthermore, full viral suppression is possible in antiretroviral naïve patients on non-nucleoside reverse transcriptase inhibitors regimens, typical of resource-limited settings, at moderate levels of adherence. Rather, the risk of drug resistance in resource-limited settings appears to be more related interruptions in therapy due to structural and financial barriers to drug supply and distribution. These interruptions in therapy lead to nevirapine monotherapy as nucleoside antiretroviral drug levels (stavudine and lamivudine) decay more rapidly than non-nucleoside reverse transcriptase inhibitor drug levels (nevirapine) following a treatment interruption ("the nevirapine tail"). While efforts to sustain and prevent declines in adherence will be important in resource-limited settings, resistance will have less to do with forgotten doses, than ensuring a reliable drug supply and distribution system.

O3

O113. Adherence to antiretroviral treatment regimens and correlation with risk of hospitalization among commercially insured HIV patients in the US

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O3

Purpose: A lower daily pill burden may improve adherence to antiretroviral treatment (ART) and improve outcomes. The goal of this study was to assess differences in adherence rates based on the number of pills taken per day and to evaluate how adherence correlates with the risk of hospitalization.
Methods: This analysis examined commercially insured patients in the LifeLink claims database. Patients were selected if they had a diagnosis of HIV/AIDS (ICD-9-CM code 042.xx) between 6/1/2006 and 12/31/2008 and received a complete ART regimen defined as 2 nucleoside/nucleotide

reverse transcriptase inhibitors (NRTIs) along with a third agent (NNRTI, protease inhibitor, CCR5 antagonist, or integrase inhibitor). Patients were grouped according to their daily pill count: one, two, or three or more pills a day, and were required to receive their regimen for at least 60 days. Outcomes included adherence (both absolute and at pre-specified thresholds) and rates of hospitalization. Adherence was measured as a proportion (medication possession ratio) by dividing the days the patient received a complete regimen by the days between the start and end of the regimen. Logistic regressions were undertaken to assess the relationship between pills per day and adherence and hospitalization while controlling for demographics, comorbidities, and ART-naïve (vs. experienced) status.

Results: 7,073 patients met the study inclusion criteria, among whom 33.4%, 5.8%, and 60.8% received one, two, or three or more pills a day, respectively. 1,829 (20.5%) patients were excluded because they had an incomplete regimen. Approximately 47% of patients receiving one pill a day achieved ≥95% adherence, compared to 41% of patients receiving two pills a day, and 34% of patients receiving three or more pills a day. Based on regression results, patients receiving one pill a day were 61% more likely to reach a 95% adherence threshold vs. patients receiving three or more pills a day (odds ratio [OR]=1.61, P<0.001). Regardless of number of pills per day received, patients were 40% less likely to have a hospitalization if they were adherent to therapy (OR=0.62, P<0.001). Patients receiving one pill a day were 21% less likely to have a hospitalization vs. patients receiving three or more pills a day (OR=0.770, P<0.01).

Conclusions: We found receiving an ART regimen consisting of one pill a day was associated with better adherence and a lower risk of hospitalization.

O4

O114. Long-term probability of detecting drug-resistant HIV in patients starting antiretroviral therapy within the first year of HIV infection

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Background: The development of drug resistance is often cited as a disadvantage of early initiation of cART. However, little is known about the long-term probability of detecting drug resistance in individuals initiating cART early.

Methods: We followed-up patients in CASCADE with well-estimated dates of HIV seroconversion from cART initiated within 1 year of the first HIV positive test to the earlier of: date of detection of drug resistance (IAS-USA list) or last recorded VL. We included patients with a drug resistance test following VL>1000 c/mL and those with VL always <1000 c/mL. The latter were assumed to have no drug resistance. Median survival from cART initiation to detection of drug-resistance was estimated using Kaplan-Meier methods, and log-rank tests were used to explore the association between detection of drug resistance and sex, risk group, cART class, as well as age, calendar year and CD4 at cART initiation.

Results: Of 609 included patients, median (IQR) age 34 (29,42) years and CD4 count of 364 (243,517) cells/mm3 at cART initiation, 151 had a drug resistance test before cART initiation of whom 7 (4.6%) had transmitted drug resistance (TDR). 29% interrupted treatment for ≥15 days after a median of 0.86 (0.39,1.77) years. 67% and 26% initiated PI and NNRTI-containing cART, respectively. Among 122 patients with at least one resistance test, drug resistance mutation was detected in 19 with during 2392 py follow-up (8/1000 py). Among patients who were detected with a drug resistance mutation, 2 had TDR. The cumulative risk of drug resistance detection was 3% and 7% at 4 and 8 years after cART initiation, respectively. While there was some evidence of effect of CD4 at cART initiation (p=0.043) with higher CD4 being associated with a decreased risk of drug resistance detection, we found no significant association with the other risk factors.

Conclusions: Although one third of our patients interrupted cART, detection rate of resistance was remarkably low compared to those reported in individuals initiating cART in chronic infection. Our data do not support early cART initiation being associated with long-term probability of drug resistance detection.

O5

O115. Low-level residual viremia and risk of virological failure

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O5

Purpose: The clinical relevance of residual low level viremia (LLV) in patients on steady HAART is debated. Similarly the clinical usefulness of HIV-RNA cut-offs lower than 50 copies/ml is questioned. Aim of this study was to analyze the dynamics of LLV in patients on HAART by means of a high resolution test for HIV-RNA.

Methods: This is a prospective, single-center, cohort study in patients on stable HAART (mean time on HAART 109 months, SD 28). All patients with a confirmed viremia <50 copies/ml were enrolled. Patients were monitored prospectively with determinations of HIV-RNA every 4 months performed with an enhanced PCR test with a lower limit of detection of 3 copies/ml. ITT analysis is reported.

Results: A total of 505 patients (78% males) with a mean age of 45.6 years (SD 7.6) were enrolled. At baseline the mean CD4 count was 667 cells/μl (SD 268) and VL was < 3 copies/ml in 73.9% and between 3 and 50 copies/ml in the remaining 26.1% of cases. Over the following 8 months period, patients with a baseline VL < 3 copies/ml presented a stable HIV-RNA below this threshold in 72.8% of cases, a level between 3 and 50 copies/ml in 27.2% of cases while no patient steadily rebounded above the 50 copies/ml threshold. On the contrary, patients with a baseline HIV-RNA between 3 and 50 copies/ml, in the follow-up, presented a stable VL < 3 copies/ml in 43.8% of cases, a VL between 3 and 50 copies/ml in 53.1% of cases, while 3.1% of patients steadily rebounded above the 50 copies/ml threshold (P < 0.0001). In the multivariate analysis the only variable significantly associated with viral dynamics was the third drug in the HAART regimen. A steady VL < 3 copies/ml, a VL between 3 and 50 copies/ml or a steady VL > 50 copies/ml was detected, respectively, in 71.8%; 27.7% and 0.6% of NNRTI-treated patients, while the same figures for PI-treated subjects were 56.2%; 42.9% and 1.0% (P = 0.029).

Conclusions: The presence of a LLV is associated to a low risk of virological failure; however, in selected patients it may be indicative of effective virus replication leading to virological rebound. Patients treated with a NNRTI-based HAART compared to those receiving a PI-based regimen show a statistically significant more pronounced and steady control of viral replication. Further, prolonged studies are needed to assess the clinical relevance of residual LLV and eventually define new cut-off values predictive of a better control of virus replication.

O6

O116. The EuResist expert model for customised HAART optimisation: 2010 update and extension to newest compounds

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O6

Background: The design of an optimal highly active antiretroviral therapy (HAART) customised on patient's background and viral genotyping, is still a challenge. EuResist has been the first data-driven

system to be implemented as a free web-service for customised HAART optimisation, and was proven to be superior to all existing genotypic interpretation systems (GIS) since it takes into account not only genotype but multiple other variables.

Data and methods: The EuResist database stores and updates periodically demographic, clinical, and genomic information of HIV+ patients from several countries in Western Europe. The EuResist system is trained on treatment change episodes (TCE) drawn from the EuResist data base, composed of a new drug regimen with a baseline HIV-1 RNA load and a CD4+ count, a baseline viral pol genotype, demographic and previous treatment information. Each TCE is associated to an HIV-1 RNA measurement after 8 weeks, which is used for the definition of virological success (below 500 copies/ml or >2 Log10 reduction from baseline HIV-1 RNA). The system is a combination of three independent machine learning models (based on logistic regression, random forests, and Bayesian networks). The 2010 update has been trained on >5,000 TCE, composed of 20 FDA/EMEA approved nucleoside/tide, non-nucleoside, and protease inhibitors, including the recently approved compounds (RAC) tipranavir, etravirine and darunavir.

Results: The EuResist combined system performance in predicting the correct virological success of a TCE after 8-weeks (validation set, n=561) exhibited an area under the receiver operating characteristic (AUROC) of 0.8 (whereas Stanford HIVdb GIS assessed to 0.73, p=0.002). The inclusion of therapy history, clinical, and demographic covariates was shown to increase significantly prediction performance. In the subset of regimens containing RAC (n=151), the EuResist AUROC was 0.7 and Stanford HIVdb AUROC was 0.63, not allowing to assess a significant difference owing to the small sample size. See Figure 1.

Conclusions: Based on patient's information and virus genotype, the EuResist web-service ranks the most effective HAART regimens by the probability to achieve an undetectable HIV-1 RNA load after 8 weeks. Thus, it might be useful in clinical practice. The 2010 update includes also RAC and achieved fair performance, which is expected to increase with expanding training data.

O7

O121. Consensus statement of the European guidelines on clinical management of HIV-1 tropism testing

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Introduction: Testing for HIV tropism is recommended before prescribing a chemokine receptor blocker. To date, in most European countries HIV tropism is determined using a phenotypic test. Recently, new data have

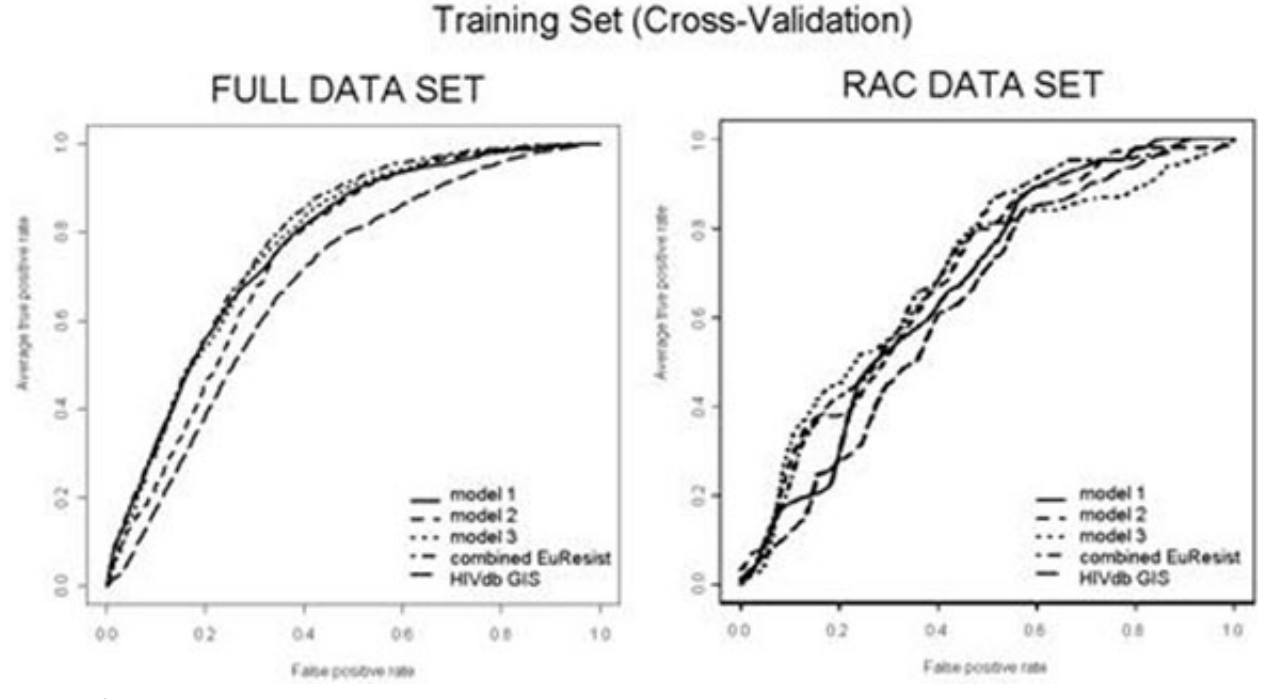

Figure 1 (abstract O6)

emerged supporting the use of a genotypic HIV V3-loop sequence analysis as the basis for tropism determination. The European guidelines group on clinical management of HIV-1 tropism testing was established to make recommendations to clinicians and virologists.
Methods: We searched online databases for articles from Jan 2006 until March 2010 with the terms: tropism or CCR5-antagonist or CCR5 antagonist or maraviroc or vicriviroc. Additional articles and/or conference abstracts were identified by hand searching. This strategy identified 712 potential articles and 1240 abstracts. All were reviewed and finally 57 papers and 42 abstracts were included and used by the panel to reach a consensus statement.
Results: The panel recommends HIV-tropism testing for the following indications: i) drug-naïve patients in whom toxicity or limited therapeutic options are foreseen; ii) patients experiencing therapy failure whenever a treatment change is considered. Both the phenotypic Enhanced Trofile assay (ESTA) and genotypic population sequencing of the V3-loop are recommended for use in clinical practice. Although the panel does not recommend one methodology over another it is anticipated that genotypic testing will be used more frequently because of its greater accessibility, lower cost and shorter turnaround time. The panel also provides guidance on technical aspects and interpretation issues. If using genotypic methods, triplicate PCR amplification and sequencing testing is advised using the G2P interpretation tool (clonal model) with an FPR of 10%. If the viral load is below the level of reliable amplification, proviral DNA can be used, and the panel recommends performing triplicate testing and use of an FPR of 10%. If genotypic DNA testing is not performed in triplicate the FPR should be increased to 20%.
Conclusions: The European guidelines on clinical management of HIV-1 tropism testing provide an overview of current literature, evidence-based recommendations for the clinical use of tropism testing and expert guidance on unresolved issues and current developments. Current data support both the use of genotypic population sequencing and ESTA for co-receptor tropism determination. For practical reasons genotypic population sequencing is the preferred method in Europe.

O8

O122. Calibration and accuracy of the geno2pheno co-receptor algorithm for predicting HIV tropism for single and triplicate measurements of V3 genotype

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Background: The geno2pheno algorithm (g2p) can give dichotomous tropism based on a selectable "false positive rate" (FPR), reflecting the proportion of individuals inappropriately called "non-R5" and falsely excluded from taking CCR5 antagonists. The effect of replicate genotype measures and different FPR values remains controversial. Here we characterize different FPR "cut-points" in predicting tropism for single vs multiple replicates for interpreting V3 genotype based on data from the clinical trials of Maraviroc (MVC) in experienced patients.
Methods: The first study population comprised all patients screened for MOTIVATE 1 (N=1399; 44% non-R5 by original Trofile) for whom both triplicate and single V3 genotypes were available. We also examined virological response (defined as a week 8 decrease ≥2 logs and/or to <50 copies/ml) in an outcome dataset of 547 patients who received MVC+optimized background therapy in the MOTIVATE-1, 2 or A4001029 studies with very limited background antiviral activity from other agents (wSS <1).
Results: Triplicate sequence analyses typically identified 10-25% more individuals with non-R5 virus compared to single replicates. A comparison of the predicted FPR by g2p to the virologically defined FPR at different g2p cut-points showed an excellent correlation (r2 =0.99; see Table 1), but appeared to be calibrated conservatively (slope =1.5 for single assays or 1.7 for triplicate assays). Some of this miscalibration likely reflects a contribution from background therapies. For comparison, the FPR of Trofile in this population was 3.9% (N=49 DM patients).
Conclusions: The g2P algorithm shows the expected association with observed virological response, but this testing procedure may be more conservative than expected from the nominal FPR values, particularly for triplicate sequence analysis. A g2p FPR value above 10 likely excludes too many individuals who could respond to therapy if this cut-off is employed to screen individuals for maraviroc.

Table 1 (abstract O8)

	MOTIVATE-1 Screening (N=1399)		Virological Outcome Set (N=547)			
G2p FPR	Number non-Rf		Number Non-Rf		Actual FPR	
	(single)	(triplicate)	(single)	(triplicate)	(single)	(triplicate)
1	100	114	6	9	0.6	0.6
2	241	288	25	36	1.3	1.3
3	303	368	39	47	2.3	2.6
4	362	427	48	57	3.6	4.2
5	396	459	52	64	4.5	5.2
5.75	**423**	**486**	**57**	**71**	**6.1**	**7.4**
6	433	496	62	77	6.8	8.4
7	476	533	71	89	8.4	10.0
8	507	563	78	98	9.7	11.7
9	548	605	88	114	12.0	13.9
10	**562**	**620**	**89**	**116**	**12.3**	**13.9**
15	646	715	132	161	21.4	23.6
20	**742**	**805**	**174**	**205**	**28.5**	**32.4**

O9

O123. Short-term variation of HIV tropism readouts in the absence of CCR5 antagonists

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O9

Background: Spontaneous tropism changes (from R5 to non-R5 or vice-versa) were observed in approximately 10% of patients between screening and study baseline in the maraviroc (MVC) clinical trials. Little is known of the biology of these apparent short-term tropism fluctuations.
Methods: Population-based and "deep" V3-loop sequencing were performed in 53 MVC recipients in the MERIT, MOTIVATE and A4001029 studies who spontaneously changed tropism readout by the original Trofile assay between screening and baseline (~4-8 weeks) and 72 randomly sampled patients who did not change. Tropism was inferred by "geno2pheno" with previously defined cutoffs: 2% X4 prevalence with a 3.5% false-positive rate (fpr) for "deep" sequencing; 5.75% fpr for population-based sequencing.
Results: Patients changing Trofile readout from R5 to non-R5 had significantly higher screening non-R5 prevalence by "deep" sequencing than those who remained R5, and this increased slightly by the baseline timepoint (Table 1). Similarly, patients who changed tropism from non-R5 to R5 in the A4001029 trial had a lower percentage of non-R5 viruses at screening and baseline. Although there was no difference in total viral load, absolute CXCR4-using plasma virus load was higher in those who changed tropism at screening (2.7 vs. 0 $\log_{10}$ copies/mL, p=0.02 in MERIT; 3.1 vs. 0 $\log_{10}$ copies/mL, p<0.0001 in MOTIVATE) and baseline (3.0 vs. 0 $\log_{10}$ copies/mL, p=0.04 in MERIT; 3.8 vs. 0 $\log_{10}$ copies/mL, p<0.0001 in MOTIVATE). Non-R5 was reported at screening in 26% and 49% of patients who changed phenotype to non-R5 by population and deep-sequencing, respectively.
Conclusions: In most cases, the prevalence of non-CCR5 usage inferred from "deep" sequencing was stable over the short term between screening and baseline. Where apparent phenotypic tropism changes from R5 to non-R5 occurred, non-R5 virus was generally detectable at the screening timepoint by genotype, coupled with relatively small increases

Table 1 (abstract O9)

	# Genotyped		Screening X4% [IQR]			Baseline X4% [IQR]		
	No Change	Changed	No Change	Changed	p	No Change	Changed	p
MERIT	25	13	0 [0-0]	1.9 [0-3.3]	0.01	0 [0-0.1]	7 [0-16.3]	0.04
MOTIVATE	25	32	0 [0-0.1]	2.4 [0.1-21.3]	0.0001	0 [0-0.1]	9.1 [0.4-32.7]	<0.0001
A4001029	22	8	5.0 [0.2-91.5]	1.8 [0.4-30.6]	0.5	4.3 [0-76.6]	0.4 [0-47.5]	0.3

in non-R5 virus by baseline. Small variations in CXCR4-using HIV populations around the phenotypic assay detection limit, rather than coreceptor switch, contributed to apparent tropism switching from R5 to non-R5.

O10

O124. Impact of baseline HIV-1 tropism on viral response and CD4 gains in antiretroviral-naïve patients

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Purpose: To evaluate the influence of HIV-1 tropism on virologic and immunologic responses in antiretroviral-naïve HIV-1-infected patients enrolled in the ArTEN trial (atazanavir/r vs. nevirapine along with tenofovir/emtricitabine).
Methods: Baseline plasma samples from patients enrolled in the ArTEN trial were tested genotypically for HIV tropism using geno2pheno (5.75% FPR) and PSSM (enhanced for X4 detection; Poveda et al, JAC 2009). Univariate and multivariate analyses were performed to find variables associated with virologic/immunological outcome. Parameters examined included gender, Hepatitis coinfection, HIV subtype, treatment arm, viral tropism, baseline CD4 counts and VL.
Results: 428 out of 569 randomized and treated patients could be analyzed, 146 on ATZ/r and 282 on NVP. Overall, 332 (76.9%) subjects were infected with subtype B variants and 45 (10.4%) were HCV coinfected. The V3 successful amplification rate was 92.1% (394/428). X4 variants were found in 14% (55/394) by geno2pheno and 29.2% (115/394) by PSSM, with no significant differences between treatment arms or HIV clade. See Table 1.
At baseline, patients with X4 viruses by geno2pheno had higher VL (5.4 [IQR:5-5.7] vs. 5.2 [4.7-5.6] log copies/mL, p=0.044) and lower CD4 counts (145 [62-200] vs. 188 [134-260] cells/mm3, p<0.001) than those with R5 viruses. At weeks 24 and 48, the proportion of patients with VL <50 copies/mL was similar in both treatment arms, but lower in those with X4 than R5 viruses. The multivariate analysis confirmed HIV tropism as independent predictor of virologic response at week 24, along with baseline VL and CD4 count. In contrast, the extent of CD4 gains was not significantly determined by HIV tropism, but it was by baseline VL, CD4 count and treatment arm.
Conclusions: HIV-1 tropism is an independent predictor of virologic response at week 24 in ARV-naïve patients treated with NVP or ATZ/r plus TDF/FTC. In contrast, CD4 gains are not determined by viral tropism. This observation may have important clinical implications, as it may be worthwhile testing for viral tropism, besides VL, CD4 counts and resistance before beginning any HAART regimen.

Reference

1. Poveda E, *et al*: Design and validation of new genotypic tools for easy and reliable estimation of HIV tropism before using CCR5 antagonists. *J Antimicrob Chemother* 2009, **63**:1006-10.

O11

O125. Influence of amount and percentage of CXCR4-using virus in predicting week 48 responses to maraviroc in treatment-naïve patients

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Background: Both population and ultra-deep sequencing (UDS) of the HIV-1 V3 loop are useful in selecting candidates for maraviroc (MVC) therapy. We used mathematical modeling to determine that patients whose non-R5 HIV comprises <2% of the viral population by UDS are likely to respond to a MVC-containing regimen. However, the predictive value of absolute amount of non-R5 HIV is unknown.
Objective: To determine whether non-R5 viral load contributes to predicting response to a MVC-containing regimen.
Methods: Patients enrolled in the MERIT study (MVC or efavirenz plus zidovudine/lamivudine in treatment-naïve patients) with R5 virus at screening (by original Trofile assay) and randomized to the twice-daily MVC arm were included. UDS was performed with a 454/Roche GS-FLX instrument. Tropism was predicted using the "geno2pheno" co-receptor algorithm (g2p). A sample was considered R5 if <2% of variants had a score below 3.5 FPR. MVC responses at Week 48 were predicted by descriptive statistics and mathematical modeling.
Results: Samples for 343 patients (308 R5, 35 non-R5) were available. Baseline median CD4 and mean viral load (VL) were 247 and 232 cells/μL and 4.9 and 4.6 $\log_{10}$ c/mL in patients with R5 and non-R5 virus. No CXCR4-using viruses were detected in 249/343 (73%) patients. Among the 94 patients with detectable CXCR4-use, median (q25, q75) percent and absolute levels of CXCR4-using viruses were 0.8% (0.4-8.1) and 2.9 (2.3-3.5) $\log_{10}$ c/mL, respectively. Week 48 virologic responses are shown in Table 1.
In univariate models, baseline CD4 and percent of CXCR4-using virus were not significant predictors of week 48 response (p=0.12; p=0.26); VL and absolute amount of CXCR4-using virus were significant (p=0.02; p=0.03)

Table 1 (abstract O10)

Endpoint	HIV tropism (g2p)				Treatment arm			
	R5	X4	p(uni)	p(multi)	ATZ/r	NVP	p(uni)	p(multi)
Week 24								
% of patients with VL<50 copies/mL	83.2	60.9	0.001	0.012	77.2	82.1	0.281	0.384
CD4 gain (cells/mm^3)	116[56-197]	117[66-172]	0.979	0.439	116[72-203]	111[45-111]	0.316	0.173
Week 48								
% of patients with VL<50 copies/mL	91.6	76.9	0.009	0.061	88.5	92.0	0.340	0.434
CD4 gain (cells/mm^3)	156[83-244]	180[86-235]	0.729	0.616	180[99-251]	152[78-230]	0.037	0.008

Table 1(abstract O11)

Baseline level of CXCR4-using virus	<50 HIV-1 RNA c/mL at Week 48, n/N (%)
Percentage	
<2%	207/308 (67.2)
2%—<10%	7/13 (53.8)
≤10%	11/22 (50.0)
Amount (log_{10} copies/mL)	
<1.0	171/251 (68.1)
1.0—<2.0	12/15 (80.0)
2.0—<3.0	23/36 (63.9)
3.0—<4.0	13/25 (52.0)
≤4.0	6/16 (37.5)

and were included in the multivariate model (p=0.02 for both in final model).

Conclusion: In MVC-treated patients in the MERIT study, baseline VL and absolute amount of CXCR4-using virus were predictive of Week 48 response. It is possible that total burden of CXCR4-using virus in drug-naive individuals may play a greater role than the percentage of such virus in predicting response to regimens containing a CCR5 antagonist.

O12

O131. Treatment as prevention within the framework of current guidelines

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O12

While an outright cure or a preventive vaccine for HIV/AIDS remain elusive, remarkable advances in HIV treatment have been achieved over the past two decades. Most significant among these advances is the development of highly active antiretroviral therapy (HAART).

Available evidence increasingly supports the notion that the viral load suppression achieved by HAART has a preventive impact on the transmission of HIV. Hence, expanding HAART coverage to all those in medical need, represents a key strategy to not only decrease HIV and AIDS related morbidity and mortality but also to dramatically reduce HIV transmission by all routes.

In British Columbia, the expansion of HAART coverage has been associated with a substantial reduction in HIV new diagnoses (Montaner et al, Lancet, August 18th 2010). The role of treatment as prevention has now been formally incorporated within the UNAIDS global AIDS control strategy, under the "Treatment 2.0" initiative.

O13

O132. Treatment-as-prevention: stopping the epidemic of HIV

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O13

Anti-retroviral drugs an reduce plasma HIV viral load by 3 to 4 orders of magnitude raising the possibility that treatment can be used not only to save individual lives but also to stop transmission. Modelling studies suggest that with the effective use of ART transmission of HIV could be eliminated within ten years and HIV infection within 40 years. The ides of using treatment as prevention has generated considerable interest and a certain amount of controversy. This presentation will describe the potential impact of *treatment-as-prevention*, compare the results with treatment-as-prophylaxis, and consider some of the key factors that could compromise the impact of this approach. These include coverage, compliance, the extent of viral load suppression, the reduction in transmission, the likelihood of virological failure, viral rebound and drug resistance. Possible ways of increasing the impact through targeting of the intervention will be discussed. Finally, some consideration will be given as to how best to test and possibly implement a programme of using treatment as prevention.

O14

O133. Test and treat — community perspectives

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O14

Antiretroviral treatment (ART) has dramatically changed the lives of people living with HIV/AIDS. Until recently and despite the benefits of antiretroviral therapy, people living within HIV still expressed their fears about treatment side-effects and about possible HIV transmission.

Accumulated evidence demonstrating the potent role of antiretroviral therapy in decreasing HIV transmission together with the availability of new generations of antiretroviral drugs with improved efficacy and tolerability has led to most HIV community leaders in France changing their attitudes in favor of adopting the "test and treat" approach. This change is also shared among leaders of HIV community-based associations in French speaking Africa. However, such an approach will not be possible without major changes in HIV policies. More than simply providing treatment availability it requires

i. a global policy against HIV discrimination and against HIV stigma in order to facilitate access to testing and treatment,

ii. the involvement and empowerment of those communities most concerned by HIV

iii. strong political leadership to both change the representation of HIV/AIDS in the general public and to implement innovative funding mechanisms.

It also implies the development of a strong international HIV policy for universal access to HIV care and prevention including respect of human rights, especially of sexual minorities, migrants and drug users. Today, the "test and treat" approach represents an important tool in curbing the HIV epidemic not only because it pushes political leaders to give top priority to HIV on their political agendas but also because it influences HIV policies which in turn encourage civil society to become directly involved in doing "with people" and not "for people".

O15

O134. HIV treatment as prevention — human rights issues

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Recognizing access to HIV treatment as a human right has been important in efforts to ensure greater resources for the scale up of ART globally. However, it has not always been accepted by governments, and those asserting the right to HIV treatment have sometimes been in conflict with those asserting other rights, such as the right to intellectual property. Some governments have disputed their obligations to provide universal ART because of limited resources or competing priorities, while others have - in violation of human rights principles of non-discrimination and equality - challenged their obligation to provide it on an equitable basis to all within their borders, leaving out specific, often socially marginalized, groups. Understanding how HIV treatment can be successful as prevention will first require attention to these neglected issues. In addition, one of the greatest barriers to access to HIV treatment when available has been the failure of governments to protect individuals from HIV-related stigma and discrimination, which affects the willingness of individuals to be tested for HIV, to seek treatment if found to be positive and to adhere to medicines if they are attained. HIV treatment as prevention will require significantly greater efforts to address stigma and discrimination, and the promotion of truly voluntary HIV testing as a gateway to prevention and treatment, maintaining an emphasis on appropriate counseling, informed consent and confidentiality. The increasing popularity of HIV legislation that criminalizes intentional or attempted HIV transmission, and which sometimes has no exception for HIV-positive pregnant women unable to access PMTCT programs or individuals on ART with undetectable viremia, raises new challenges to

expanding HIV testing and treatment programs and should be forcefully challenged by both clinical providers and human rights advocates.

O16

O135. A pilot study to determine the prevalence of HIV in persons presenting for care with selected conditions: preliminary results from the HIV in Europe study

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Purpose of the study: A pilot study was initiated in Autumn 2009 to better define which diseases have a HIV prevalence of >0.1 % as HIV testing of populations with a HIV prevalence above this has shown to be cost-effective. The preliminary results are reported here.
Methods: A detailed questionnaire was completed for persons presenting with 8 different indicator diseases; sexually transmitted disease (STD), malignant lymphoma (LYM), cervical or anal cancer/dysplasia (CAN), herpes zoster (HER), ongoing mononucleosis-like illness (MON), unexplained leukocytopenia/thrombocytopenia lasting >4 weeks (CYT), and seborrheic dermatitis/exanthema (SEB).
Results: 1482 persons have so far been included in the pilot phase by June 2010 from 29 surveys taking place in Austria, Belarus, Belgium, Bosnia, Croatia, Denmark, Germany, Italy, Poland, Spain, Sweden and Ukraine. Selected characteristics of the patients are shown in Figure 1. Almost 40% reported a previous HIV test; this was highest in the STD (59.0%), HEP (47.5%) and SEB (44.2%) groups. Median age was highest in the LYM group (53 years), and youngest in the MON group (24 years). 104 persons (7.7%) reported one of 5 specific HIV-related symptoms in the previous 5 years (mononucleosis, oral candidiasis, herpes zoster, unexplained leukocytopenia/thrombocytopenia or seborrheic dermatitis); these symptoms were highest in the HER (33.3%), SEB (31.1%) and LYM (21.2%) groups. 134 had visited an STD clinic in the previous 5 years including over half of the STD group (56.3%). 152 had been hospitalised in the previous 5 years; the highest proportion was seen in the HEP group (70.3%). Many of the planned surveys have shown difficult to implement because of reluctance towards introducing routine HIV testing among specialists who are not used to/worried about performing an HIV test. A number of persons have tested HIV-positive.
Conclusions: The first results of this pilot study demonstrates the potential benefit of guided HIV testing of patients with selected indicator diseases, as a number of persons have been identified to be HIV-positive. A significant proportion of the persons had previously been hospitalised or reported HIV-associated symptoms but had not been tested. Physicians in some specialities are however reluctant to adopt this testing strategy.

O17

O211. The state of PI monotherapy and NRTI-sparing therapy

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Current consensus about treatment of HIV infection is that HAART must include two nucleoside reverse transcriptase inhibitors plus a third drug (one non-nucleoside reverse transcriptase inhibitor, a boosted protease inhibitor, an integrase strand transfer inhibitor and possibly a CCR5 inhibitor). There is a lot of interest about changing the basic structure of the antiretroviral regimen so we can be able to use nucleoside-sparing regimens. The main reason to support the investigation of NRTI-sparing strategies is the concern about the long-term toxicity of tenofovir and abacavir.
In antiretroviral naïve patients candidates for nucleoside sparing regimens have included a boosted or unboosted protease inhibitor as the backbone drug to which a non-nucleoside reverse transcriptase inhibitor, an integrase inhibitor, a single nucleoside or a CCR5 inhibitor has been added. In patients who have already achieved suppression it is possible that a boosted protease inhibitor used as monotherapy might be all what is needed to maintain suppression. It is reasonable to predict that, compared to triple-drug HAART, the long term toxicity of these single and dual-drug regimens would be lower. Finding the right number of antiretrovirals that offers the optimal balance of long-term efficacy and toxicity is therefore a very important scientific question.
This presentation would review the clinical trials that have explored NRTI sparing strategies for the treatment of antiretroviral naïve patients and also for maintenance of viral suppression. The presentation would highlight the possible benefits associated to NRTI-sparing strategies and the most promising candidates.

Characteristics of 1428 persons included in preliminary study of indicator-disease guided HIV testing

		All	STD	LYM	CAN	HER	HEP	MON	CYT	SEB
		1428 (100)	192 (13.5)	104 (7.3)	63 (4.4)	80 (4.2)	800 (56.0)	118 (8.3)	46 (3.2)	45 (3.1)
Gender[1]	Male	892 (62.7)	156 (81.7)	45 (43.3)	22 (34.9)	28 (46.7)	509 (64.0)	77 (65.3)	20 (43.5)	35 (77.8)
Ethnicity[2]	White	1259 (93.2)	160 (92.0)	103 (99.0)	14 (100.0)	55 (91.7)	734 (92.7)	116 (99.2)	42 (93.3)	35 (77.8)
Sexual	Hetero	1154 (85.4)	95 (54.6)	100 (96.2)	14 (100.0)	54 (90.0)	705 (89.0)	108 (92.3)	39 (86.7)	39 (86.7)
Orientation[2]	Homo/Bi	89 (6.6)	72 (41.4)	1 (1.0)			7 (0.9)	5 (4.3)		4 (8.9)
	Unknown	108 (8.0)	7 (4.0)	3 (2.9)		6 (10.0)	80 (10.1)	4 (3.4)	6 (13.3)	2 (4.4)
Prev test[3]	Yes	549 (39.3)	112 (59.0)	9 (8.7)	10 (16.1)	16 (20.6)	370 (47.5)	12 (10.3)	1 (2.2)	19 (44.2)
Age[4]	Years	42 (31–55)	32 (27–39)	53 (39–61)	38 (33–45)	47 (37–56)	46 (36–56)	24 (21–30)	58 (44–71)	36 (28–50)
Any HIV Symp last 5 yr[5]		104 (7.7)	4 (2.3)	22 (21.2)		20 (33.3)	34 (4.3)	7 (6.0)	3 (6.7)	14 (31.1)
STD clinic in last 5 yr[6]		134 (11.7)	98 (56.3)	1 (1.0)		2 (3.6)	28 (4.3)	4 (3.9)		3 (7.0)
Hosp in last 5 yr[7]		152 (11.5)	2 (1.2)	29 (29.0)	2 (14.3)	16 (27.6)	80 (70.3)	9 (7.8)	7 (15.9)	7 (15.6)

STD; sexually transmitted disease, LYM; malignant lymphoma, CAN; cervical or anal cancer/dysplasia, HER; herpes zoster, MON; ongoing mononucleosis-like illness CYT; unexplained leukocytopenia / thrombocytopenia lasting ≥4 weeks, SEB; seborrheic dermatitis/exanthema. All data are N (%) or median (Interquartile range). Cells are blank for zero (N and %) or where there is insufficient data to calculate the median and IQR. Data available for [1]N=1422, [2]N=1351, [3]N=1397, [4]N=1436, [5]N=1351, [6]N=1142, [7]N=1320. All p-values for comparison < 0.0001 using chi-squared test for categorical variables and wilcoxon test for medians.

Figure 1 (abstract O16)

O18

O212. Ritonavir-boosted protease inhibitor monotherapy is 6% less effective than combination antiretroviral therapy in a meta-analysis

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Background: Ritonavir-boosted protease inhibitor (PI/r) monotherapy has several potential benefits over standard PI-based combination antiretroviral therapy (cART) and has recently been included in the European HIV treatment guidelines. However, there are concerns about its efficacy. We performed a meta-analysis comparing PI/r monotherapy to cART to examine its efficacy.
Methods: We searched electronic databases (Pubmed, EMBASE, Central) from 1996 to 2010 using keywords, "protease inhibitor", "antiretroviral", "monotherapy", relevant drug names and standard "HIV" and "RCT" search strings on March 22, 2010, without limits to language. We searched major HIV-related conferences manually from 2007 and contacted experts. Two reviewers independently assessed citations for eligibility and extracted relevant data. Assessment of bias of individual studies was performed independently by both reviewers. We did not include review articles, single-arm trials, or observational studies.
Results: Of the 137 citations identified, we reviewed 19 articles after duplicates and obviously unrelated titles were discarded. Of these, 6 met eligibility criteria. Four additional abstracts were identified from conference abstracts. Ten RCTs (1265 participants) were included in meta-analysis using random effects Mantel-Haenszel methods. Summary estimate for the outcome of viral suppression (<50 copies/ml) on PI/r monotherapy compared to cART using intention to treat analysis (ITT), where reinduction and missing data count as failure, was RR_{MHRE} 0.94 (95% CI 0.89-0.99) without evidence of heterogeneity (p-value 0.55 and I^2 0%). Using on-treatment (OT) analysis, where missing information, deaths and drug changes due to adverse events were censored, the summary estimate was RR_{MHRE} 0.90 (95% CI 0.85-0.96, 1113 participants). There was no evidence of statistical heterogeneity in the OT analysis (p-value 0.01, I^2 57%). All studies were open-label. There was variability in study populations (treatment naïve vs experienced) and in interventions (LPV/r vs DRV/r monotherapy and cART regimens). Excluding the only RCT that started PI/r monotherapy in patients with unsuppressed HIV, did not change the ITT summary estimate.
Conclusions: Our meta-analysis of 10 RCTs suggests that PI/r monotherapy is slightly but significantly less effective than cART. Subgroups of patients, however, may benefit from this promising alternative treatment strategy. Future RCTs should focus on these patients.

O19

O213. Low-level viraemia during treatment with darunavir/r monotherapy versus DRV/r + 2NRTIs in the MONET trial

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Background: Patients with HIV RNA suppression below 50 copies/mL may still have HIV RNA detectable by more sensitive PCR assay techniques.
Methods: In the MONET trial, 256 patients with HIV RNA <50 copies/mL on current HAART, and no history of virological failure, switched to DRV/r 800/100 mg once daily, either as monotherapy (n=127) or with 2NRTI (n=129). HIV RNA was evaluated by the Roche Amplicor Ultrasensitive assay (lower detection limit=50 copies/mL), for all patient visits to Week 96.

Table 1(abstract O19)

HIV RNA	DRV/r mono (n=105)	DRV/r + 2NRTIs (n=114)
HIV RNA <50, OD = background	79.0%	80.7%
HIV RNA <50, detectable	17.1%	14.9%
HIV RNA 50-400 copies/mL	2.9%	3.5%
HIV RNA <400 copies/mL	1.0%	0.9%

With this assay, "Optical Density=background" was used to assess whether HIV RNA was detectable or undetectable below 50 copies/mL.
Results: Patients were 81% male, 91% Caucasian, and had median baseline CD4 count of 575 cells/uL. At the baseline visit, the percentage of patients with HIV RNA undetectable below 50 copies/mL (OD=background) was 80% in the DRV/r mono arm and 79% in the DRV/r + 2NRTI arm. The percentage with HIV RNA at different levels at the Week 96 visit is shown in Table 1 (observed data analysis)
Including all samples from patient visits from Week 4 to Week 96, HIV RNA was above 50 copies/mL in 69/1009 samples in the DRV/r monotherapy arm (50-400: 84%, 400-1000: 12%, >1000: 4%) and 47/1051 samples in the DRV/r + 2NRTI arm (50-400: 83%, 400-1000: 8.5%, >1000: 8.5%).
Conclusions: In this study for patients with HIV RNA <50 copies/mL at baseline, switching to DRV/r monotherapy showed similar levels of HIV RNA suppression to DRV/r + 2NRTIs, using more sensitive PCR assay techniques.

O20

O214. Virological findings from the SARA trial: boosted PI monotherapy as maintenance second-line ART in Africa

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Background: The SARA trial recently demonstrated a non-inferior CD4 response, over median follow-up of 60 weeks, with a boosted protease inhibitor monotherapy (bPImono) maintenance second-line regimen compared with continuous combination therapy (CT), suggesting this approach could maintain effectiveness whilst improving tolerability and decreasing costs [International AIDS Conference 2010, LBPE16]. Analysis of virological response and genotypic drug resistance is reported here.
Methods: Eligible participants in the DART trial who received 24 weeks of lopinavir/ritonavir-containing second-line CT were randomised to maintain current CT or to reduce to bPImono within a nested pilot trial (SARA). No real-time virology was performed, but stored plasma samples from time at switch to second-line, randomisation after 24 weeks of second-line, and 24 weeks after randomisation were assayed for HIV-1 RNA viral load (VL) by Roche Amplicor v1.5. Genotypic resistance was assessed on samples with VL >1000 c/ml at this latest time point, along with paired samples at switch to second-line. All analyses are intention-to-treat.
Results: 192 participants were randomised to CT (n=95) or bPImono (n=97). 77% (135/173) had VL<50 c/ml at randomisation. 44 (23%) participants were taking bPI with NRTI only, 29 (15%) with NNRTI only, and 119 (62%) with both. Virological suppression at week 24 was higher (trend test p=0.007) for participants on CT vs bPImono: 77% (70/91) vs 60% (56/94) had VL <50 c/ml, 90% (82) vs 74% (72) had VL <200 c/ml, and 94% (86) vs 84% (81) had VL <1000 c/ml. Restricting to patients with VL <50 c/ml at randomisation, 85% (57/67) vs 66% (43/65) had VL <50 c/ml at week 24. Of the 18 participants with VL >1000 c/ml at week 24, 12 (2 CT, 10 bPImono) have been assessed genotypically. IAS major PI mutations at week 24, not present at switch to second-line, were detected in 2 bPImono participants only. One participant (VL=3600 c/ml)

had I54V only, the other (VL=1490 c/ml) M46IM+V82AV. Both isolates were considered fully susceptible to darunavir.
Conclusions: In this study based on retrospective virological testing, bPImono following 24 week second-line induction was associated with an increase in low level viraemia, although generally in the absence of PI resistance. Longer-term trials are required before definitive conclusions can be drawn about the effectiveness of PI monotherapy in populations without access to virological monitoring.

O21

O215. Virological outcomes in ARV-naïve patients switching or not from a first successful boosted PI-regimen to efavirenz, nevirapine or abacavir regimens

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Objectives: To compare virological outcomes in patients who switched to a cART including efavirenz (EFV), nevirapine (NVP) or abacavir (ABC) with patients who continued on a first virologically successful boosted protease inhibitor (PI)-containing cART, and to assess virological differences between the switch regimens.
Methods: Using the French Hospital Database on HIV (FHDH-ANRS Co4), 439 antiretroviral (ARV)-naive patients with undetectable viral load (VL) who switched from a first boosted PI-containing cART to a combination including EFV (n=196), NVP (n=123) or ABC (n=120) were selected. Each patient was matched with 3 patients who did not change their cART on the basis of sex, age, CD4 cell count, VL and date of the first cART initiation and duration of undetectability. Time to virological failure (VF) was analysed using Kaplan-Meier curves and Cox models. Potential confounding variables considered for the analyses were HIV transmission group, at the date of first PI-cART initiation: NRTI backbone, PI drug; at the index date: AIDS status, CD4 cell count, NRTIs background, calendar period, time since inclusion in the database, time since first PI-cART initiation, time between undetectability and switch. Each variable associated with VF in the univariate model ($p<0.20$) was included in a multivariable model designed to evaluate the impact of the sole switch first, then the impact of the switch regimen, on the risk of VF. Each model was stratified by the matched groups (exposed/matched non-exposed patients).
Results: 12-month probabilities of VF were 3.7% in patients not switching and 5.7% in patients switching, 3.9%, 7.2% and 9.0% in patients switching to EFV-, NVP- and ABC-cART, respectively. After adjustment on PI at first cART, CD4 cell counts and AIDS status at the date of switch, switch was not associated with VF (crude HR, 1.20; 95%CI,0.81-1.77; adjusted HR (aHR), 1.19; 95%CI, 0.80-1.76, compared to no switch). Patients switching to ABC-cART had a higher risk of VF (aHR, 1.99; 95%CI, 1.05-3.79) than patients not switching, patients switching to EFV (aHR, 0.82; 95%CI, 0.41-1.65) or NVP (aHR, 0.96; 95%CI, 0.44-2.07) having similar risk of VF compared to patients not switching.
Conclusions: In previously ARV-naive patients, virologically successfully treated with a boosted PI-cART, switch to a NNRTI-cART, either EFV or NVP, is virologically safe, while switch to an ABC-cART should not be recommended.

O22

O221. The clinical development of NRTIs — cautionary tales

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The history of HIV is also the history of antiretroviral therapy (ART), the single most important measure in combating the HIV pandemic. The outcomes and in particular the interpretation of some early ART trials have greatly influenced the development of treatment guidelines and the course of ART implementation. A review of the development of NRTIs to date could be seen as a handbook of cautionary tales, relevant to the development of all future HIV therapies.
The early studies examining the use of acyclovir in the treatment of HIV and the incremental implementation of new drugs, progressing from mono and dual therapy to triple ART therapy, are good examples of the influence that particular studies have had on the subsequent treatment of HIV in the clinic. But the consistent modest effects in trials were not always given sufficient consideration and we did not always define the mechanisms at work. A number of trials were also needed before we understood that studying the right population - and using the right combination of therapy - was essential, if we were to avoid overlooking effective treatments options. Other slowly-learned lessons were that long-term follow-up studies are necessary to avoid those complications that are not detected in standard trials; they are also needed to detect in a reliable and timely way those issues which raise safety concerns.
The progression to cART of course was not without complications; good examples being the recognition and investigation of the underlying mechanisms of lipodystrophy, and the identification of an association between abacavir and myocardial infarction. The development of ART demonstrates the importance not only of the original ART trials but also continued investigation of specific drugs and regimens in the clinic to identify and manage any subsequent treatment issues that may become apparent after the rollout of these therapies. NRTIs are the backbone of therapy but only two drugs in the class are presently preferred in the current guidelines and there are too few active candidates in the pipeline. The future of this essential component of cART is uncertain.

O23

O222. Major issues and their solutions in the management of HIV and TB — from the laboratory to the patient and population

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HIV is the strongest known risk factor for developing active tuberculosis. In individuals with Mycobacterium tuberculosis infection, the risk of developing active disease is 20 or more times greater in persons living with HIV than HIV negatives. Tuberculosis is the most common HIV-associated illness in resource poor settings and the most common opportunistic infection in patients receiving HAART in developed countries. Of the 33 million people estimated to be living with HIV globally in 2008, approximately 1.5 million were also tuberculosis patients. In that same year, tuberculosis was responsible for 25% of all deaths in HIV-infected individuals. Given the synergistic consequences of the two epidemics, has recommended several collaborative activities as part of core HIV and TB prevention, care and treatment services. In this conference, some of the most important recent advances in prevention, diagnosis, and treatment will be critically reviewed.

O24

O223. Population pharmacokinetics of lopinavir and ritonavir in combination with rifampicin-based antitubercular treatment in HIV-infected children

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Objectives: Children with HIV associated tuberculosis often require co-formulated lopinavir/ritonavir (LPV/RTV)-based antiretroviral treatment with rifampicin-based antitubercular treatment (ATT). Rifampicin (RIF), a potent inducer of drug-metabolizing systems, profoundly reduces the bioavailability of LPV. The aims of this study were to develop an

integrated population pharmacokinetic (PK) model describing LPV and RTV PK in children with and without concomitant ATT using two different dosing approaches and to estimate doses of LPV/RTV achieving target exposures during ATT in young children.
Methods: A population PK analysis was conducted in NONMEM. During ATT 15 children were given LPV with extra RTV (LPV/RTV ratio 1:1) and 20 children were given twice the usual dose of LPV/RTV (ratio 4:1) 12 hourly; 39 children without tuberculosis and 11 children undergoing repeated sampling after ATT were treated with standard 12 hourly doses of LPV/RTV (median LPV dose 11.6 mg/kg). Goodness-of-fit plots and visual predictive checks were used to evaluate the models.
Results: In a one-compartment model with first-order absorption to describe LPV PK, and a one-compartment model with transit absorption for RTV, the dynamic influence of RTV concentration on the clearance of LPV was modelled as direct inhibition with an Emax model. Allometric scaling for weight was used for clearance and volume of both LPV and RTV. During ATT, the relative oral bioavailability of LPV was reduced by 79% in children receiving twice the usual dose of LPV/RTV. The clearance of RTV was 18 L/h with, and 13 L/h without, ATT. The baseline clearance of LPV, when RTV was undetected, estimated 4.34 L/h. With increasing concentrations of RTV, clearance of LPV decreased in a sigmoid relationship (EC50 0.051 mg/L). Volume of distribution for LPV and RTV were 11.7 and 102 L, respectively. Simulations predicted that children weighing 4-6, 6-8, 8-12 and 12-18 kg need respective doses of 65, 50, 37 and 30 mg/kg LPV/RTV (4:1) 8 hourly in order to maintain LPV concentrations > 1 mg/L in at least 95% of children.
Conclusions: The model describes the drug-drug interaction between LPV, RTV and RIF. Using 8 hourly doses, approximately 2.5 to 5.5 times the standard doses are required to maintain therapeutic LPV concentrations in young children during ATT.

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O25

O231. Growing old with HIV — dealing with co-morbidities

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The prevalence of HIV and AIDS among persons 50 years of age and older continues to increase as a consequence both of improved antiretroviral efficacy extending survival among individuals who contracted the disease earlier in the epidemic and continued primary infection in older individuals. Management of older HIV-infected patients is complicated by the presence of comorbidities that are more common with increasing age, such as diabetes mellitus, cancer, and cardiovascular, renal, hepatic, and bone diseases. Some of these conditions have specific links to HIV infection or with its treatment. Others are consequences of remaining alive to reach an older age. While a determination of the relative contribution of age, HIV status, and antiretroviral exposure to these comorbidities is an important research question, there are also important management issues. In particular, it is important to establish if management of these co-morbidities should differ because of the HIV status of the patient. While these research issues are being resolved, the assessment of comorbidities in older persons should become part of routine care, and at the very least routine age-specific guidelines should be used for screening. Management of older persons with HIV should include baseline evaluation of cardiovascular risk and regular monitoring of fasting lipid and glucose levels, renal function, and markers of bone disease. Furthermore, co-morbidities have an important influence on antiretroviral selection, as avoidance of metabolic and other toxicities or drug-drug interactions is a key issue.

O26

O232. HIV therapy in an ageing population — the challenge of polypharmacy

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Pharmacokinetic drug interaction studies performed during the drug development process, or post-licensing provide the substantive data base from which recommendations regarding the use of certain drug combinations are made. However given the sheer number of potential interactions, especially in the context of an ageing population with inevitable co-morbidities and polypharmacy, we need to be able to make informed decisions even in the absence of study data. Thus knowledge of drug handling (the role of various metabolic enzymes and transporters etc.) is essential so that pre-clinical data (determining whether the drug is a substrate or an inhibitor of a particular enzyme or transporter; use of in vitro/in vivo extrapolation tools etc.) can be the basis for deciding how to proceed. However we also need to appreciate that with the ageing process drug absorption and clearance can alter so the challenge then is to understand how this may impact on the magnitude of a drug-drug interaction. While the major focus in the HIV field has been on CYP450 enzymes (for the obvious reason that many of the drugs are extensively metabolised and/or are inducers/inhibitors) there is a growing awareness of the key role for other proteins - in particular UDP-glucuronyltransferases (UGTs) and transporters (ABC transporters such as P-gp, MRPs; SLCO transporters such as OATP1B1, OCTs, OATs). This is a rapidly emerging field and one which is going to impact on our understanding of mechanisms of drug-drug interactions. In addition the variable expression of enzymes and transporters due to pharmacogenetic changes is another important consideration. Unexpected interactions will continue to emerge and will need to be managed. Ultimately the key to management of patients on multiple drugs is clinical vigilance, access to adequate resources to help inform (e.g. web based resources), and in some cases the careful use of therapeutic drug monitoring.

O27

O233. Impact on life expectancy of late diagnosis and treatment of HIV-1 infected individuals: UK CHIC

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Purpose of the study: Life expectancy (LE) is an important health indicator that informs decisions both by individuals and public policymakers. The pattern of the HIV epidemic and LE varies by country. Previous estimates of LE in HIV-infected populations have included few UK patients[1]. We assess time trends, sex-differences and the impact of delayed treatment on LE in treated HIV patients in the UK and compare with the LE of the UK population.
Methods: We analysed data from the UK CHIC cohort study on patients aged over 20 years who started cART in 1996-2008 with CD4≤ 350cells/mm^2 (excluding injection drug users). All-cause mortality was ascertained from clinic records and by linkage to the death registry. Abridged life tables were constructed from age-specific mortality rates (5year age bands) to estimate LE for ages 20-65 years. Results are presented as LE at exact age 20, the average additional years that will be lived by a person after age 20, according to the cross-sectional age-specific mortality rates during the study period. We estimated LE overall and by period (1996-99, 2000-02, 2003-05, 2006-08). We compared LE in those treated for HIV with the UK population stratified by sex. To assess the impact of late treatment, we estimated LE stratified by CD4 cell count at start of cART in those treated post 2000 who were ART-naive.
Results: 1248/17661 eligible patients died during 91203 pyrs fup. 75% of patients were male, 58% white. Transmission risk group was 54% MSM, 37% heterosexual and 9% unknown. At start of cART, median age (IQR) was 37(32-43) years, median CD4 cell count 166 (75-241) and the proportion with no ART exposure prior to cART increased from 54% in 1996-99 to 96% in 2006-08. LE (standard errors) at exact age 20 years

increased from 30.0 (1.2) to 45.8 (1.7) years from 1996-99 to 2006-08. Over the study period LE for male patients was 39.5(0.45) and for female 50.2(0.45) years compared with 57.8 and 61.6 years for men and women in the UK population (1996-2006). LE was 37.9 (1.3), 41.0 (2.2) and 53.4 (1.2) years in those starting cART with CD4<100, 100-199 and 200-350 cells/mm^2 respectively (N=9657).

Conclusions: LE of those treated for HIV-infection in the UK has increased by over 15 years during 1996-2008, but remains about 13 years less than that of the UK population. The higher LE of women compared with men is magnified in the HIV-infected population. Earlier diagnosis through improved screening and timely treatment might increase LE.

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O28

O234. Mitochondrial ageing and antiretroviral therapy exposure

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Purpose: Normal human ageing is thought to be driven by the progressive accumulation of molecular defects, including somatic mitochondrial DNA (mtDNA) mutations. Certain nucleoside analogue anti-retroviral drugs (NRTIs) are known to cause reversible mtDNA depletion, but it is unknown whether they affect age-associated mtDNA mutation.

Methods: We have recruited adult HIV-infected patients, all aged 50 years or under. Subjects were stratified according to cumulative (lifetime) exposure to those NRTIs previously implicated in disruption of mtDNA replication. Proportional level of the age-associated mtDNA common deletion (CD) was measured by means of a novel real-time PCR assay. Based on these and prior observations from our group, we then developed a validated model of mtDNA replication [1,2], and incorporated a period of partial mtDNA replication failure due to NRTI exposure.

Results: Amongst all patients CD levels increased with subject age (r=0.467, p=0.005). Mean CD levels were significantly higher in NRTI-exposed than unexposed patients (mean $\log_{10}$(CD/mtDNA) ±SEM: NRTI+, -3.46 ±0.24; NRTI-, -4.62 ±0.29; p=0.006). Lifetime NRTI exposure was predictive of CD level (r=0.419, p=0.052). In silico modelling demonstrated that a finite period of partial replication failure was seen to lead to a period of mtDNA depletion during the exposure which corresponded to that expected for the relevant NRTI. During this period rapid expansion of pre-existing mtDNA deletion mutations was observed within individual simulated cells. This effect led to an increase in the proportion of cells with a functional mitochondrial defect which continued to increase after the period of exposure due to the continued effects of ageing. Longer exposure, exposure to more potent inhibitors of mtDNA replication and exposure later in life had the most profound effects on eventual cellular defect.

Conclusions: Cumulative exposure to certain NRTIs accelerates the accumulation of age-associated mtDNA deletion mutations, which appears to be irreversible, and mirrors that expected much later in life due to normal ageing. This effect could be caused simply by accelerated expansion of pre-existing age-associated somatic mtDNA mutations, mediated by finite periods of NRTI exposure. These data plausibly provide a novel biological mechanism for the phenomenon of accelerated ageing recently described in long-term treated HIV-infected patients.

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O29

O311. Hepatitis C new drugs

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Hepatitis C virus infection remains a significant global health problem with more than 130 Million individuals being chronically infected world-wide. Since 2001, the standard therapy of chronic hepatitis has been PEG-IFNa + ribavirin. A large number of new direct acting antiviral agents is currently explored in clinical trials. Different viral proteins are targeted by these novel agents. The first HCV protease inhibitors telaprevir and boceprevir are expected to be approved in 2011 as phase III trials have been completed in summer 2010. At this stage, Direct Acting Anti-Viral agents will only be used in combination with PEG-IFNa and ribavirin. Triple therapy will increase sustained virological response rates by 25-30% for treatment naïve patients infected with HCV genotype 1 to 70-80% and previous nonresponder patients may now have chance of 30-50% to cure the infection. Moreover, treatment will be "response guided" meaning that patients who are already HCV RNA negative by week 4 can be treated shorter for only 24-28 weeks while slow responder still have to treated for 48 weeks. Resistance will be a problem for first generation HCV protease inhibitors, in particular if only suboptimal doses of PEG-IFNa and ribavirin can be administered. Finally, the new drugs will add additional side effects as telaprevir may cause rashes in 5-10% of patients and boceprevir can induce nausea. Both drugs can induce anaemia which may be more pronounced for boceprevir.

Additional drugs including "second wave protease inhibitors", nucleosidic and non-nucleosidic polymerase inhibitors, NS5A inhibitors as well as cyclophilin inhibitors are currently explored in phase II studies. All oral therapies without PEG-IFNa are also explored by different companies. In addition therapeutic vaccine trials aiming to induce immune control are also still ongoing. It is very likely that the entire treatment concept for HCV infection will completely change within the next 5 years. Additional challenges will not only include management of viral resistance but also management of new side effects which may become of particular importance in patients with advanced liver disease.

O30

O312. Host genetics of HCV disease — *IL28B*

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Co-infections with HCV and HIV are common, because both viruses share routes of transmission and establish chronic infections. The standard treatment for chronic hepatitis C, a combination of peginterferon-α and ribavirin, is poorly tolerated and only successful in about half of the treated patients. Thus, identification of accurate predictors of treatment response is highly desirable.

Several independent genome-wide association studies have recently identified human genetic variants around the *IL28B* gene (coding for IFN-λ3) that strongly associate with spontaneous clearance of HCV and with treatment success, both in HCV mono-infected and in co-infected patients. I will put these findings in perspective and discuss their practical and theoretical implications with regard to drug development, clinical trial design and clinical management of chronic HCV infection. Results of detailed genetic and functional analyses of the *IL28B* gene region will also be presented.

O31

O313. Hepatitis C — feedback from the Consensus Conference on the Management of Acute Hepatitis C (AHC) in Paris, May 2010

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Since 2000 several outbreaks of acute HCV infections have been reported among HIV-positive patients. The majority of AHC infections have been

observed in Europe and have been almost exclusively limited to men who have sex with men. The epidemic is still ongoing, has been recognized in several large HIV-cohorts and recent outbreaks have also been reported from Australia and the USA. Risk factors for sexual transmission in HIV-infected patients appear to be concurrent sexual transmitted diseases such as syphilis or lymphogranuloma venereum or rough sexual practices, both thought to disrupt mucosal integrity and facilitate permucosal infection. Non-injecting drug use has also been more frequently found among HIV-positive patients with AHC compared to HIV-positive without history of AHC. While tremendous efforts have been undertaken to better understand the epidemic, the natural history and pathogenesis of AHC, and to develop concepts on diagnosis and management of AHC in HIV-infected patients there is still a lack of guidance informing us how to best manage our patients.

As data from clinical trials and cohort studies has become available, evidence-based guidelines are timely to permit the best management of these patients. To address this issue, the European AIDS Treatment Network (NEAT) invited members of the European AIDS Clinical Society (EACS) hepatitis group, the European Association for the Study of the Liver (EASL), the European Study Group on Viral Hepatitis (ESGVH) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European AIDS Treatment group (EATG) and other experts to attend a consensus conference on acute HCV infection in HIV-infected individuals in Paris, France, on May 21st, 2010. On behalf of the consensus panel this presentation will report on the consensus statements developed.

O32

O314. Efficacy and safety of peginterferon alfa-2a + RBV in cHCV/HIV- vs cHCV-infected patients: interim analysis of a multicenter German cohort

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Purpose of the study: Eradicating cHCV is necessary for the subsequent management of patients with HIV and every HIV/HCV co-infected patient should be considered for treatment. We describe differences between cHCV mono-infected and cHCV/HIV co-infected patients in baseline factors and outcome of cHCV-treatment with peginterferon alfa 2a + RBV in the worldwide largest cHCV cohort.

Methods: Noninterventional prospective multicenter German cohort, started January 2008 and still recruiting. Interim analysis of cHCV patients, stratified for cHCV mono-infection and cHCV/HIV co-infection. The results are based on a cross-sectional analysis of all available data in April 2010.

Results: This interim analysis included 5.390 patients, who received HCV-treatment. 397 were cHCV/HIV co-infected (CI) and 4.993 cHCV mono-infected (MI). Main baseline- characteristics: 85.9% were GT1/4/5/6 patients in the CI-Group and 63.4% in the MI-Group, age was 41.0 (CI), 42.0 (MI) yrs, 89.7 (CI), 62.9 (MI)% were male, BMI was 22.8 (CI), 24.9 (MI) kg/m^2, naïve/relapse/non-responder/re-infection: 86.4/3.8/4.5/5.3(CI), 88.0/6.1/5.3/0.6 (MI) %, source of infection (>1 answer possible): iv drug use 25.2(CI), 44.9(MI) %, sexual transmission 60.7 (CI), 4.1(MI)%, other 8.0 (CI), 24.0 (MI), unknown 13.1(CI), 33.0 (MI)%. 86.4 % of the co-infected patients received antiretroviral HIV-treatment (ART), 66.2 % of them had an HIV-RNA level below 50 copies/mL, median CD4-cells/µ count was 502. From those patients who finished treatment, 52.9% of the CI-Group and 67.7% of the MI-Group completed the planned course. Reasons for discontinuation (>1 answer possible) were non-response (59.3% in CI, 45.5 % in MI) and patient request (24.7% in CI, 14.5% in MI). Other reasons were tolerability (11.1% in CI, 12.0% in MI) and compliance issues (12.3% in CI, 10.5% in MI).Treatment response rates, stratified by genotypes, were already available regarding RVR and EVR (see Figure 1).

Conclusions: In this preliminary analysis HCV/HIV co-infected patients seemed to respond similar according to RVR and EVR in GT1/4/5/6 as HCV-mono infected patients on HCV-treatment. Treatment discontinuation due to non-response and patient request was much more common in the co-infected group. Other reasons for discontinuation like tolerability and compliance are equal in both arms.A more detailed analysis, in particular the influence of the HIV-ART on HCV-therapy outcome, may help interpreting these data. An updated analysis will be presented.

O33

O315. The pharmacokinetic and safety profile of raltegravir and ribavirin, when dosed separately and together, in healthy volunteers

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O33

Purpose of the study: Treatment of chronic hepatitis C virus (HCV) infection in HIV-1 co-infected individuals remains challenging due to numerous factors including drug-drug interactions. The aim of this study was to assess the safety and pharmacokinetic (PK) profile of raltegravir, a recently licensed antiretroviral agent, and ribavirin, when dosed separately and together.

Methods: Fourteen healthy volunteers (mean (standard deviation) age 35 (10) years, 71% male) entered this phase I PK study and received single dose ribavirin (800 mg) on day 1 (*phase 1*). Following a wash-out period,

	cHCV/HIV			cHCV		
	Overall	GT 1/4/5/6	GT 2/3	Overall	GT 1/4/5/6	GT 2/3
RVR % (n)	37.1 (111/299)	33.6 (86/2569	59.6 (25/42)	46 (1773/3858)	30.4 (789/2597)	78.1 (976/1250)
EVR % (n)	79.3 (207/261)	78.6 (173/220)	82.9 (34/41)	84.3 (3182/3775)	81.4 (2021/2484	90.0 (1155/1284)

Figure 1 (abstract O32)

Table 1 (abstract O33)

	mean(95% CI)	mean(95% CI)	GMR (95% CI)
Ribavirin PK parameters	phase I (ribavirin alone)	phase 3 (ribavirin with raltegravir)	
T ½, h	6.04 (5.29 - 6.90)	6.77 (5.56 - 8.25)	1.12 (0.86 - 1.46)
Tmax, h	1.61 (1.12 - 2.11)	2.23 (1.65 - 3.01)	1.39 (1.08 - 1.78)
Cmax, ng/mL	630.09 (490.91 - 808.54)	496.71 (407.38 - 605.76)	0.79 (0.62 - 1.00)
Cmin, ng/mL	184.71 (148.59 - 229.61)	186.98 (157.83 - 221.56)	1.01 (0.87 - 1.18)
AUC0-12	3325.83 (2703.34 - 4091.66)	2941.03 (2323.27 - 3722.20)	0.88 (0.73 - 1.07)

subjects received raltegravir (400 mg twice daily) on days 15-19 (*phase 2*) and single dose ribavirin (800 mg) with raltegravir (400 mg) on day 20 (*phase 3*). Intensive PK sampling was undertaken on days 1, 19 and 20 and differences in geometric mean ratios (GMR) for PK parameters between study periods assessed.

Results: No statistically significant differences in PK parameters were observed for raltegravir between *phases 2* versus *3*. A statistically significant decrease in maximum plasma concentration (Cmax) and increase in time to maximum plasma concentration (Tmax) was observed for ribavirin in *phase 3* compared to *phase 1* (GMR (95% CI) 0.79 (0.62 - 1.00) and 1.39 (1.08 - 1.78), respectively; Table 1) whereas no significant differences in other ribavirin PK parameters were observed between study phases including area under-time-curve (AUC) or minimum observed plasma concentration (Cmin). No clinically significant safety concerns were reported.

Conclusions: The PK profile of ribavirin is altered when administered with raltegravir (reduced Cmax and increased Tmax). This is unlikely to be of clinical significance or have an impact on the antiviral effects of ribavirin in HIV-1 and HCV co-infected subjects.

O34

How early to start: what do observational data suggest?

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O34

National and international guidelines on antiretroviral therapy for HIV infection recently changed to recommend earlier treatment, following the publication during 2009 of two collaborative analyses of HIV cohort studies [1,2]. These studies used different methodologies, and reached different conclusions about the benefits of very early treatment. I will describe their methods, and possible reasons for differences in their results.

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O35

HIV/HAART and the brain — what's going on?

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O35

In the past 3-5 years cognitive impairment have been reported in 15-50% of long-term infected and long-term treated patients. Not full-blown HIV-dementia, but more subtle memory problems and slowness, difficulties in concentration, planning, and multitasking are the characteristic complaints. Even in patients who are systemically well-controlled these problems do occur.

So what is going on after so many years of apparently controlled HIV-infection in the CNS? How severe is the problem? Is it HIV-driven? Was HIV-infection well under control in all patients without complaints or have we missed ongoing replication in the brain? Has this ongoing replication led to chronic immune-activation and progressive damage to the brain? And what is the role of co-morbidity in an HIV-infected population that has entered their fifties and sixties. Do the "normal", non-HIV-related aging of the brain with vascular white matter abnormalities cause additional damage to the brain? Do we see cognitive problems, similar to the patterns that we see in Alzheimer's disease or sepsis where inflammatory changes in the brain seem to play an important role? Is the process of normal aging accelerated in HIV-infection?

Chronic HIV-driven inflammation in an aging brain could be the cause of what we see clinically today. It is likely that HIV-replication in the brain is not the only factor. Better CNS-penetrating drugs will not be the only answer. Clinical characteristics, diagnostic tools (new imaging techniques and CSF-analysis), course and prognosis, possible interventions, antiretroviral and adjunctive therapies will be discussed. The research agenda for HIV-neurology is filled for the years ahead.

O36

Adolescents with perinatally acquired HIV — coming your way

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O36

In resourced settings with access to highly active antiretroviral therapy (HAART), perinatally acquired HIV-1 infection has become a chronic disease of childhood. Reduced mortality due to HAART, combined with high uptake of antenatal HIV testing and a marked reduction in rates of mother-to-child transmission has resulted in significant increases in the average age of paediatric cohorts in these regions and hence increasing numbers of children born with HIV are surviving to early adulthood and completing the process of transition from paediatric to adult services. Advances in antiretroviral therapy, reductions in pill burdens and drug side effects, new classes and new drugs within existing antiretroviral classes offer enormous benefits, although serious issues around adherence during adolescence continue. Questions persist around the optimal timing and sequencing of antiretroviral agents to maintain future treatment options, particularly with global recommendations for the earlier initiation of therapy across the paediatric age range. The longer term impact of exposure to HIV and antiretroviral therapy throughout childhood are becoming apparent, with growing concern over neurocognitive, cardiovascular, renal and bone health requiring further elucidation. Adolescents living with perinatally acquired HIV have additional psychosocial issues including the impact of HIV on other family members, roles as young carers, experience of parental and sibling bereavement, and live with a disease that is potentially transmissible to future sexual partners before they themselves have had sex. Increasing numbers of young women born themselves with HIV are becoming sexually active and having uninfected infants of their own and the long term outcomes for the next generation require monitoring. The benefits of HAART far outweigh the potential risks and the careful follow up of this early perinatal cohort as they progress through adulthood will hopefully aid the future management of the growing numbers of adolescents surviving worldwide as access to therapy improves.

Table 1 (abstract O37)

	DART	DART	DART	DART	ARROW	ARROW	ARROW	ARROW	ARROW	ARROW
Age (years)	18+	18+	18+	18+	4-15	4-15	4-15	0-3	0-3	0-3
pre-ART CD4/CD4%	0-49	50-99	100-149	150-199	0-49	50-99	100+	0-4%	5-9%	10%+
N	1106	784	759	661	131	56	552	27	87	348
Deaths in 1st year	103	36	23	17	14	2	7	2	4	9
Days after ART				Estimated	cumulative	mortality				
14	0.4%	0.1%	0.1%	0.1%	0.5%	0.1%	0.0%	0.4%	0.1%	0.1%
30	1.5%	0.6%	0.3%	0.3%	1.7%	0.5%	0.1%	1.5%	0.6%	0.3%
90	4.9%	2.1%	1.4%	1.1%	5.9%	2.3%	0.6%	5.2%	2.4%	1.3%
180	7.2%	3.4%	2.3%	1.8%	8.3%	3.5%	1.0%	7.4%	3.6%	2.0%
365	9.4%	4.5%	3.2%	2.5%	10.1%	4.5%	1.3%	9.1%	4.6%	2.6%

O37

Early mortality following ART initiation in HIV-infected adults and children in Uganda and Zimbabwe

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O37

Purpose of study: Adults initiating ART in low-income countries have higher mortality in the first 3 months on ART than those in high-income countries, with more similar mortality risks after 6 months. However, the specific pattern of changing mortality risk after ART has not been investigated. It is also not known whether children initiating ART are at the same high risk of early mortality as adults in resource-limited settings.
Methods: We used flexible parametric proportional hazards models to investigate how the risks of death vary over the first year on ART in adults (18+ years) from the DART trial and children (6 months-15 years) from the ARROW trial. We then estimated survival after ART initiation according to pre-ART CD4/CD4% and investigated the impact of age, sex and CD4/CD4% in multivariable models.
Results: Similar changes in early mortality were observed in both adults and children. At all CD4/CD4%, mortality risk increased from enrolment to a maximum between days 30-45, then declined rapidly to day 180, then declining more slowly throughout the rest of the first year on ART. Estimated mortality 14, 30, 90, 180 and 365 days after ART initiation is shown in Table 1a.
Pooling data across adults and children, after adjusting for CD4/CD4% group there was no evidence of an impact of age (p=0.29) or sex (p=0.17) on mortality during the first year on ART. There was also no evidence of a difference in mortality risk between those 4+ years with CD4<50 cells/mm3 and 0-3 with CD4%<5% (p=0.68), those 4+ years with CD4 50-99 and 0-3 with CD4% 5-<10% (p=0.48) or those 4+ years with CD4 100+ and 0-3 with CD4% 10%+ (p=0.24).
Conclusions: Children do not have significantly poorer survival on ART than adults. However, children aged 4 years and over and adults with low CD4 have remarkably similar, and high, risks of mortality in the first 3 months after ART initiation compared to those with higher CD4. Children under 4 years with low CD4% are also at similar higher mortality risks.

O38

Highlights of the 12th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV, London, November 2010

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O38

This presentation will review highlights from the 12th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV that will be held in London on 4-6 November 2010. As in the past, the meeting will consist of plenary lectures by experts from outside the field of HIV medicine as well as oral presentations and posters selected from abstracts submitted by attendees. The plenary speakers for this year's meeting include John Adams (vit D insufficiency), Remy Burcellin (microbial translocation), Kenneth Feingold (TLRs and lipid metabolism), Rolf Jäger (neuroimaging), Cliff Rosen (bone and fat) and Heiner Wedemeyer (ADRs in HBV treatment.). Abstract categories include: adipocyte biology, insulin resistance, aging and associated disorders, lipid metabolism, body composition, liver disease and hepatotoxicity, bone metabolism and toxicities, mitochondrial disorders, cancer in patients with HIV/AIDS, neurocognitive disorders, cardiovascular disease, renal toxicities, clinical management of ADRs, other toxicities and hepatitis.

O39

Fatal and non-fatal AIDS and non-AIDS events in HIV-1 infected patients with high CD4 counts

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O39

Introduction: The risk of uncontrolled viral replication in HIV+ patients who are not immune compromised on the development of serious clinical events is not fully understood. We aimed to compare the incidence of fatal and non-fatal AIDS and non-AIDS events occurring at CD4 counts >350 cells/mm^3 in different viral load strata (≤500, 501-10000, >10000 copies/ml).
Methods: Patients contributed person years at risk if the most recent CD4 count was >350 cells/mm^3 and viral load was measured in the 6 months prior. Poisson regression investigated the relationship between viremia and clinical events, after adjustment for confounding variables.
Results: 10998 patients were included contributing 43524 person-years of follow-up (PYFU). The majority of follow-up (80%) was with a viral load ≤500, 12% between 501-10000 and 8% >10000. 95%, 72% and 64% of the follow-up in each strata respectively was in patients who had started cART. 379 AIDS events (14 deaths) occurred. There was a lower incidence of AIDS events in patients with a viral load ≤500 (IR 0.69 per 100 PYFU, 95%CI 0.60-0.78) compared to a viral load >10000 (IR 2.38 per 100 PYFU, 95%CI 1.87-2.89). 532 non-AIDS events (131 deaths) occurred. Patients with a viral load ≤500 had an incidence of non-AIDS events of 1.50 per 100 PYFU (95%CI 1.36-1.64), and 1.43 per 100 PYFU (95%CI 0.96-1.89)

when viral load >10000. As shown in Figure 1, after adjustment, patients with a viral load >10000 had a 3 times higher incidence of AIDS events than those with a viral load ≤500(p<.0001). In univariate analysis the incidence of non-AIDS events was similar in different viral load strata (p=0.90) but after adjustment, particularly for age and starting cART, there was a 50% and 42% higher incidence of non-AIDS events in patients with a viral load 501-10000 (p=0.008) and >10000 (p=0.05) respectively, compared to a viral load ≤500. The effect of viral load was independent of current CD4 count and was similar in different CD4 count strata (test for interaction p>0.05 for both endpoints).

Conclusions: In patients with a CD4 count >350 cells/mm^3 an increased incidence of fatal and non-fatal AIDS and non-AIDS events was found in patients with uncontrolled viral replication, even after adjustment for current CD4 count and use of cART. The association between viral replication and AIDS events was clear and consistent with a biological effect, but with non-AIDS events was less clear without a difference between intermediate and high viral replication.

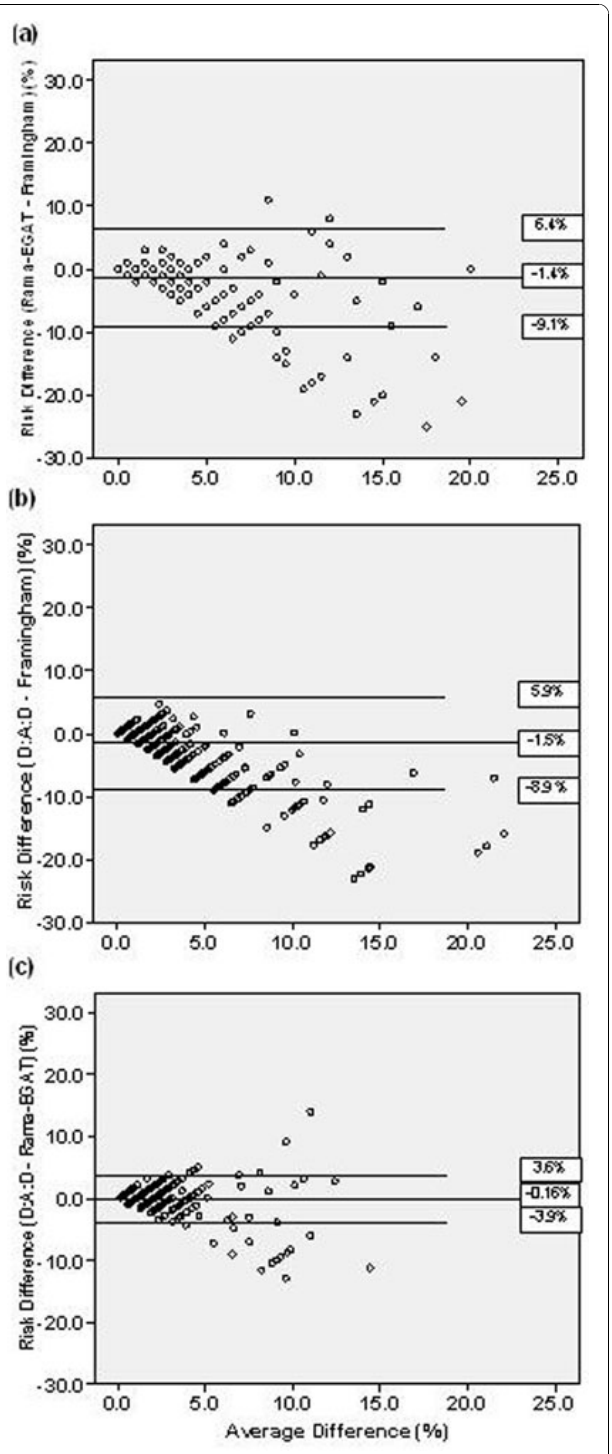

Figure 1 (abstract O39)

O40

Cardiovascular risk assessment in persons with HIV in the developing world: comparing three risk equations in a cohort of HIV-infected Thais

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O40

Purpose: There are growing concerns of cardiovascular disease in HIV-infected individuals and in developing countries, such as Thailand. We described the ten-year risk of coronary heart disease (CHD) in a Thai HIV-infected cohort using 3 cardiovascular risk equations, and assessed the level of agreement between their predictions.

Methods: Cross-sectional analysis of data from 785 Thai subjects followed prospectively in the HIV Netherlands Australia Thailand Collaboration (HIV-NAT) cohort study from 1996-2009. Cardiovascular risk factor history, along with relevant laboratory and clinical data, was collected at follow-up clinic visits. Ten-year risks of CHD were calculated using the Framingham, Ramathibodi-Electricity Generating Authority of Thailand (Rama-EGAT), and Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) risk equations.

Results: Mean age was 41.0 years; 55% of subjects were male. Mean CD4 count was 569 cells/mm3 after a mean of 7.7 years on anti-retroviral therapy. The prevalence of cardiovascular risk factors was low, with the most common risk factor being low high density lipoprotein (36.3%). The prevalence of high cardiovascular risk scores (defined as ten-year risk of CHD ≥10%) was also low: 9.9%, 2.1%, and 0.8%, by the Framingham, Rama-EGAT, and D:A:D scoring systems, respectively. Only 8 subjects (1.0%) had a history of CHD. Bland-Altman plots revealed that the Framingham risk score was, on average, 1.4% (S.D. 3.9%) higher than the Rama-EGAT and 1.5% (S.D. 3.7%) higher than the D:A:D (Figure 1a,b). The limits of the difference showed that the Framingham could be as high as 9.1% above or as low as 6.4% below the Rama-EGAT, and as high as 8.9% above or as low as 5.9% below the D:A:D. The Bland-Altman plot comparing the D:A:D and Rama-EGAT equations (Figure 1c) demonstrated a smaller average difference (-0.16%) and narrower limits of the difference (-3.9% and 3.5%). All differences were most pronounced for subjects with higher average risk scores.

Conclusions: The predicted cardiovascular risk in this HIV-infected Thai cohort was relatively low. The Framingham equation predicted the highest cardiovascular risks, which is consistent with its known tendency to over-predict risk in Thais. The agreement between the Rama-EGAT and D:A:D risk scores suggests that both equations may be appropriate estimators of cardiovascular risk in this and other developing world populations with low background risk.

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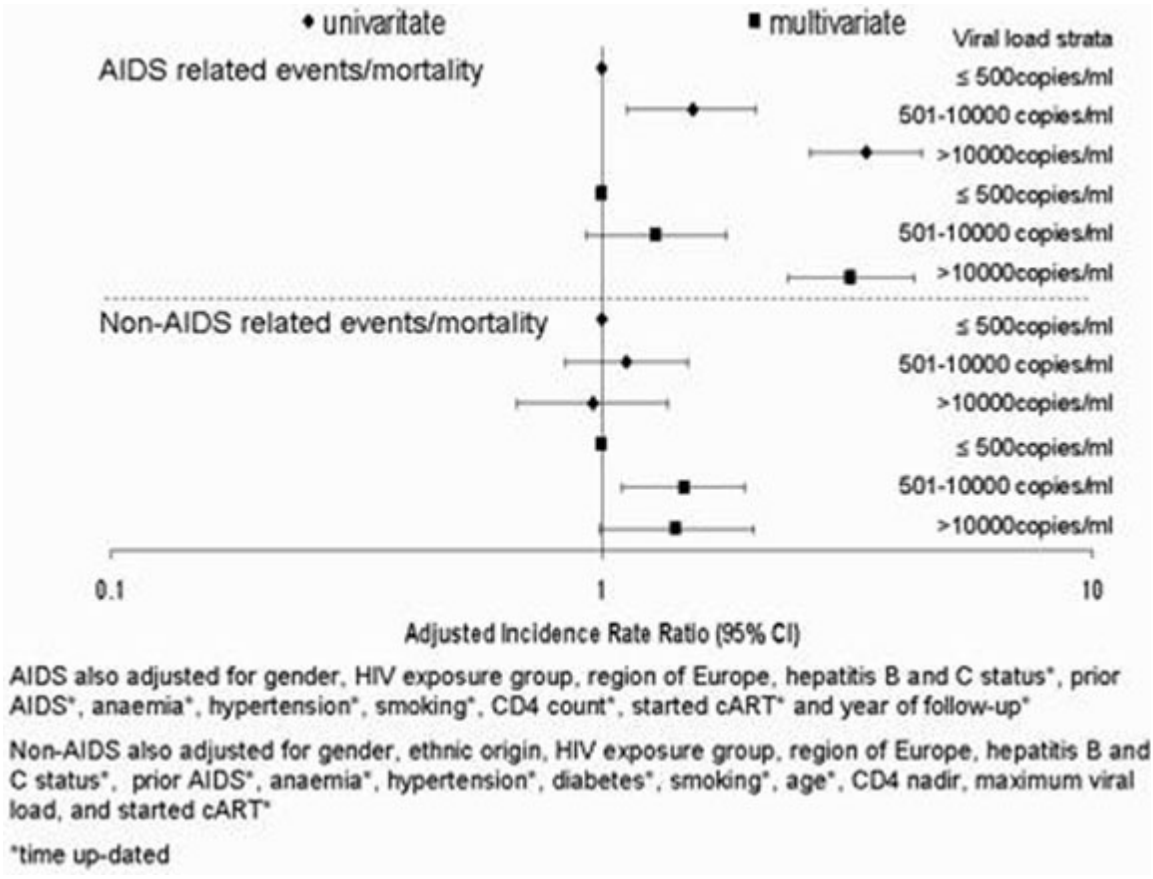

Figure 1 (abstract O40)

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O41

What affects the bone in our HIV-positive patients?

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O41

Osteopenia and osteoporosis are frequent in HIV infected patients, with a prevalence of 66% and 15% reported in a metaanalysis. In an aging population, low bone mineral density (BMD) will translate in fracture-related morbidity and mortality over time. As a matter of fact, increased fracture rates in HIV positive patients have recently been reported, particularly if older than 40-50 years. The etiology of low BMD is multifactorial. HIV independent risk factors may thereby overweight HIV dependent and treatment related factors. Low BMI, malnutrition, vitamin D deficiency, substance abuse, hypogonadism, physical inactivity or osteotoxic medication (e.g. steroids), chronic liver or kidney disease are overrepresented in many HIV positive populations. HIV positivity correlates with increased bone turnover. Viral replication results in continuous cytokine production that directly and indirectly (through RANKL) activates osteoclasts. On the other hand, SMART and several other studies have correlated cART initiation with accelerated bone loss irrespective of the regimen used. Remarkably, this effect stabilized within the first year of treatment and might thus be related to IRIS. Most, but not all, associations of bone loss with protease inhibitor treatment disappeared after correction for HIV-independent risk factors for low BMD, in particular low BMI. Upon Tenofovir initiation, a similar pattern has been observed even in switch studies with suppressed viremia. Again, these findings normalized within a year. Based on a concomitant increase in serum alkaline phosphatase and PTH levels, osteomalacia secondary to drug-related renal phosphate wasting has been postulated, but lacks strong evidence. Still, monitoring of phosphatemia and the correction of vitamin D deficiency has been suggested for Tenofovir-treated patients.

Taken together, HIV positive patients carry a relevant risk for low-impact fractures. This merits a systematic assessment of risk factors for low BMD and falls. Given that a prevalent vertebral fracture indicates an equal risk for a subsequent fracture as documented osteoporosis, particular attention should be paid to identify subclinical fractures. For patients aged over 40, FRAX® can be used to identify patients qualifying for bone density measurement (DXA) or biphosphonate treatment according to national guidelines. HIV may thereby be considered as a secondary cause of osteoporosis.

O42

Vitamin D and HIV: shine a light

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Over the past several years there has been growing interest in the high prevalence of vitamin D deficiency in both the general population and among people living with HIV infection. Vitamin D deficiency in the setting of HIV infection is likely multi-factorial with contributions from environmental factors as well as possible associations with HIV therapy. This lecture will highlight recent data on the prevalence and possible

consequences of vitamin D deficiency in the setting of HIV with a focus on the relationship between vitamin D deficiency and HIV disease progression and possible metabolic and inflammatory consequences of chronic vitamin D deficiency. Finally, the talk will attempt to shine a light on areas for further investigation.

O43

Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study

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Journal of the International AIDS Society 2010, **13(Suppl 4):**O43

Purpose of study: Since 25-hydroxy vitamin D (25(OH)D) deficiency has been associated with higher risk of morbidity and mortality in different settings, this study examined the association between 25(OH)D level and disease progression in HIV-infected patients with prospective follow-up in the EuroSIDA study.

Methods: A group of 2000 patients were randomly selected from those with stored samples after stratification by region. 25(OH)D levels were measured in a single laboratory from stored plasma samples. The 1985 available 25(OH)D results were stratified into tertiles. Factors associated with 25(OH)D levels and associations of 25(OH) levels with subsequent risk of all-cause mortality, AIDS and non-AIDS events were analysed, using Poisson regression.

Results: Thirty-six percent of patients had 25(OH) levels below 12 ng/ml, 31,3% between 12.1 and 20 ng/ml, and 32.7% above 20 ng/ml. In a cross sectional analysis, older persons, patients of Black ethnic origin, living outside Southern Europe and Argentina, sampled during winter, and infected with HIV through non-homosexual exposure were at higher risk of having low 25(OH)D levels, while patients receiving protease inhibitors were at a lower risk. Compared to those in the lowest 25(OH)D tertile, those in the medium and high tertiles had a significantly lower risk of clinical progression. Adjusted incidence rate ratios (IRR; see figure 1) for all-cause mortality were 0.68 (95%CI : 0,47-0,99, P=0.045) and 0.56 (95% CI : 0.37-0.8, P=0.009), and for AIDS events were 0.58 (95%CI : 0,39-0,87, P=0.0086) and 0.61 (95%CI : 0.40-0.93, P=0.020), for the medium and high tertiles, respectively. There was a non-significant reduced incidence of non-AIDS defining events in the medium and high tertiles, and a significant lower IRR of non-AIDS related death in the highest 25(OH)D tertile : 0.60 (95%CI : 0.37-0.98, P=0.043).

Conclusions: This observational study demonstrated that 25(OH)D deficiency is frequent in HIV-infected patients, and is independently associated with a variety of outcomes, reflected by a higher risk of mortality and AIDS events. Whether the relationship between vitamin D deficiency and clinical events is causal should be addressed because of potentially major consequences in terms of public health.

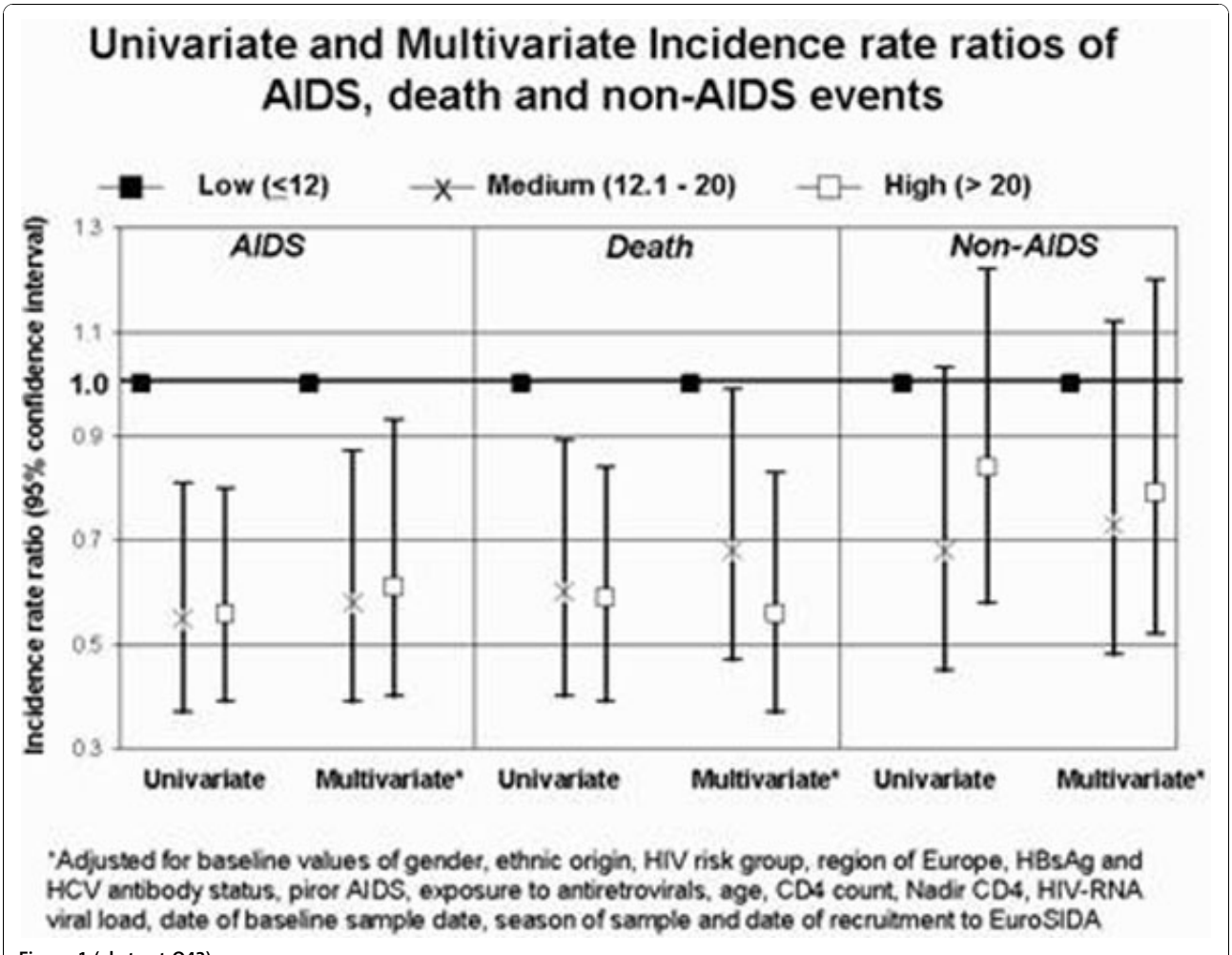

Figure 1 (abstract O43)

O44

Maraviroc intensification for HIV-1-positive immunological non-responders (INRs) despite virological suppression during HAART

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Purpose: 15-30% of HAART-treated HIV-1-positive patients (pts) lack CD4+ increase despite full HIV viremia suppression. The increased risk for INR to progress till AIDS led us to investigate maraviroc (MVC) as a tool to intensify HAART in terms of immunological recovery.

Methods: Randomised, multicentre, proof-of-concept study enrolling 100 pts divided into 2 arms (1:1), A:HAART+MVC, B:HAART. Inclusion criteria were: CD4 count ≥200 cells/μL and/or a recovery of CD4 cells <25% compared to the HAART initiation and with a stable virologic suppression after 1 year of HAART. Ultrasensitive HIV-RNA was quantified via Amplicor HIV-1 Monitor Kit v1.5. Naive CD45RA+, memory CD45RA-, activated HLA-DR+CD38+, proliferating Ki67+, CD4+, CD8+ T-cells were measured by flow cytometry. T-test was used for intra and inter-group comparisons.

Results: 100 pts have been randomized 64 pts reached week(w) 12: 37 in A and 27 in B arms. At baseline (BL), CD4/CD8 and immune-phenotype were comparable in arm A and B. At w12 no significant changes in mean CD4 recovery (+41.9 vs +24.5/μL; p=.241) and a statistically significant change in mean CD8+ count (+164.2 vs -27.3/μL; p=.004) were observed between pts in arm A and B.

At BL and w12 an immunological study was carried out in 24 pts (13:arm A, 11:arm B): at w12, while B pts experienced a contraction of naïve CD4 (81 to 67%; p=.02) and CD8 (81 to 77%; p=.04) with a parallel rise in memory CD4 (16 to 30%; p=.02) and CD8 (13 to 17%; p=.06), no significant loss of naive CD4 (70 to 57%; p=.18) and CD8 (69 to 66%; p=.42) was displayed by A pts with a tendency to higher gain in memory CD4 (24 to 40%; p=.06) and CD8 (11 to 25%; p=.008). By w12, a similar reduction in activated HLA-DR+CD38+ CD8 and CD4 was shown in B (p=.05) and A pts (p=.03 and p=.02 for CD8 and CD4). A trend to Ki67 +CD8 reduction was shown in A (p=.06) and not in B pts (p=.45). HIV-RNA quantification evidenced a trend to higher median values (BL vs w12) in B pts: 2 vs 5 cp/mL (p=.37).

Conclusions: MVC does not seem to increase CD4 amount at significant level compared to arm B. Treatment with MVC is associated with a significant CD8+ gain, a preservation of phenotypically naïve CD4+ and parallel rise of memory pool, suggesting a role of MVC in reducing peripheral antigen-driven T-cell death, possibly preserving new T-cell production. MVC is able to further reduce T-cell activation and proliferation, suggesting a possible influence in better controlling the pro-inflammatory status.

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O45

Maraviroc (MVC) increases CD4+ and CD8+ cells: long-term data from the MVC clinical development program

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Background: Across the MVC development program, patients who received MVC-containing regimens experienced greater increases in CD4+ cell counts than those observed in comparator arms in primary analyses. Here we present longer term immunological data from this program.

Material and methods: Long-term (96 week) data from subjects with CCR5-tropic HIV infection in the following ongoing MVC studies were included in the analysis: (1) MOTIVATE study (MVC QD and BID vs placebo (PBO), each combined with optimized background therapy in treatment-experienced [TE] subjects); and (2) MERIT study (MVC BID vs EFV, each combined with ZDV/3TC in treatment-naïve [TN] subjects). Additionally, interim week 24 data from the ongoing 96-week 1078 study (MVC QD vs TDF/FTC, each combined with ATV/r in TN subjects) were summarized. Descriptive statistics are presented for data at baseline and at week 96 (MERIT/MOTIVATE) or week 24 (1078) pertaining to change in CD4+ and CD8+ cells.

Results: Greater increases in CD4+ cells in MVC-containing groups persisted through 96 weeks in the MOTIVATE and MERIT studies, and through 24 weeks in the 1078 study (Table 1). Similarly, changes in CD8+ cells from baseline to weeks 96 or 24 favored MVC-containing regimens in all three studies. In a combined LOCF analysis of patients from all three studies at week 24, CD4+ counts increased by a median 100.5 cells/μL in 1260 recipients of MVC-containing regimens, compared with 84.5 cells/μL in 631 recipients of comparator regimens; CD8+ counts increased by a median 153 cells/μL in the MVC group, compared with a decrease of 61 cells/μL in the comparator group. At week 96, a combined analysis of patients from the MOTIVATE and MERIT studies showed median CD4+

Table 1 (abstract O45)

Population	Treatment-experienced			Treatment-naive			
Study	MOTIVATE – 96 Weeks			MERIT – 96 Weeks		1078 – 24 Weeks	
Arm	MVC QD	MVC BID	PBO	MVC BID	EFV	MVC QD	TDF/FTC
N	414	426	209	360	361	60	61
BL HIV RNA (median $\log_{10}$ cp/mL)	4.86	4.85	4.86	4.88	4.85	4.59	4.66
Baseline CD4 count (median cells/μL)	171	167	171	244.3	258.5	344.5	358.0
Baseline CD8 count (median cells/μL)	867.5	836.5	820.8	791.5	860.0	859.8	890.0
CD4 change from BL (median cells/μL)	89.0	112.5	21.0	224.3	195.0	195.3	173.0
CD8 change from BL (medican cells/μL)	138.0	157.0	31.5	-3.00	-94.5	4.5	-78.5

increases from baseline of 129.5 and 100.3 cells/μL in the MVC (N=1177) and comparator (N=554) groups, respectively; CD8+ changes were 96 and -72 cells/μL, respectively. In all studies, differences in CD4+ and CD8+ counts between treatment groups were independent of differences in viral load changes (data not shown).
Conclusions: Greater increases in CD4+ and CD8+ counts were consistently achieved with MVC-containing regimens, compared to regimens without MVC, and persisted through at least 2 years of therapy in both TN and TE patients. These differences were independent of changes in HIV-1 RNA and are evident with multiple different MVC-containing regimens.

O46

HIV entry blocked by maraviroc can cause an overestimation of viral load

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Purpose of the study: As a chemokine coreceptor antagonist, maraviroc (MVC) inhibits HIV infection by preventing viral entry into the host cell. As this effect is extracellular, we hypothesized that virus might be returned to plasma upon antagonism of CCR5 by MVC and that this thereby influences measurement of plasma viral load by qRT-PCR, in contrast to other drug classes that act intracellularly.
Methods: PM-1 and TZM/bl cells were infected with titrations of a CCR5 tropic reference virus in the presence of inhibitory concentrations of MVC (500nM), efavirenz (EFV) (500nm), and raltegravir (RAL) (1μM). Viral inoculation varied between 10^4-10^7 copies of viral RNA/ml. Cells were centrifuged and supernatant viral load was measured by qRT-PCR for viral RNA at various times from shortly after infection through 48 hours after infection.
Summary of results: At the highest inoculum used, the amounts of viral RNA detected in culture supernatants following treatment with MVC were consistently higher by ~ 0.5 log copies HIV-1 RNA/ml than found with untreated cells despite no detectable infection in the presence of MVC as revealed by production of p24 Ag in the case of PM-1 cells and expression of luciferase in the case of TZM/bl cells. At lower levels of inoculum, the results were consistent although less striking, but there was always a significant difference in regard to the use of MVC versus other drugs. In contrast, the results obtained with EFV and RAL resembled those obtained in the absence of drug, despite no detectable infection.
Conclusions: These results suggest in a tissue culture model that MVC can return virus to plasma, where it may contribute to viral load despite complete inhibition of infection. In contrast, for drugs that act at an intracellular level, cells can absorb residual virus before such virus it is inhibited by the compound. Consequently, such virus will not contribute to viral load. In view of the fact that viral production by infected cells is an ongoing process, these findings imply that the true effectiveness of MVC is currently underestimated when viral load is used as a sole indicator of clinical success. These data may also be relevant for other classes of entry inhibitors.

O47

The SENSE trial: etravirine shows lower prevalence and severity of neuropsychiatric adverse events compared to efavirenz in treatment-naïve patients

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Background: Efavirenz (EFV) treatment is associated with a range of neuropsychiatric (NPS) adverse events (AEs), which differ in duration and severity.
Methods: In this double-blind placebo-controlled trial, 157 treatment-naïve patients with HIV RNA >5000 copies/mL, were randomised 1:1 to either etravirine (ETR) 400mg once daily (n=79), or EFV 600mg once daily (n=78), plus two NRTIs. After 12 weeks of randomised treatment, the type and frequency of NPS AEs was compared between treatment arms.
Results: Overall, the patients were 81% male, 85% Caucasian, with a median age of 36 years. Median baseline CD4 Count was 302 cells/uL, median HIV RNA 4.8 log10 copies/mL. In the primary analysis, 13/79 patients (16.5%) in the ETR arm, versus 36/78 (46.2%) in the EFV arm, showed at least one Grade 1-4 treatment-emergent drug-related NPS AE ($p<0.001$). The most common nervous system was dizziness, reported for 3 patients in the ETR arm versus 15 in the EFV arm. The most common psychiatric adverse events were sleep disorders, reported in 7 patients in the ETR arm versus 25 patients in the EFV arm. The prevalence of Grade 1-4 all cause NPS AEs showed a peak at Week 2 (21.5% in the ETR arm and 43.6% in the EFV arm), but at the Week 12 visit, the percentage with an ongoing Grade 1-4 all cause NPS AE remained different between the arms (21.7% with ETR and 35.7% with EFV). In the ETR arm, 29 all cause NPS adverse events were reported: 20 Grade 1, 7 Grade 2 and 2 Grade 3. In the EFV arm, 93 NPS adverse events were reported: 55 Grade 1, 34 Grade 2 and four Grade 3. New medication for NPS adverse events was started for 7.6% of patients in the ETR arm versus 16.7% of patients in the EFV arm. One patient in the ETR arm and five in the EFV arm discontinued randomized treatment with NPS AE's.
Conclusions: In the SENSE trial, first-line treatment with ETR 400mg once daily +2NRTIs led to significantly fewer NPS AEs, compared with EFV + 2NRTIs. These NPS AEs were mainly Grade 1 or 2 in severity. The difference between the arms emerged at Week 2, but persisted through Week 12.

O48

Pooled week 48 safety and efficacy results from the ECHO and THRIVE phase III trials comparing TMC278 vs EFV in treatment-naïve, HIV-1-infected patients

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Introduction: Pooled 48-week primary analysis results of two double-blind, randomised, TMC278 Phase III trials, ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725), are presented.
Methods: Treatment-naïve adult patients (N=1368) received (1:1) TMC278 25mg qd or EFV 600mg qd, plus TDF/FTC (ECHO), or TDF/FTC, AZT/3TC or ABC/3TC (THRIVE). The primary objective was to demonstrate non-inferiority (12% margin) of TMC278 to EFV in confirmed virologic response (viral load [VL] <50 copies/mL ITT-TLOVR algorithm) at Week 48.
Results: Overall virologic response rates at Week 48 were high (Figure 1). TMC278 showed non-inferior efficacy versus EFV. The impact of adherence, in addition to other factors, such as baseline viral load and exposure, on virologic response will be presented. Incidences of the following tolerability measures were significantly lower in the TMC278 group than in the EFV group: adverse events (AEs) leading to discontinuation (3% vs. 8%, respectively; $p=0.0005$), grade 2-4 AEs at least possibly related to treatment (16% vs. 31%; $p<0.0001$), rash (3% vs 14%; $p<0.0001$), dizziness (8% vs. 26%; $p<0.0001$), abnormal dreams/nightmare (8% vs. 13%; $p=0.0061$), and grade 3/4 laboratory abnormalities for lipids ($p\leq0.001$).
Conclusions: At Week 48, TMC278 demonstrated a high virologic response rate (≥83%) and non-inferior efficacy versus EFV when administered with NRTIs in both Phase III trials. The virologic failure rate was significantly higher with TMC278, while the incidences of AEs leading

	TMC278 25mg qd (n=686)	Efavirenz 600mg qd (n=682)	Difference between groups
Efficacy (Week 48 outcomes)			
VL <50 copies/mL (ITT-TLOVR), % [95% CI]*	84	82	2.0 [-2.0,6.0]
ECHO, n (%) [95% CI]	287/346 (83)	285/344 (83)	0.1 [-5.5,5.7]
THRIVE, n (%) [95% CI]	291/340 (86)	276/338 (82)	3.9 [-1.7,9.5]
VL <50 copies/mL (per-protocol, ITT-TLOVR), n (%) [95% CI]	569/669 (85)	548/662 (83)	2.3 [-1.7,6.2]
Virologic failures,† %	9	5	ND
Discontinued due to AE/death, %	2	7	ND
Discontinued for other reasons, %	5	6	ND
Mean [95% CI] increase from baseline in CD4 count (NC=F‡), cells/mm^3	192 [181,203]	176 [165,188]	NS
Resistance**			
Virologic failure,§ n	72	39	p=0.0014
Failures with resistance data, n	62	28	ND
Failures developing phenotypic resistance to their treatment NNRTI, n	31/62	12/28	ND
Failures developing NNRTI mutations, n	39/62	15/28	ND
Failures developing IAS-USA NRTI mutations, n	42/62	9/28	ND
Most frequent NNRTI and NRTI mutations	E138K, M184I	K103N, M184V	NA
Safety,¶**			
Grade 2–4 AE at least possibly related to treatment, %	16	31	p<0.0001#
Serious AEs, %	7	8	NS
AEs leading to discontinuation, %	3	8	p=0.0005
AEs of interest at least possibly related to treatment¥, %			
Psychiatric	15	23	p=0.0002#
Abnormal dreams/nightmare	8	13	p=0.0061#
Neurological events of interest	17	38	p<0.0001#
Dizziness	8	26	p<0.0001#
Rash (any type)	3	14	p<0.0001#

ITT-TLOVR = intent-to-treat-time-to-loss of virologic response; CI = confidence interval; ND = not determined because not predefined; NS = non-significant; NA = not applicable. *Based on normal approximation; **p-value for Fisher's Exact test; †Rebound or never suppressed; ‡NC=F = non completer = failure: missing values after discontinuation imputed with change = 0; Last observation carried forward otherwise; §Virologic failure determined in the ITT population with all available data, regardless of time of failure and reason for discontinuation; ¶Safety analyses performed using all available data, including beyond Week 48; #Predefined analysis for these AEs; ¥Observed in ≥10% of patients in the TMC278 group or EFV group and excluding laboratory abnormalities reported as an AE

Figure 1 (abstract O48)

to discontinuation were significantly lower with TMC278. Grade 2-4 AEs at least possibly related to treatment were half as frequent with TMC278 compared with EFV. In addition, incidences of dizziness, abnormal dreams/nightmare and rash were significantly lower for TMC278, and TMC278 had significantly fewer grade 3/4 lipid abnormalities than EFV.

O49

Lersivirine: a new NNRTI active across HIV-1 subtypes with a unique resistance profile

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Purpose of the study: Lersivirine (UK-453,051), a new potent NNRTI, displays novel binding with a unique *in vitro* resistance profile, and shows potential for use against transmitted NNRTI resistant virus and as a candidate for sequential NNRTI therapy. Further *in vitro* analyses have been performed to establish the breadth of activity and identify potential populations that might benefit from lersivirine therapy. Lersivirine activity against various HIV-1 subtypes and viruses with decreased susceptibility to etravirine (ETR) were characterised.
Methods: The PhenoSense™ assay was used to assess the antiviral activity of lersivirine against different HIV-1 subtypes (A, A1, B, BF, C, C/H, D, F, F1, G and H), and the circulating recombinant forms (CRFs) CRF01_AE and CRF02_AG. All were obtained from treatment-naïve patients. Nineteen additional clinical viruses with NNRTI resistance associated mutations (RAMs) were selected based on their reduced susceptibility to ETR.

Summary of results: Lersivirine was active against a panel of 80 clinically- derived viruses representing subtypes A to H, including several CRFs, from a range of geographical origins (geometric mean IC_{50} fold change [FC] to reference virus was 0.92). IC_{50} FC were < 2 for all viruses with the exception of 1 subtype BF and 1 subtype C (geometric mean IC_{50} FC: subtype BF = 0.98, 95% CI 0.64 - 1.49, n=7; subtype C = 1.07, 95% CI 0.88 - 1.30, n=25). Lersivirine retained activity (< 10 FC IC_{50}) for 11 of the 19 viruses with ETR resistance (> 2.9 FC IC_{50}, lower clinical cut-off). Overall, a direct correlation between lersivirine and ETR susceptibility was not found (R^2 = 0.002). This is consistent with different genotypic resistance profiles. Indeed to date, reduced susceptibility to lersivirine and ETR is associated with the presence of different specific NNRTI RAMs.
Conclusions: Lersivirine showed comparable activity across a range of viruses representing subtypes A to H. The activity of lersivirine against ETR- resistant viruses reflects significant differences in the resistance profiles of lersivirine and ETR consistent with the unique binding of lersivirine in the NNRTI binding pocket. Lersivirine has a distinctive *in vitro* resistance profile and may provide an additional therapy choice for patients with evidence of NNRTI resistance.

O50

Once-daily S/GSK1349572 combination therapy in antiretroviral-naïve adults: rapid and potent 24-week antiviral responses in SPRING-1 (ING112276)

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Purpose of study: S/GSK1349572, a next-generation HIV-1 integrase inhibitor, has previously demonstrated potent antiviral activity in Phase 2a with once-daily, unboosted dosing. SPRING-1 is an ongoing dose-ranging study designed to select a dose to for Phase 3 evaluation.
Methods: SPRING-1 is a Phase 2b, multicentre, partially-blinded study in therapy-naïve adults, randomized 1:1:1:1 to 10mg, 25mg or 50mg of S/GSK1349572 or efavirenz(EFV) 600mg once-daily with either co-formulated TDF/FTC or ABC/3TC.
Summary of results: 205 subjects received study drug: 86% male, 20% non-white, 26%>100,000c/mL HIV-1 RNA, 67% TDF/FTC. Plasma HIV-1 RNA declined rapidly across all S/GSK1349572 doses with no differences in NRTI subgroups. Three protocol-defined virologic failures occurred, 1 on EFV (<1log10 decline by Week 4), and 2 on S/GSK1349572 (Week 4 and 24 rebound >400c/mL with no INI mutation detected). No dose-related clinical or laboratory toxicities were observed. More drug-related AEs of moderate-or-higher intensity were reported on EFV (20%) than S/GSK1349572 (6%) arms; none occurred in more than 1 S/GSK1349572 subject. The most frequent category of such events reported by subjects receiving EFV and S/GSK1349572 were gastrointestinal (4% vs. 2%, respectively); other frequent events on EFV were psychiatric (6%) and rash (4%) disorders. No SAE was considered related to S/GSK1349572. Six subjects (2: S/GSK1349572 and 4: EFV) withdrew due to AEs. Mean change from baseline in LDL cholesterol was +0.023mmol/L among S/GSK1349572 subjects and +0.468mmol/L among EFV subjects. S/GSK1349572 demonstrated low pharmacokinetic variability and drug exposure increased with dose. Table 1.
Conclusions: S/GSK1349572 administered once-daily without a PK booster was well tolerated with potent antiviral activity at all doses explored in SPRING-1. The greater CD4+ cell increases on S/GSK1349572 merit further observation and confirmation.

O51

Activity of the integrase inhibitor S/GSK1349572 in subjects with HIV exhibiting raltegravir resistance: week 24 results of the VIKING study (ING112961)

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Background: S/GSK1349572(572) showed potent activity in Phase 2 studies in INI-naive HIV-infected subjects and limited cross-resistance to raltegravir (RAL) and elvitegravir in vitro. VIKING is an ongoing 24-week Phase 2b pilot study assessing 572 in subjects with RAL-resistant HIV. A good antiviral response during the functional monotherapy phase (through Day 11) of this pilot study was observed with a strong correlation between baseline susceptibility to 572 and response.
Methods: 27 RAL-experienced, adult subjects, with screening plasma HIV-1 RNA ≥1000c/mL and genotypic resistance to RAL and ≥ 2 other ART classes, received 572 50mg QD in Cohort I while continuing their failing regimen (without RAL). At Day 11 the background regimen was optimised, where feasible, and 572 continued. The antiviral activity (primary end-point at Day 11), tolerability, safety and virology data through Week 24 of Cohort I are presented. A higher dose is being assessed.
Results: At Baseline, subjects harboured viruses displaying high level resistance to RAL (median fold change in susceptibility [FC] 161, range: 0.57->166) and low median FC to 572 (1.46, range: 0.55-35). Median (IQR) Baseline CD4+ and plasma HIV-1 RNA were 110 cells/mm^3 (40, 230) and 4.47 log10c/mL (3.9, 4.9), respectively. Median number (range) of prior ART drugs was 18 (10, 23). Twenty one (78%) subjects achieved plasma HIV-1 RNA<400 c/mL (n=11) or ≥ 0.7 log10 c/mL decline (n=10) at Day 11 (primary end-point). Post Day 11, the optimised background regimen (OBR) phenotypic susceptibility score (PSS) was 0, 1 and ≥ 2 for 12 (44%), 7 (26%) and 8 (30%) subjects, respectively. 17 subjects continued therapy through Week 24 when 14/27 (52%) and 11/27 (41%) subjects achieved < 400 c/mL and < 50 c/mL, respectively by TLOVR. Response correlated with OBR PSS: 2/12 (17%) subjects with PSS =0, 4/7 (57%) with PSS=1 and 8/8 (100%) with PSS ≥2 achieved <400 c/mL at Week 24. Drug related AEs (any grade) were observed in 6 (22%) subjects. Two subjects with advanced AIDS died after withdrawal from study for SAEs (brain mass, non-Hodgkin's lymphoma with febrile bone marrow aplasia) unrelated to 572.
Conclusions: Despite high level baseline resistance to RAL and the limited activity of the OBR co-administered with 572, the majority of subjects achieved < 400 c/mL at Week 24 with improved response rates in those receiving at least one active background ART. S/GSK1349572 was generally well tolerated in this advanced population.

Table 1 (abstract O50)

Planned Week 24 Interim Analysis Results	S/GSK1349572 10 mg (n=53)	S/GSK1349572 25mg (n=51)	S/GSK1349572 50mg (n=51)	EFV control (n=50)
Mean baseline HIV-1 RNA (log10 c/mL)	4.42	4.38	4.58	4.46
%<50c/mL at 24 wks (by TLOVR)	96% (51/53)	90% (46/51)	92% (47/51)	78% (39/50)
Median baseline (change from baseline at 24 weeks) CD4+ cells/mm3	289 (+159)	330 (+206)	305 (+167)	308 (+110)†

†p=0.008; Wilcoxon two-sample test vs. S/GSK1349572 arms (median change: +176)

POSTER PRESENTATIONS

TREATMENT STRATEGIES

P1

Health-related quality of life and fatigue in HIV-1 infected patients diagnosed during primary versus chronic infection

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P1

Background: Health-related quality of life (HRQOL) is affected by chronic HIV-infection (CHI). No data are available if and to what extent HRQOL is affected in patients who were diagnosed during primary HIV-1 infection (PHI).
Methods: Included were Dutch, male, adult, HIV-1 infected patients, attending the AMC outpatient clinic who seroconverted after December 31st of 1996. 59 Patients identified during PHI and a randomly selected group of 99 patients that were identified with CHI in the same period were eligible. Patients were excluded if they ever had an CDC-C event or suffered any significant comorbidity. Subjects were asked to complete the SF-36 and the Multidimensional Fatigue Inventory (MFI-20) questionnaires. SF-36 and MFI-20 scores were compared with age- and gender-matched Dutch or German general population norms, respectively.
Results: 123 patients were included: 48 from the PHI group and 75 from the CHI group. Patients in the PHI group tended to be younger, fewer were on HAART and they had at the moment of diagnosis a higher CD4 count and a higher plasma viral load. The PHI group was more severely impaired and in more dimensions of HRQOL than the CHI group. Likewise, although fatigue was present in both PHI and CHI groups. PHI patients scored higher in every dimension. Figure 1.
Conclusions: HIV-infected patients in the HAART-era have severely impaired HRQOL and suffer from fatigue. Patients that presented with PHI in the past are impaired to a larger extent and in more dimensions than patients diagnosed with HIV during CHI. This difference is present in both HRQOL and fatigue.

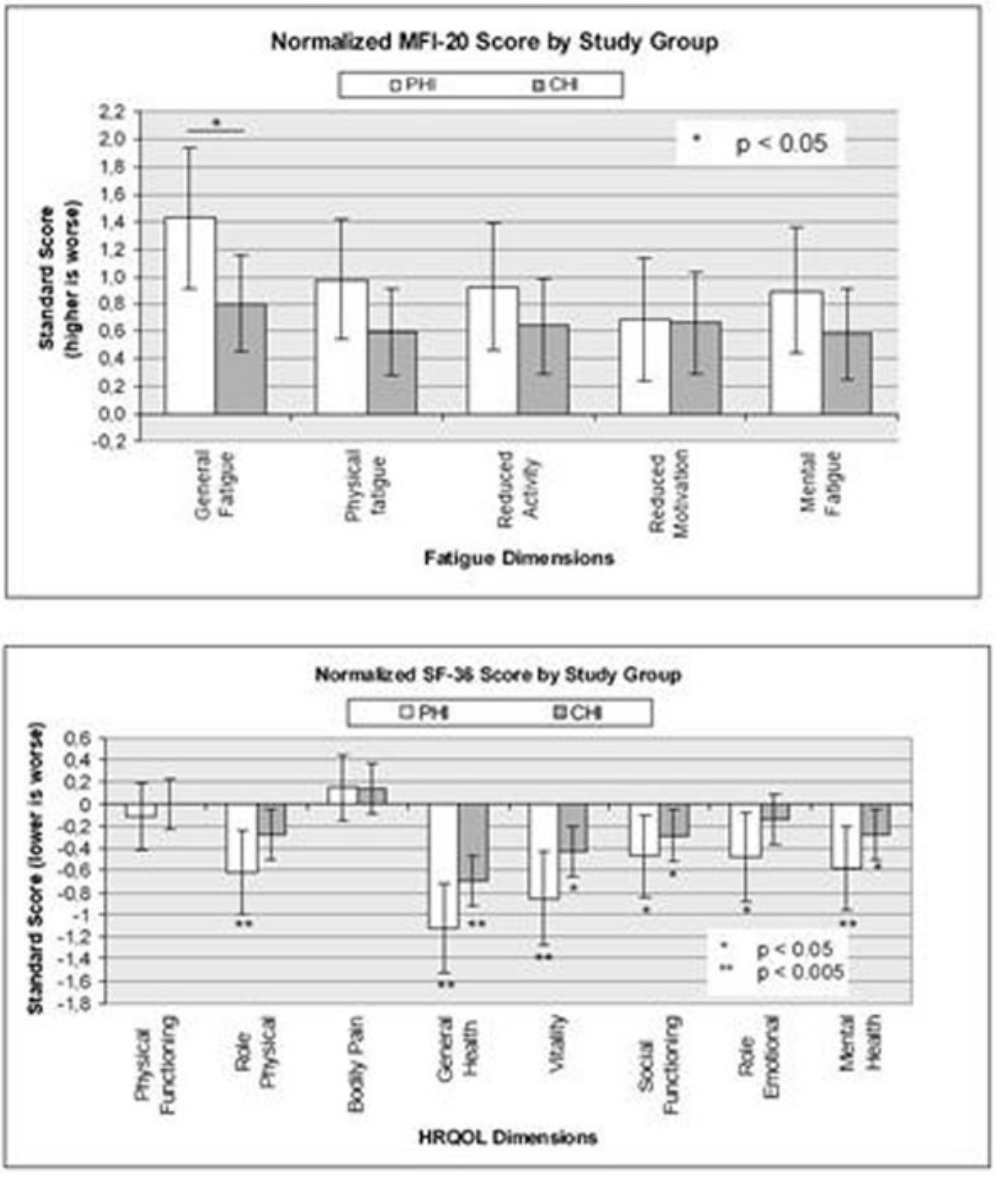

Figure 1 (abstract P1)

P2

The management of acute retroviral syndrome

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P2

Background: Guidelines recommend starting treatment in HIV infected patients earlier than before, but there is no consensus on the exact moment when treatment should be initiated. Would treatment started and maintained in patients with acute retroviral syndrome, make an impact on disease progression, and outcome?
Study objective: to follow and assess patients diagnosed with acute retroviral syndrome (ARS) in our facility and evaluate short-term differences between patients on continuous antiretroviral treatment and patients who were treated only during the acute phase.
Materials and methods: A retrospective study of patients diagnosed with ARS in our facility between 1999-2009, who had previously tested negative at an ELISA test and consequently had a positive or negative ELISA and a viral load of over 10.000 copies/ml were included in the study. Patients were divided into two groups: patients who were only treated initially and then therapy was stopped (group 1) and patients who continued treatment (group 2).
Results: Sixteen patients met the criteria (11 males and 5 females), median age of 28.5 years. Eleven were diagnosed after 2005. Patients were followed for a median duration of 42 months (12-132 months). Five patients were included in the first group and 11 in group 2. Median age of patients was higher in group 1 vs group 2 (34 vs 25 years). Symptoms and signs reported at diagnosis were: fatigue (16 patients), fever (12), dysphagy (12), lymph node enlargement (10), rash (10), myalgias (8), exudative pharyngitis (6), thrush (6), oral ulcerations (6), weight loss (6), meningitis (4) and genital ulcers (2). The median CD4 count at diagnosis was 394 cells/mm^3 (range 123-1184 cells/mm^3) and the median viral load was 772000 copies/ml. The total duration of antiretroviral therapy (ARVT) was between 12 and 100 months. The median CD4 count at the last evaluation was higher in group 2 (579 cells/mm^3) vs group 1 (467 cells/mm^3), but the rise in CD4 count during follow-up did not differ significantly between groups, since patients in group 2 had a median CD4 count on inclusion of 397 cells/mm^3 vs 280 cells/mm^3 in group 1. Median viral load in patients without ARVT was 6358 copies/ml while in those under therapy was undetectable.
Conclusions: Even though the follow up period was relatively short (median of 72 months for group 1 and 27 months for group 2) continuing therapy after the acute phase did not have an impact on the immunological status of the patients.

P3

ARTEMIS: 192-week efficacy and safety of once-daily darunavir/ritonavir (DRV/r) vs lopinavir/r (LPV/r) in treatment-naïve HIV-1-infected adults

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P3

Background: ARTEMIS was a Phase III, randomised, open-label study assessing efficacy and safety of DRV/r 800/100mg qd versus LPV/r 800/200mg total daily dose (qd or bid) in treatment-naïve HIV-1-infected adults. At 96 wks, DRV/r demonstrated non-inferiority and superiority to LPV/r in virological response. Wk 192 results are reported.
Methods: Patients stratified by baseline (BL) viral load (VL [HIV-1 RNA] < or ≥100,000 copies/mL [cpm]) and CD4 cell count (< or ≥200 cells/mm^3) were randomised 1:1 to DRV/r qd or LPV/r. Primary efficacy parameter: non-inferiority (≤ −12%) of DRV/r to LPV/r in virological response (VL <50 cpm, ITT-TLOVR). DRV/r superiority (≤ 0%) was assessed if non-inferiority was demonstrated.
Results: 689 patients (30% female; mean BL VL 4.85 $\log_{10}$ cpm; median CD4 225 cells/mm^3) were randomised. Overall, significantly more DRV/r than LPV/r patients had VL <50 cpm at Wk 192, confirming DRV/r qd non-inferiority (p<0.001) and superiority (p=0.002) (Table 1). In patients with virological failure (VF; TLOVR non-VF censored) no developing primary PI mutations were identified in either arm; all VFs with paired BL/endpoint phenotypes that were susceptible at BL to amprenavir, atazanavir, indinavir, lopinavir, saquinavir or tipranavir remained susceptible after treatment.

Table 1 (abstract P3)

	DRV/r		LPV/r		DRV/r-LPV/r [95% CI]
	N	%	N	%	
VL <50cpm (ITT-TLOVR)					
All patients	343	68.8	346	57.2	11.6 [4.4-18.8]
BL VL <100,000	226	69.5	226	60.2	9.3 [0.5-18.1]
BL VL ≥100,000	117	67.5	120	51.7	15.9 [3.5-28.3]
BL CD4 <200	141	65.2	148	54.1	11.2 [-0.1-22.5]
BL CD4 ≥200	202	71.3	198	59.6	11.7 [2.4-21.0]
VL <50cpm (sensitivity analyses)					
TLOVR non-VF censored	270	87.4	245	80.8	6.6 [0.3-12.9]
On protocol TLOVR	340	69.1	345	57.1	12.0 [4.8-19.2]
Missing=failure	343	68.5	346	60.1	8.4 [1.3-15.5]
FDA snapshot	343	68.5	346	59.8	8.7 [1.5-15.8]
Treatment-emergent adverse events (AEs)					
AEs leading to permanent stop of study medication	343	7.6	346	14.5	p=0.005*
Grade 2-4 treatment-related diarrhoea	343	5.0	346	11.3	p=0.003*
Changes in lipid parameters, median increase mmol/L (min; max)					
Triglycerides‡	254	0.1 (-5; 3)	228	0.6 (-3; 10)	p<0.0001¶
Total cholesterol§	254	0.6 (-2; 4)	228	1.0 (-1; 4)	p<0.0001¶

*Fisher's Exact test; ‡NCEP normal level <1.69mmol/L; §NCEP normal level <5.17mmol/L; ¶Wilcoxon Rank Sum test

Conclusions: DRV/r qd demonstrated sustained efficacy with non-inferiority and superiority to LPV/r over 192 wks. Development of resistance was low in both arms. DRV/r was associated with smaller median increases in total cholesterol and triglycerides than LPV/r, and a lower incidence of grade 2–4 diarrhoea.

P4

Nevirapine (NVP) vs ritonavir-boosted atazanavir (ATV/r) combined with tenofovir/emtricitabine (TDF/FTC) in first-line therapy: NEWART 48-week data

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Purpose of study: Until recently, few prospective data existed to indicate safety/efficacy of NVP with entry CD4 count restricted to <250 (women) or <400 (men) cells/mm^3. Two phase IV trials, ARTEN and NEWART, compared virologic safety/efficacy of NVP vs ATV/r on a background of TDF/FTC in HIV+ patients within these CD4 ranges. NEWART (US) was designed to be confirmatory of ARTEN and to supplement ARTEN data [1].
Methods: In NEWART, treatment naïve patients were randomized to open-label NVP 200mg BID (lead-in dose 200mg QD x 14 days) or ATV/r (300/100mg) plus TDF/FTC (300/200mg). Women had CD4 counts (cells/mm^3) <250; men <400. Primary endpoint was virologic response prior to and at week 48 defined as confirmed HIV viral load (VL) <50 copies/mL without subsequent rebound or therapy change. A point estimate of -6.5% or higher for difference in proportion of responders (NVP-ATV/r) was considered consistent with a successful ARTEN study.
Summary of results: 152 patients were treated: 89% male, 68% White, 31% Black. At baseline, mean $\log_{10}$ VL was 4.9 and median CD4 count (cells/mm^3) was 176 (NVP) and 193 (ATV/r). Table 1 summarizes key outcome measures. Mean plasma lipid (mg/dL) changes from baseline through 48 weeks (last observation carried forward) were as follows (NVP and ATV/r arms, respectively): total cholesterol (TC) 18.2 and 13.8 (P=0.73); HDL cholesterol (HDLc) 9.6 and 3.5 (P=0.016); LDL cholesterol (LDLc) 8.7 and 6.9 (P=0.93); and triglycerides -4.7 and 8.4 (P=0.36).
Conclusions: NVP + TDF/FTC was noninferior to ATV/r + TDF/FTC. Although trial discontinuations were greater in the NVP arm, VR was similar because of less documented VF. HDLc increased and TC/HDLc decreased significantly more for NVP than for ATV/r.

Reference

1. Soriano V, Köppe S, Migrone H, *et al*: International AIDS Society - 5th Conference on HIV Pathogenesis. *Treatment & Prevention* 2009.

P5

Efficacy and safety of an NRTI-sparing regimen in antiretroviral-naïve HIV-infected patients: once-daily maraviroc plus lopinavir/ritonavir

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Current guidelines recommend three drug combinations to treat antiretroviral naïve HIV-infected patients; some data of novel strategies with NRTI-sparing regimen in this setting are now available [1,2]. The study compares immunovirological efficacy and safety of once daily maraviroc (MVC) plus lopinavir/ritonavir (LPV/r) to tenofovir/emtricitabine (TDF/FTC) plus LPV/r.
This is an ongoing, proof-of-concept, randomized, open-label, 48 weeks trial. Data were collected at baseline (BL) and at 4, 12 , 24, 36 and 48 weeks. Comparisons between groups evaluated by the chi-square or Mann-Whitney rank-sum test. Results reported as median (Q1-Q3) or frequency (%), as appropriate.
Up to date, 13 pts (7 MVC, 6 TDF/FTC) reached week 24 (W24), 10 (5 MVC, 5 TDF/FTC) week 12 (W12), 1(MVC) week 4 (W4) without modification of the initial regimen; age 41.1 (41.7-49.9) years, 1/24 (4%) female, infected since 3.8 (2.3-7.6) years, CD4 nadir 266 (240-321) cells/μL. At BL: CD4 284 (260-325) cells/μL; CD4% 17.6 (13.9-22.5), HIV-RNA 4.3 (3.9-4.9) $\log_{10}$ copies/mL. No difference in BL characteristics were found between the two treatment groups.
At W24, all patients in both groups had HIV-RNA<50 copies/ml; decrease in viral load was similar in both groups at each timepoint. CD4 cells count increased in both groups, more rapidly in MVC group and was similar at week 12 and week 24, possibly due to the small number of subjects [CD4 change at W4: MVC group 183(134-225); TDF/FTC group 60 (25-147), p=0.027; at W12: MVC group 161.5(141.5-216); TDF/FTC group 122(53.5-203), p=0.087; at W24: MVC group 174(72-179); TDF/FTC group 171(53.5-203), p=0.158].
Treatment was well tolerated, without grade 3 or 4 adverse events. No significant differences between the two groups were observed in bone marrow function, AST, ALT and CPK values, creatinine value, glucose profile (fasting glucose and insulin) and lipid profile (total cholesterol, LDL and HDL cholesterol) expect for triglycerides that significantly increased in TDF/FTC group [W24 increase in MVC group: 40 mg/dl (-3-299); TDF/FTC group: 119 (-29-137), p=0.037].
In this small sample size, NRTIs-sparing regimen with Maraviroc QD and lopinavir/ritonavir is similar in efficacy and tolerability to conventional treatment in naïve-patients. A more favourable trend in immunological recovery was observed but it needs to be confirmed in larger samples. Regimens NRTIs-sparing in HIV-infected patients naïve to antiretroviral therapy should be explored.

References

1. Mills A, *et al*: Safety and immunovirological activity of once daily maraviroc in combination with ritonavir-boosted atazanavir compared

Table 1 (abstract P4)

Outcome Measure (48 wks)	NVP 200 mg BID (n=75)	ATV/r 300/100 QD (n=77)	P value	Difference (95% CI) from model adjusting for screening VL and CD4+
Virologic Response (VR)	46 (61.3%)	50 (64.9%)	0.71	-4.1% (-18.3% to 10.1%)
Virologic Failure (VF), Protocol Defined	10 (13.3%)	12 (15.6%)	0.63	-2.6% (-13.1% to 7.9%)
Early withdrawals†	24	18		
- due to investigator-defined VF	5	0		
- due to adverse events	9*	9		
- due to other reason	10	9		
Mean Change in TC/HDLc [baseline to week 48 (LOCF)]	-0.38	-0.02	0.038	-0.33 (-0.64 to -0.02)

*NVP arm: 1 DAIDS grade 3 hepatobiliary AE (viral hepatitis); no grade 3/4 rash †2 deaths: 1-NVP (suicide); 1-ATV/r (lymphoma)
For NEWART and ARTEN (combined), VR for NVP 200mg BID was 65% (171/263) vs 65% for ATV/r (176/270) [P=0.75 (CI= -7.7% to 10.7%)].

to TDF/FTC QD+ATV/r in treatment-naive patients infected with CCR5 tropic HIV-1 A week 24 planned interim analysis. *XVIII IAC* , Abs THLBB203.
2. Reynes J, *et al*: Lopinavir/ritonavir combined with raltegravir demonstrated similar antiviral efficacy and safety as lopinavir/ritonavir combined with TDF/FTC in treatment-naive HIV-1 infected subjects. *XVIII IAC* , Abs MOAB0101.

P6

5-year safety and efficacy of the once-daily antiretroviral regimen of efavirenz (EFV)/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF)

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Background: The goal of highly active antiretroviral therapy (HAART) is to suppress HIV RNA to undetectable levels over many years and is primarily dependent on adherence, which is aided by using a once daily regimen with good tolerability and low pill burden. In Study 934 the time to discontinuation for the twice daily regimen of EFV qd + zidovudine/lamivudine bid was significantly shorter than for the once daily regimen (EFV+FTC+TDF) (p=0.003). Herein are the 5 year safety and efficacy data for this once daily regimen.
Methods: 160 subjects (89% male, 64% white, mean age 41 yrs) in Study 934 originally randomized to the once daily regimen of EFV+FTC+TDF who completed 144 weeks agreed to switch to the single tablet formulation (EFV/FTC/TDF) and remain on study for an additional 96 weeks for a total of 240 weeks.
Results: At baseline (BL), mean HIV RNA= 5.03 $\log_{10}$ c/mL, mean CD4 count= 243 cells/mm^3, and 88% had symptomatic HIV or AIDS. After 240 weeks of follow-up:
87% had HIV RNA <400 c/mL and 84% <50 c/mL (M=F); mean CD4 cell increase from BL= 346 cells/mm^3. The mean (range) adherence rate was 97% (83-100%). Seventeen subjects discontinued EFV/FTC/TDF: withdrew consent (6); lost to follow-up (5); adverse events (2: osteoporosis (1) and anal cancer (1)); incarceration (2); non-adherence (1); and relocated (1). No patient discontinued due to renal adverse events. Mean change from BL in estimated glomerular filtration rate (e-GFR) by Cockcroft-Gault was -7 mL/min (Mean BL e-GFR, 129 mL/min).
Conclusions: Through 240 weeks, the once daily HAART regimen of EFV +FTC+TDF (dosed as single tablet regimen, EFV/FTC/TDF, from Week 144-240) demonstrated durable antiretroviral efficacy and immunologic recovery in antiretroviral-naïve patients. The decline in e-GFR was mild and not clinically significant.

P7

SUPPORT: 48-week results of fosamprenavir/ritonavir vs efavirenz with abacavir/lamivudine in under-represented, antiretroviral-naïve patients

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Purpose of study: The objective of this study was to evaluate the efficacy, tolerability, and safety of fosamprenavir/ritonavir (FPV/r) versus efavirenz (EFV), both in combination with abacavir/lamivudine (ABC/3TC), in a population that is often underrepresented in U.S. clinical trials.
Methods: In this ongoing 96-week, open-label, prospective, randomized, multicenter study, we compared once-daily ABC/3TC 600 mg/300 mg with FPV 1400 mg/r 100 mg or EFV 600 mg in ARV-naïve, HIV-1-infected subjects with entry viral load (VL) >5,000 c/mL, were HLA-B*5701 negative, and did not have major resistance mutations to study drugs. The primary endpoint was time to switch of third drug or time to development of any treatment-related Grade 3 or 4 adverse events (AEs). Results from the planned 48-week analysis are reported.
Summary of results: SUPPORT enrolled 32% (32/101) women and 79% (80/101) non-Caucasians. Baseline and demographic characteristics were generally similar between groups. A total of 84 subjects (83%) completed study through W48. Eight patients met the primary endpoint: 3 (6%) and 5 (10%) on FPV/r and EFV, respectively. At W48, by ITT-Exposed missing-equals-failure analysis, 76% (39/51) and 82% (41/50) of subjects achieved VL <50 c/mL on FPV/r vs. EFV, respectively. Median change from baseline to W48 in CD4 cell count was 178 cells/mm^3 in each group. Rate of treatment-related grade 2-4 AEs was lower in the FPV/r-arm (9/51, 18%) vs. the EFV-arm (15/50, 30%) primarily due to EFV-related rash and dizziness (8% each). Rates of treatment-related serious AEs and grade 3-4 lab abnormalities were similar between FPV/r vs. EFV. A total of 8 virologic failures occurred through W48. At failure, HIV PRO or RT treatment-emergent mutations were present in 4 of 5 EFV patients and 1 of 3 FPV/r patients selected an RT mutation. Median change from BL in total/HDL cholesterol ratio was unchanged in both groups but the FPV/r arm had larger changes in triglycerides (32 vs. 7 mg/dL) and in LDL cholesterol (22 vs. 11 mg/dL).
Conclusions: Through 48 weeks, in a diverse population, virologic/immunologic responses were not demonstrably different between FPV/r and EFV when given with ABC/3TC, but the EFV regimen had slightly more patients meeting the tolerability endpoint, treatment-related grade 2-4 AEs, virologic failures, and treatment-emergent mutations at failure.

P8

HRQoL improves in treatment-naïve HIV-1 subjects initiated on lopinavir/ritonavir (LPV/r) with raltegravir (RAL) or tenofovir/emtricitabine (TDF/FTC)

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Purpose: The clinical status of HIV-1 infected patients initiated on modern anti-retroviral (ARV) therapy is consistently improved as indicated by reduced viral load (VL) and increased CD4+ T-cell count, however, the reported impact on patients' health related quality of life (HRQoL) has been variable. An appropriate assessment of HRQoL response over time in ARV-naïve HIV-1 infected subjects initiated on LPV/r combined with RAL or TDF/FTC could reveal the impact of these therapies on functional status and wellbeing.
Methods: The PROGRESS study is an ongoing, randomized, open-label 96-week trial of LPV/r 400/100 mg BID combined with either RAL 400 mg BID (n=101) or TDF/FTC 300/200 mg QD (n=105) in ARV-naïve subjects. Subjects completed the MOS-HIV, a validated, disease-specific HRQoL instrument, at baseline and weeks 8, 24, and 48. The MOS-HIV comprises 35 items in eleven dimensions. Dimension specific scores and the two summary scores (Physical Component Summary [PCS], Mental Component Summary [MCS]) each range from 0 to 100 points, with higher scores indicating better function or well being. Changes in score from baseline were analyzed using ANCOVA with the following covariates: baseline score, treatment arm, gender, race/ethnicity, age, time since HIV-1 diagnosis, baseline CD4+ T-cell count, and plasma HIV-1 RNA level (VL).
Results: Both LPV/r + RAL and LPV/r + TDF/FTC treatment arms achieved similar VL and CD4+ T-cell endpoints at 48 weeks; a similar proportion of subjects in each arm discontinued the study prematurely. For each assessment period, >79% of all subjects completed the MOS-HIV survey. There were no statistically significant differences between treatment arms in MOS-HIV scores on any dimension or summary score at any assessment period (p>0.100). When pooling data across all subjects, MCS improved significantly from baseline at week 8 (mean change: +2.3, p = 0.013), week 24 (+3.5, p<0.001), and week 48 (+2.2, p=0.041). PCS improved significantly from baseline only at week 24 (+1.8, p=0.033). The General Health Perceptions dimension, an overall evaluation of health, was significantly improved at week 8 (+5.4, p= 0.009), week 24 (+7.9, p<0.001), and week 48 (+6.0, p=0.019).

Conclusions: LPV/r in combination with either RAL or TDF/FTC improved HRQoL related to both mental and physical states as well as overall health in ARV naïve, HIV-1 infected subjects at weeks 8, 24, and 48. Additional HRQoL data through week 96 are being collected.

P9

Outcomes in antiretroviral-naive HIV-infected patients initiating therapy with TDF/FTC plus either atazanavir/r or another third recommended drug

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Background: Atazanavir/r (ATV/r) is a recommended PI option for treating ART-naive patients in recent guidelines. TDF/FTC is the most commonly used recommended backbone in this setting. Our objectives were to compare times 1) to discontinuation of the third drug, 2) to virologic suppression (VL< 50 copies/ml), with discontinuation of the third drug considered as failure, 3) to an increase of at least 100 CD4 cells/mm^3, with discontinuation of the third drug considered as failure, 4) to AIDS or death from any cause, with an intention to continue approach 5) to hospitalization, AIDS or death with an intention to continue approach in patients initiating with ATV/r or another recommended third drug plus TDF/FTC.
Methods: ART-naive patients in the FHDH ANRS CO4 cohort who started cART containing TDF/FTC plus either ATV/r or another recommended third drug (LPV/r, f-AMP/r or EFV) after 31/12/2003 and at least 12 month before the closing date of the database were analyzed. Multivariable Cox's proportional hazards models were used to control for the following potential confounders: Age, sex, geographical origin, transmission group, baseline CD4 cell counts and viral load, AIDS stage, HCV co-infection and year of starting.
Results: 2910 patients (ATV/r=517 and Other=2393) were analyzed, with a median follow-up of 19.1 months (IQR: 9.8-30.4). The third drug was EFV in 1129 (47.2%), LPV/r in 1045 (43.7%) and f-APV/r in 219 (9.2%). Baseline median CD4 was 246 for ATV/r and 228 for other drugs (p=0.0064) and viral load 4.87 for ATV/r and 4.89 for other drugs (p=0.0688). At 24 months, the rates of the different outcomes were for ATV/r versus other drugs:
• Discontinuation of the 3rd drug: 24% and 27% (aHR: 0.76 (0.61-0.94))
• Virologic suppression (VL< 50 copies/ml): 83% and 84% (aHR: 0.93 (0.84-1.04))
• Increase of at least 100 CD4 cells/mm^3: 83% and 80% (aHR: 1.09 (0.98-1.21))
• AIDS or death: 7% and 10% (aHR: 0.88 (0.61-1.28))
• Hospitalization, AIDS or death: 17% and 21% (aHR: 0.93 (0.73-1.18))
Sensitivity analyses using propensity scores and subgroup analyses in patients with CD4<200/mm^3 depending of the level of viral load (< or >=100 000 copies/ml) will also be presented.
Conclusions: In this observational settings in ART-naive patients, use of ATV/r as third drug was associated with a lower rate of discontinuation and with no difference in terms of virologic suppression, immunological and clinical outcomes as compared to other recommended third drugs.

P10

Comparing the effectiveness of efavirenz and nevirapine for first-line antiretroviral treatment amongst an adult treatment cohort from South Africa

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Purpose of the study: There is an ongoing debate about when to use efavirenz (EFV) or nevirapine (NVP) for first line antiretroviral treatment (ART) in developing countries, fuelled by EFV's link with teratogenicity in rats and NVP's risk of hepatotoxicity with increasing CD4 levels and it's interactions with Rifampicin. This paper compares the effectiveness of these two drugs in a multicentre adult cohort of ART patients attending public health facilities in South Africa.
Methods: A retrospective cohort analysis of routine data on 27350 ART naïve adults initiated between March 2004 and March 2007 at 56 public health sites across 4 provinces was completed. Stata 9 was used to conduct analyses which included Kaplan Meir survival analysis, logistic regression, generalised estimating equations and Cox proportional hazard models.
Summary of results: Median follow up time was 9.3 months and median baseline CD4 count 113 cells/mL (IQR= 57-165). Multivariate analyses showed patients receiving first line regimens containing EFV to have been more likely to suppress virologically both at 6 months (OR=1.30; 95%CI:1.11-1.54) and at any time between 6 and 36 months (OR= 1.28; 95%CI:1.16-1.41), less likely to change regimen (OR=0.53; 95%CI:0.48-0.59) and more likely to die (AHR= 1.24; 95%CI:1.07-1.45). A subset analysis of 18527 patients with pregnancy and tuberculosis status reported showed no difference in hazard rates for death between the two groups (AHR=1.17; 95%CI:0.99-1.37).
Conclusions: This data shows superior results for patients on EFV with respect to all outcomes except death. Retrieval of missing data about pregnancy and tuberculosis status may push this last association toward the null. Protease inhibitors are an alternative to non-nucleoside reverse transcriptase inhibitors (NNRTIs) for first line use; but are currently too costly. There is an urgent need for further research into currently available NNRTIs; as well as the development of new antiretrovirals for resource depleted settings. In the interim the developing world needs to increase access and bring down the cost of existing drugs and implement more efficient treatment strategies.

P11

Comparative efficacy and safety of regimens including ritonavir-boosted lopinavir or nevirapine in antiretroviral-naïve HIV-1-infected individuals

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Purpose of the study: Ritonavir-boosted lopinavir (LPV/r) or nevirapine (NVP) combined with two nucleosides are recommended for first-line regimens in antiretroviral-naïve HIV-1 patients. There are few comparative studies between these different class-based regimens. Efficacy and safety may vary from randomized studies to actual clinical practice.
Methods: We analyzed retrospective data from 167 HIV-1 infected antiretroviral-naïve individuals initiating LPV/r or NVP plus two nucleoside transcriptase reverse inhibitors (NRTI) (between 1999 and 2006), according to current guidelines.
Summary of results: LPV/r was given to 46.7%, whereas 53.3% received NVP. Average patient age was 42 years (range, 19-80), 23.4% were women and 72.5% Caucasians. Co-infection with hepatitis viruses was present in 34.1% of all patients. The first most frequently used NRTI backbone was zidovudine-lamivudine (84.4% all patients; 38.3% LPV/r; 46.1% NVP). An alteration on NRTI backbone without study-drug discontinuation was permitted. There were no statistically significant differences between groups in the former baseline variables. Patients receiving a LPV/r-based regimen had, in average, lower baseline T CD4 cell counts (P=0.004, Mann-Withney) and a higher viral load (P<0.0001, Mann-Withney) compared with those receiving NVP. Early response to treatment was evaluated by the number of patients with a viral load decline >1.0 $\log_{10}$ after one month of treatment: 91.7% for LPV/r (n=33/36) and 77.1% for NVP (n=27/35). Undetectable viral load after one year of treatment was 79.3% for LPV/r (n=46/58) and 82.8% for NVP (n=48/58); with an increase in T CD4 cell count by 8.9 and 1.9-fold for LPV/r (n=46) and NVP (n=54), respectively (P=0.003). The overall number of patients that discontinued therapy before completing one year of treatment were, respectively for LPV/r and NVP, 17.9% (n=14/78) and 23.6% (n=21/89). Toxicity was the most referred reason for study-drug discontinuation in both groups. After one year of treatment, toxicity grade III/IV blood biochemistry analyzed values (serum transaminases,

total cholesterol, HDL, LDL and triglycerides) were 10.2% (n=27/264) for LPV/r and 8.33% (24/288) for NVP, compared to 6.44% (n=17/264) and 7.99 % (n=23/288) on baseline.
Conclusions: LPV/r seems to have a better early response and immunological improvement. However, excluding the early discontinuation of therapy due to toxicity, NVP seems to have a lesser toxicity impact in the long-term.

P12

Efficacy and safety of TDF/FTC-containing, first-line HAART in clinical practice: 3-year data from the German outpatient cohort

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Purpose of the study: First line HAART with tenofovir DF (TDF) and emtricitabine (FTC) in pivotal trials has been associated with high efficacy and good tolerability. However, real-life clinical practice often differs from clinical trials due to co-morbidities, co-infections, and less intensive clinical monitoring.
Methods: Between July 2005 and August 2006, 534 HIV$^+$ antiretroviral naïve patients (pts) from 50 German centres enrolled in this non-interventional cohort. All patients were to be followed for three years every three months to monitor and document efficacy (VL, CD4), renal safety, tolerability, regimen changes and resistance profile. All patients received TDF+FTC as a single tablet fixed-combination (Truvada, TVD) mostly in combination with either NNRTI or PI/r as their first regimen.
Summary of results: As of April 2010, three years of therapy have been documented for 330/534 (61.8%) pts; 81% male; median age was 39 years. Clinical AIDS diagnosis was documented in 22% pts; 46% pts started therapy with median 211 (IQR: 111-297) CD4 cells/mm^3. TVD was combined with NNRTI (efavirenz (EFV)27%, nevirapine 16%), PI/r (54%) or other (3%). In an as treated analysis after 36 months, 91% of pts achieved VL<50 copies/mL (VL<200 copies/mL: 97.1%; VL<500 copies/ml: 99%). Median CD4 cell count increased to 472 cells/mm^3 (IQR: 341-631). Regimen with TVD showed a good safety profile and 36 pts were switched to a single tablet regimen with EFV/TDF/FTC (Atripla); 113 adverse events (AEs) of any grade were reported in 73/534 pts (13.7%); 15 of these were rated serious. 21 (3.9%) pts discontinued the TVD regimen due to AEs. Most of them (n=13) discontinued within the first six months. Renal abnormalities of any grade were reported in 10 pts (8.8% of all AEs). Median creatinine clearance was 109.0 mL/min (n=444) at baseline and 103.3 mL/min (n=287) after 36 months. Virological failure as a reason for discontinuation was documented in 12 pts; in 11 failing pts genotyping was performed and detected M184V (n=2) or K65R (n=2) among other NRTI, PI or NNRTI mutations. One failing patient had shown M184V at baseline.
Conclusions: During three years of follow-up, overall safety of TVD was good. Virological failure was rare (12 pts) and K65R was detected in only 2 failing patients. First line HAART with Truvada (TDF/FTC) plus an NNRTI or PI/r in clinical practice showed comparable efficacy to that observed in controlled clinical trials.

P13

Reasons for treatment discontinuation in the first year after beginning antiretroviral therapy in a cohort of Portuguese HIV-infected patients

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Purpose of study: To evaluate the reasons and risk factors for antiretroviral discontinuation in a cohort of HIV-infected patients in the first year after starting combined antiretroviral therapy (cART) for the first time.
Methods: A cohort of naïve HIV-infected patients who started cART in the context of a national reimbursement program from January 2007 onwards is being prospectively followed. For each individual, the date and reason of the first discontinuation of any drug in the initial regimen was identified. Changes to same drug formulations were not counted as discontinuations.
Results: 399 patients were enrolled, with a mean follow-up of 82±48 weeks. This study concerns the 248 (62.2%) patients who have a follow-up of ≥1 year. Mean age 42.2±12.3 years (range 78-20), 71.8% were males. 98.8% were HIV-1-infected. HIV was sexually transmitted in 77.8% of the patients, 21.0% were IVDUs; in 1,2% risk was undetermined. HCV/HBV co-infection respectively in 24.6% and 4.4%. At baseline: 28.6% of the patients had AIDS. Mean CD4 cell count 185 cells/mm^3 (range 2-833). Viral load (VL) >100000 copies/mL in 55.6%. The cART regimen was based in NNRTIs /PIs in respectively 67.3% and 31.9% of the patients.
A total of 109 (44.0%) patients discontinued at least one drug in their cART regimen. The main reasons for discontinuation were: drug related adverse effects (39/35.8%), lack of adherence/lost to follow up (20/18.3%), virological failure (18/16.5%), regimen simplification (17/15.6%), increased CV risk (7/6.4%), pregnancy (4/3.7%). Four patients died. Low median CD4 count (p=0.021) and high median viral load (p=0.075) were found to be associated with virological failure.
Conclusions: Drug related adverse effects were the main cause of antiretroviral discontinuations in this cohort, with a rate higher than the combined rates for lack of adherence/lost to follow-up and virological failure. Continued attempts to improve the tolerability of cART regimens and patient adherence may help to minimize drug discontinuation rates over the longer term.

P14

Insights into antiretroviral treatment changes in previously naïve patients: results of a Portuguese cohort

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Purpose of the study: Since the use of more tolerable and less toxic combined antiretroviral (ARV) therapy, most drug-naïve HIV patients achieve viral suppression and immunologic recovery, combined with less AIDS related events. Nevertheless, drug switches are still frequent both as a mean of adherence and toxicity management and as a response to virologic or immunologic failure. The aim of the study was to analyse the number, timing and cause of modifications in the first ARV regimen in order to elucidate more about adverse drug reactions in the current HIV ARV therapy guidelines, indirect signs of adherence and premature virological failure.
Methods: Non-controlled, observational, retrospective study, based on the clinical files and on a national questionnaire audit for all naïve-patients that began cARV therapy between January 2007 and Mars 2010, followed in an Infectious Diseases Clinic in a central Hospital in Lisbon. SPSS 15.0 was used for statistical analysis.
Results: During study period, 69 patients of the 285 naïve-patients who started ARV therapy changed their regimen, 64% were male, with a median age of 43 years old. A significant group was born in African Portuguese speaking countries (30%). Most switches occurred on the first 6 months (n=42), 22% on the first month and just 11% after one year of treatment, with more than one modification in 15% of patients. The drug regimen prior to modification included a NNRTI in 62% of the patients. The back-bone regimen included TDF/FTC in 66%, ABC/3TC in 12% and still AZT/3TC in 22% of them. Adverse drug reactions were the most frequent cause of therapy modification (59%), including toxicity in 19 cases and intolerability in 22, reflecting the known side effects of the drugs. Other switch causes were the evidence of virological failure (15%), the simplification of the regimen (10%) and the adjustment during pregnancy (5%). About a fifth of the patients had adherence irregularities. The rate of viral suppression at week 24 of ARV was significantly lower in the group of patients who switched ARV (39% vs 60%; p=0.006), which had also worse immunological recovery at 24 and 48 weeks of ARV.

Conclusions: Toxicity and intolerability remain the main reasons to change the first ARV regimen, more frequently during the first to sixth months of therapy, witch reinforce the need to evaluate early events that can compromise the adherence, the emergence of resistances and long term toxicity and longevity of this patients.

P15

Factors associated with treatment modification during the first year of contemporary HAART

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Purpose of the study: To estimate the short-term probability of HAART change and to evaluate factors associated with treatment modification during the first year of contemporary HAART.
Methods: We evaluated by logistic regression and Cox proportional model analysis factors associated to treatment modification during the first year of HAART in antiretroviral naïve patients from a single HIV unit in Madrid. Variables included in the analysis were: Basic sociodemographic characteristics, data on the clinical course, VHC coinfection, antiretroviral therapy and immunologic and virologic variables.
Results: From Jan/06 to Dec/09, 301 patients started HAART (mean age 38.6, 75.4% male). Median CD4: 246, mean viral load: 4.67 logs, 22.3% HCV coinfected. Patients started HAART including TDF/FTC (84.7%), ABC/3TC (8.3%), AZT/3TC (7%), EFV (53.5%), NVP (7.7%), LPV/r (23.6%), DRV/r (2.0%) ATV/r (2.7%), FPV/r (6.3%), SQV/r (0.5) and RAL (3.7%). One-year probability of HAART modification was 0.26 (95%CI 0.21-0.26). Reasons for HAART modification were toxicity (11%), simplification (10.6%, including 8.31% of patients who switched from TDF/FTC+EFV to TDF/FTC/EFV), Lack of efficacy (1.3%) and other (i.e. poor adherence, pregnancy termination 3.3%). Most common toxicities leading to HAART modification were skin rash (3.32%), CNS adverse events (1.66%), gastrointestinal (1.33%) lipoatrophy (1.66%), renal (1%), and osteopenia (1%). Patients who modified HAART were less likely to achieve 1 year viral load suppression than patients who didn't change HAART (83.5% vs 94.6%, p = 0.02) with no differences in CD4 cell recovery. Multivariant logistic regression analysis showed that a prior AIDS-defining condition [OR 1.90 (1.07-3.37)] and AZT/3TC as nucleoside backbone [4.81 (1.88-12.3)] were significantly associated to HAART modification. A sensitivity analysis excluding TDF/FTC+EFV to TDF/FTC/EFV switches showed two additional factors associated to treatment modification: female sex [2.62 (1.30-5.27)] and time since HIV diagnosis.
Conclusions: Treatment modification is still common during the first year of HAART occurring in one quarter of patients. While lack of efficacy of HAART is an uncommon reason for change, toxicity and treatment simplification remain important reasons for change. Women, patients with a prior AIDS diagnosis and patients receiving AZT/3TC as a backbone were more likely to change therapy.

P16

Impact of timing HAART initiation on immune status and clinical course in the cohort of the German competence network for HIV/AIDS

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Purpose of the study: Optimal time of HAART initiation is still unknown. Several studies investigating this issue showed inconsistent results. Our study investigated whether there is a clinical benefit as to treated patients (pts) by an earlier start of therapy at CD4 between 350-449c/µl, compared to the range of 250-349c/µl. An analysis was conducted on basis of the open, retrospective and prospective, multi-center and nationwide cohort of the Competence Network for HIV/AIDS.
Methods: For analysis, pts had to be observed at least 3 months before initiation of HAART. Medication had to start later than 1996, with at least three substances. At time of therapy start (t_o), pts had to have 250c/µl <CD4-cells<450c/µl, no prior AIDS defining conditions and CD4 cells never below 200c/µl. Afterwards, pts were stratified in groups by initial CD4 cells between 250-349c/µl (group 1) and 350-449c/µl (group 2). Primary outcomes death, AIDS and first drop of CD4 cell count/µl<200 cells were evaluated as censored event times between t_o and the date of first event resp. last observation. Time dependent probabilities of event free intervals since start of HAART were estimated by Kaplan-Meier estimation, compared by Log-rank-tests. Cox-regression models were fitted, adjusted for time since infection.
Summary of results: 822 pts met inclusion criteria. Group 1 consisted of 526 pts, group 2 of 296. Mean observation time in group 1 was 5.1 years/pt (2,683 years overall), in group 2 4.9 years/pt (1,450 y overall). In group 1, 0.64 deaths occurred per 100 pt years vs. 0.17 events in group 2. 1.38 AIDS events were developed per 100 pt years vs. 0.78 events in group 2. In group 1, 2.64 per 100 pts years dropped <200c/µl vs. 0.77 in group 2. Kaplan-Meier estimations showed borderline significant difference as to developing death (ten years probabilities for having no event as to death: group1 94%, group2: 97%, p=0.063), significant difference as to CD4 drop<200c/µl (group1 80%, group2: 94%, p=0.0004), but no significant differences as to AIDS (group1 92%, group2: 90%, p=0.219). Hazard ratio (group 2 vs. 1) was significant for CD4 drop<200c/µl (0.302, p=0.001), but not for death (0.268, p=0.0829) and AIDS (0.577, p=0.153).
Conclusions: Results showed a tendency for better outcome of pts by start of therapy with CD4 cell count ≥350c/µl regarding death, clear evidence regarding first CD4 drop <200. These results may be a hint to start therapy earlier.

P17

Efficient immune reconstitution in HIV+ naïve patients (pts) starting a first lopinavir/ritonavir-containing regimen with low CD4 counts

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Purpose of the study: Investigate immune restoration profile, T-cell activation and microbial translocation in HIV+ naïve pts starting a first LPV/r-containing regimen with low CD4.
Methods: 40 HIV+ antiretroviral-naive pts starting a first tenofovir/emtricitabine + LPV/r-containing ART with CD4 <350 (20 Late Presenters —LPs, CD4 <100/µL and 20 Non-Late Presenters —NLPs, CD4, 200—350/µL) were followed for 12 months (T12). Microbial translocation (MT) by plasma lipopolysaccharide (LPS) and sCD14 (LAL assay and ELISA), CD38+CD8, CD45R0+38+CD8, CD127+CD4/CD8 (flow cytometry), and plasma IL-7 (ELISA) were tested at T0 and T12. T0 and T12 differences were analyzed by Mann Whitney U test.
Summary of results: At T12, all 40 HIV+ pts displayed a significant CD4 rise, HIV viremia reduction (p=0.0006; p<0.0001, respectively) and a decrease in activated CD38+CD8 (p<0.0001), with a trend to an increase in CD127+CD8 (p=0.07). By T12, both LPs and NLPs displayed a significant CD4 increase (LPs: p=0.0001; NLPs: p=0.001), with LPs maintaining significantly lower CD4 at T12 (p=0.0001). At T12, NLPs and LPs displayed a significant reduction in CD38+CD8+ (p=0.009; p=0.018, respectively); only NLPs displayed a decreasing trend in terminally-differentiated CD45R0+CD38+CD8 (p=0.077). Compared to LPs, NLPs featured higher CD127+CD4 proportions at all timepoints (T0, p=0.0001; T12, p=0.001), with a significant increase in CD127+CD8 by T12 (p=0.012), whereas no changes were seen in LPs. NLPs also displayed a significant rise in circulating IL-7 (p=0.049), whereas LPs showed a decreasing trend (p=0.074). At T0, NLPs showed higher levels of MT markers (LPS: p=0.01; sCD14: p=0.007). By T12, only NLPs

displayed a significant reduction in LPS (p=0.022) and in sCD14 (p=0.005), whereas no changes were shown in LPs.
Conclusions: In HIV+ antiretroviral-naive pts with low CD4, LPV/r-containing regimens resulted in adequate immune reconstitution and restoration of the IL-7/IL-7R system. Interestingly, microbial translocation was efficiently controlled only in patients with less advanced HIV infection. However, LPV/r-based treatment resulted in a significant reduction of peripheral T-cell activation also in patients with late presentation. Given that T-cell activation is predictive of disease progression, our data advocate the efficacy of LPV/r regimens in broad immune reconstitution in HIV-infected pts with advanced infection.

P18

Immunological response among patients with undetectable viral load followed for 5 years

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Purpose of the study: to assess the immunological response at 5 years in HIV-1 infected patients under ART and with persistently undetectable plasma viral load.
Methods: of 1450 patients currently on ART, 504 HIV-1 infected patients with persistently undetectable viral load for 5 or more years (mean = 8±2 years) were selected. Results of plasma viral load (performed by PCR RNA-HIV, Amplicor 1.5®) and CD4 count of all patients obtained every 3 or 6 months were abstracted. The distribution of 5-year CD4 count was described using medians and compared between classes of clinical and demographic variables using Wilcoxon's or Kruskal-Wallis' test. Variation in CD4 count over 5 years was described using means and compared between classes using Student's t test or ANOVA. In order to quantify the associations between independent variables and CD4 count variation, linear regression coefficients and respective 95% confidence intervals (95% CI) were calculated, and adjusted for sex, naïve status, transmission mode, baseline viral load and age at viral load suppression.
Summary of results: In crude analysis, 5-year CD4 count (per mm^3) was significantly higher in women (medians: 656 vs. 573, p=0.006), in younger patients (<30 years-old: 656 vs. 526 in those over 49), in non-AIDS patients (637 vs. 513.5 in AIDS patients, p<0.001) and in those with the highest baseline CD4 count (>350: 826 vs. 459 in those under 100; p<0.001). Mean CD4 variation was greater in women (467.5 vs. 401.3, p=0.022), in naïve patients (437.9 vs. 361.8, p=0.006), in those with the highest baseline viral load (>750000 copies: 490.3 vs. 271.0 in those under 10000 copies) and correspondingly in patients with the lowest baseline CD4 count (<100: 469.7 vs. 359.5 in those over 350). Patients on NNRTI had larger improvement than those on PI (436.2 vs. 403.0) but no significant differences in CD4 count were found after 5 years. In multivariate analysis, mean CD4 count improvement remained significantly higher in women and lower in older patients. Improvement was also directly associated with baseline viral load.
Conclusions: Even though patients with the lowest CD4 count at baseline had greater immunological improvement over 5 years, average CD4 count remained lower than in those whose baseline count was higher. Importantly, the gap in immunological response (regarding final CD4 count and mean improvement) widened over the follow-up period between women and men and between younger and older patients.

P19

Epidemiological features, therapeutic strategies and long-term immunological outcomes in virologically suppressed HIV+ very late presenters

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Purpose of the study: In the Western world, approximately 30% of HIV-infected individuals are still very late presenters. The aim of this retrospective study is to describe epidemiological and clinical characteristics, as well as long-term immunological outcome in virologically suppressed HIV+ very late presenters.
Methods: We reviewed the medical records of all consecutive HIV+ patients with CD4 cell count < 200/ mmc3 at presentation, who had attended our clinic between 1996-2006, and had achieved a persistent virological suppression for at least 1 year. Demographic, clinical, virological and immunological data at baseline and at follow up visits were collected. The changes in CD4+ cell count during follow up was also examined, stratifying the population according to baseline age, HIV risk factors, CD4+ cell counts, HIV viral load , HCV co-infection.
Summary of results: Overall 164 very late presenters with a persistent virological response were examined. Caucasian and heterosexual males represent the largest part of this cohort of virological responder, very late presenter patients. IDUs and HCV coinfected patients were under-represented as compared to our HIV population, probably due to a lower adherence. Epidemiological and clinical characteristics of the study population: 61.2% had CD4+ cell count <50/μl. 123 patients started a protease inhibitor-based regimen (75%). Respectively 25% and 52% of initial NNRTI and PI-based regimen were modified during follow up (toxicity was the most common cause of switch). After 5 years of therapy a good immunological recovery (> 500 CD4 cell/μl) was observed in 30.7% and 46% of patients with baseline CD4+ cell count < 50/μl and 51-200/μl respectively. CD4+ cell count increased even after 5 years, reaching a full immunological recovery (>700/μl) only in 17% of patients. Patients aged ≥ 50 years, IDUs and HCV co-infected had a slower and/or lower immune recovery; no significant differences in immunological response according to baseline viral load were observed.
Conclusions: A fair immune recovery over 5 years of HAART was seen. The CD4+ cell count restoration was conditioned by baseline values, age, HCV coinfection, and a complete immunological recovery was achieved in a very limited subset of patients.

P20

Sex matters: retrospective data collection on the date of commencement of ART for HIV-positive women and men in the German KompNet cohort (1991-2009)

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Background: In Germany the majority of people living with HIV/AIDS are males and little is known about the characteristics and epidemiology of female HIV patients. The German KompNetKohort is a large, national retro- and prospective, multicenter, HIV-specific cohort, that documents HIV-positive patients since 1991. One important question we wanted to answer is in how much these two populations differ and whether a gender specific treatment approach is needed.
Methods: A thorough database analysis was conducted and male and female HIV patients of the German KompNetKohort were stratified for baseline characteristics, immunologic status (CD4+ counts, VL, opportunistic infections) before commencing ART, country of origin, way of transmission as well as the initial therapy regimen.
Results: We analysed 3793 Patients (590 women (15.5%), 3203 men (84.4%)). The median age was 43,6 years for women and 47,64 for men. 137 female (23.3%) and 751 male (32.9%) had CD4- counts < 200 /μl, whereas 451 women and 1529 men showed CD4- counts > 200 CD4/μl (p< 0.001). The initial therapy regimen was documented for 2216 patients. 215 women and 687 men started with a PI-based regimen, whereas 199 women were treated with an NNRTI and 1314 men (p< 0.001). Other regimens where used 176 times in women and 1403 in men.
Conclusion: In the German KompNetCohort men had lower CD4-counts at the time of starting ART. Women were much more frequently treated with PI than men. A reason could be the restrictions in child bearing age for efavirenz and the CD4-cell count for nevirapine use.
It is not clear if the lower CD4-Cellcount at time of starting ART in men is due to late presentation. Further investigations are warranted.

Table 1 (abstract P21)

	WOMEN (318)	MEN (772)	P
Immigrants, %	45.6	31.1	<0.001
Age, years (IQR)	35 (29-41)	39 (33-44)	<0.001
Median viral load (IQR)/CD4 (IQR)	4.7 (4.2-5.2)/ 217 (113-300)	5.0 (4.5-5.4)/ 190 (69-280)	0.001/0.002
Coinfection with HBV or HCV %	25.2	29.3	0.32
Stage C/Late diagnosis, %	21.2/49.0	29.0/59.0	0.006/0.003
Median time from diagnosis of HIV infection to initiation of HAART, mo (IQR)	15 (2-43)	16 (2-49)	0.55
Median TTF, wk	147	171	<0.001
VF/OI, %	5.3	6.3	0.52

Educational level and occupational status were significantly poorer in women. The adjusted risk of treatment failure in women was not significantly different from that of men (HR, 1.101; 95% CI, 0.79-1.53). The increase in CD4 lymphocytes was equivalent (185 vs 205). TTF was shorter among (IW) than autochthonous women (AW): 124 weeks (95% CI, 64-183) vs 152 (95% CI, 127-174). Most immigrant women were African and Latin American, and their dropout rate (25.5 vs 11.6) was double that of AW.

P21

Response to HAART according to sex and origin (immigrant vs autochthonous) in a cohort of patients who initiate antiretroviral treatment

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Purpose: Although poorly studied, gender differences can affect the efficacy of HAART. Immigrant women (IW) may also be at risk of treatment failure due to greater marginalization, cultural differences, or reduced access to health care. This subanalysis examined differences in baseline characteristics and response to HAART according to sex and geographic origin.
Methods: Subanalysis of GES-5808 (retrospective comparative study autochthonous/immigrant patients initiating HAART Jan05-Dec06). Late diagnosis was defined as a CD4+ count ≥200, and/or AIDS at initiation of HAART. The primary endpoint was time to treatment failure (TTF), which was defined as virological failure (VF), death, opportunistic infection (OI), interruption of HAART, or loss to follow-up. Survival was analyzed using a univariate (Kaplan-Meier) and multivariate (Cox regression) approach.
Results: Patient Characteristics at Initiation of HAART (Table 1)
Conclusions: Response to HAART was similar in both sexes. Men started HAART later and women had higher loss to follow-up and more treatment switches. This was even more common among IW. Earlier diagnosis is necessary for men; measures to improve adherence should be promoted among women, especially IW.

P22

Eligibility for the initiation of HIV treatment in the context of the updated EACS guidelines: results of a clinical audit

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Background: Based on the recent update (November 2009) of the European AIDS Clinical Society (EACS) guidelines for HIV-1-infected patients, initiation of antiretroviral therapy (ART) is now also recommended in patients with 350 to 500 CD4+ T cells/μl and additional risk factors.
Methods: In this single-center audit all ART-naïve HIV-1-infected subjects were screened for their eligibility to start ART based on CDC stage of disease, CD4+ T cell count and EACS-defined risk factors to assess the impact of implementing the new recommendations on clinical practice.
Results: In January 2010, 155 out of a total of 994 HIV-1-infected subjects (16%) under regular observation at the HIV outpatient clinic of the Vienna General Hospital were ART-naïve.
47.7% (74/155) of individuals had at least one EACS-defined risk factor. Immediate initiation of ART was indicated in 10 subjects with symptomatic HIV-disease (6.5%). Of the remaining 145 asymptomatic patients, 15 (10.3%) had two consecutive CD4+ T cell counts < 350/μl and 19 subjects (13.1%) with a CD4+ T cell count 350-500/μl had ≥ 1 EACS-defined risk factor. Of the latter 19 subjects, six had HBV and/or HCV co-infection and one patient was suffering from HIV-associated nephropathy, whereas the remaining 12 subjects had other risk factors, e.g. age > 50 years, HIV-1 RNA level > 100000 copies/ml and/or CD4+ T cell decline > 100/μl within 1 year. Thus, according to the current EACS guidelines initiation of ART was recommended in 20% (31/155) and should be considered in additional 8% (12/155) of treatment-naïve patients. In contrast, treatment would have been recommended in only 16% of patients (25/155) based on the previous version of the EACS guidelines.
Conclusions: In this clinical audit more than 1/4 of all treatment-naïve patients were eligible for the initiation of ART based on the updated EACS guidelines representing an increase of 76% over previous recommendations due to the inclusion of patients so far not considered eligible. Unless further studies show that ART initiation would be beneficial in all patients with a CD4+ T cell count <500/μl, awareness for HIV-associated and non HIV-risk factors needs to be increased to identify patients for whom treatment is recommended.

P23

Cross-sectional study of HIV living people cohort to specify indications to antiretroviral treatment in naïve patients

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Purpose of the study: To determine groups in HIV living people cohort in the aspect of further HAART.
Methods: The data on 2271 patients was investigated in a cross-sectional study. All patients at the moment of survey had no attributes of clinical progression of disease and did not receive HAART. Clinical exam and blood sampling was performed, in blood specimens HIV virus load (PCR m2000rt Abbott Biosystems analyzer, RealTime HIV-1 sets) and CD3+CD4+ and CD3+CD4- phenotypes of T-lymphocytes were analyzed (flow cytometer BD FACSCount, sets of antibodies TriTEST CD3/CD4/CD45). For 363 patients additionally CD3+CD8+ and CD3+CD4-CD8- (double negative) phenotypes of T-lymphocytes were determined. Duration of HIV infection and the age of the patient was also included into analysis. Received data was processed statistically by means of SPSS software.
Summary of results: Factor analysis with the principle component method revealed two major factors gathering 54% of the total variance.

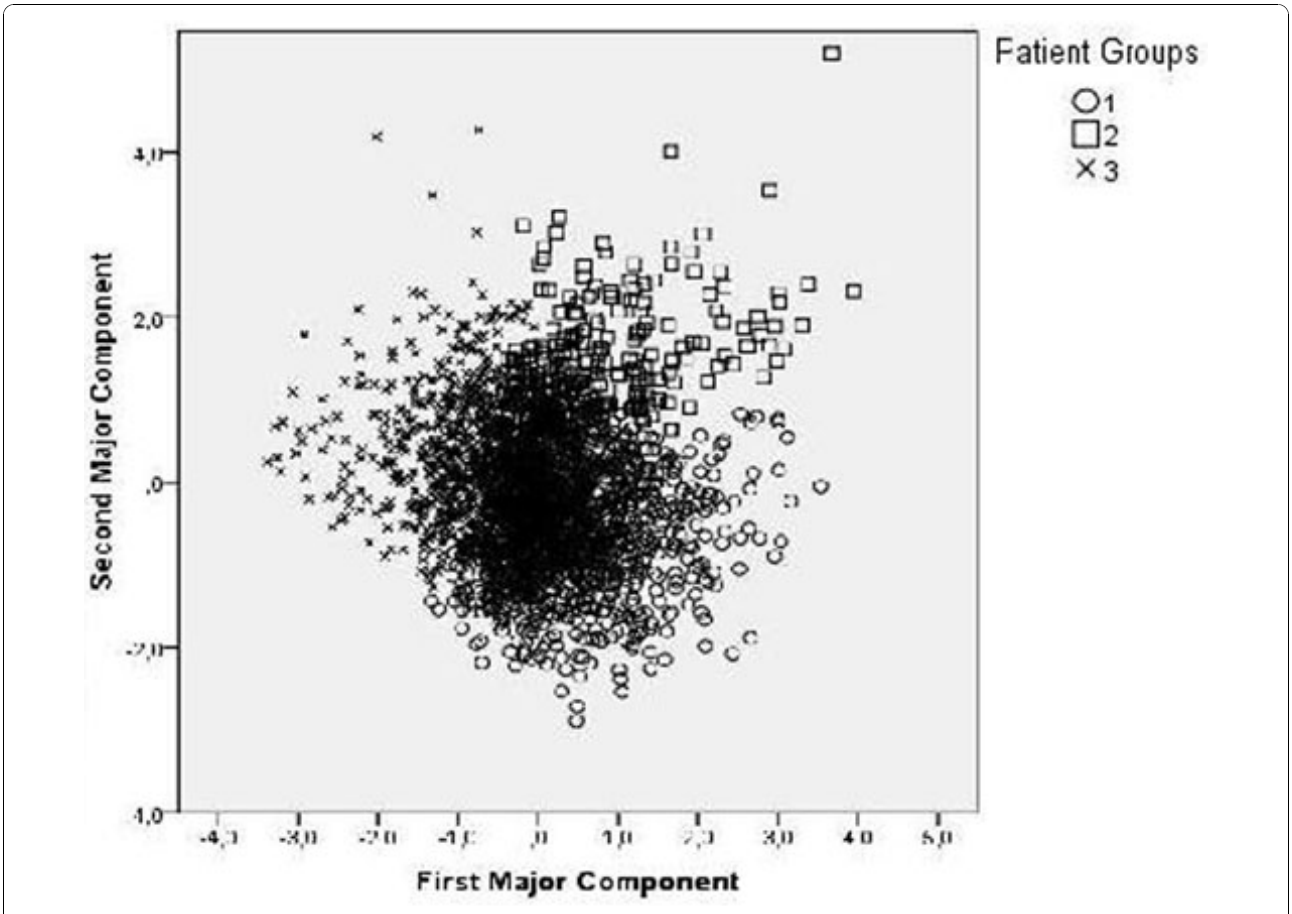

Figure 1 (abstract P23) Bland-Altman plots comparing Framingham, Rama-EGAT, and D:A:D risk scores

The first factor included CD4+ and CD3+CD4- T-lymphocyte counts with reverse influence of the viral load. The second factor included CD3+CD4- counts concordant with the viral load. Hierarchical cluster analysis by Ward method was performed in the space of these two factors and revealed 3 groups. Figure 1

The First Group had relatively small duration of disease (about 3 years), well preserved CD4 counts (650 cells/mm^3), CD3+CD8+, CD3+CD4-CD8- T-lymphocytes on the average level characteristic for the HIV-living cohort. The group was designated as temporary no progressive. The Second Group had significant duration of disease (5 years), almost intact CD4 counts, 4,1 time increase in CD3+CD8+ T-lymphocytes and 10,3 increase of CD3+CD4-CD8- counts in comparison with healthy controls. This was permanent no progressive group. The Third Group had also significant duration of disease (6 years), different (from moderate to severe) depletion of all detected subpopulations of T-cells as well as the highest viral load. This was the progressive group, the members of which had indications to HAART (27% of the population). Table 1.

Conclusions: 1. Evaluation of no progressive status (temporary or permanent) as well as diagnostics of the progressive state outlines indications to antiretroviral treatment. 2. Evaluated internal groups support approach to start HAART after CD4 cell counts are less than 500/mm^3 and the depletion level of 350 CD4 cells/mm^3 lies in the middle scope of progressive group.

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Table 1 (abstract P23)

Group Number	Group Title	CD3+ (cells/mm^3)	CD4 +(cells/mm^3)	CD8 +(cells/mm^3)	CD3+CD4-CD8- (cells/mm^3)	Viral Load (log 10 copies/ml)	Age (years)	Disease Duration (years)
1	Temporary No Progressors	2321	654	1105	411	3,42	27,76	2,80
2	Permanently No Progressors	3575	735	2243	658	4,00	36,06	4,76
3	Progressors	1771	366	969	268	4,50	32,64	6,17
4	HIV Infected Total	2363	589	1195	394	3,80	30,34	4,01
5	Healthy Controls	1554	944	545	64	-	28,62	-

P24

Changing antiretrovirals whilst viral load <50 copies/ml and relationship with CD4 count changes

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Purpose of the study: The frequency and reasons for switching antiretrovirals (ARVs) in patients on a fully suppressed cART regimen (viral load [VL] <50copies/ml) is not well described, nor is the effect of such a change on CD4 counts.

Methods: 6713 patients from EuroSIDA on cART with a confirmed VL<50 copies/ml were included; a regimen change was defined as >1 ARV change (occurring on the same day) for any reason whilst VL< 50 copies/ml. Baseline was defined as the first VL<50 copies/ml on cART; Kaplan Meier methods estimated the probability of ARV change and Cox proportional hazards models, stratified by centre, identified factors associated with ARV change. Mixed models were used to model the change in CD4 count after the first ARV change.

Results: At baseline, the median CD4 was 414/mm^3 (IQR 272—587). 1079 (16.1%) patients changed 1358 ARVs; 93 (8.6%) patients started an ARV they had previously taken. 224 (77.0%) of those starting an NNRTI (n=291) were previously naïve to NNRTIs, compared to 29 of 306 who started a PI or boosted-PI (9.5%). The incidence of changing ARVs was 11.8 per 100 PYFU (95% CI 11.1-12.5). At 1 year after baseline, 10.7% were estimated to have changed >1 ARV (95% CI 9.8-11.5). The most common reason for change was toxicity (n=521, 38.4%), followed by patient or physician choice (n=398, 29.3%). Table 1 shows the factors associated with changing ARVs.

After adjustment, changing ARVs was associated with an additional annual increase in CD4 counts of 9.3/mm^3 per year (95% CI 5.7-12.9/mm^3) compared to not changing ARVs. The increase was similar in patients who recycled ARVs compared to those starting an ARV to which they were naive, according to type of new ARV started (nucleoside, PI, boosted-PI or NNRTI), and number of new ARVs started (0, 1 or >2, p>0.05 all). Patients starting a new ARV class had higher increases in CD4 counts compared to those who changed ARVs but did not start a new class (8.0/mm^3; 95% CI 0.2-15.8/mm^3, p=0.044), although there was no differences between PI-containing or NNRTI-containing classes (p=0.54).

Table 1 (abstract P24)

		Multivariate		
		RH	95% CI	P
Gender	Female versus Male	1.29	1.09-1.53	0.0038
Risk group	Heterosexual versus other	0.83	0.70-0.98	0.033
Basline	Per year later	1.32	1.27-1.38	<0.0001
Nucleoside pair	Zidovudine/ lamivudine	1.00	-	-
	Didanosine/ stavudine	1.94	1.49-2.53	<0.0001
	Stavudine/ lamivudine	1.81	1.50-2.17	<0.0001
	Tenofovir plus 1	0.87	0.68-1.10	0.24
	Abacavir plus 1	0.62	0.46-0.83	0.0012
	Other not listed	1.06	0.80-1.40	0.68
Third drug	Single PI	1.00	-	-
	Boosted PI	0.46	0.36-0.58	<0.0001
	NNRTI	0.42	0.35-0.50	<0.0001
	Triple nucleoside	0.23	0.16-0.35	<0.0001
HCV serostatus	Positive versus negative/unknown	0.80	0.67-0.96	0.017

Conclusions: Changing ARVs whilst virologically suppressed was due to patient/physician choice or toxicity, increased in frequency over time and was more common in patients taking a single PI-regimen or in stavudine-containing regimens. Patients who changed ARVs had a small but statistically significant boost to CD4 count levels, and the increase in CD4 was higher in those who changed to a new class of ARV.

P25

Influence of demographic and disease parameters on virological response to once- vs twice-daily darunavir/ritonavir (DRV/r) at week 48 in ODIN

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Background: ODIN was a Phase IIIb, randomised, open-label trial showing non-inferiority of DRV/r 800/100mg qd vs 600/100mg bid (+ ≥2 NRTIs) in treatment-experienced HIV-1-infected adults with no DRV

Table 1 (abstract P25) % patients with HIV-1 RNA <50 copies/mL at Week 48

	DRV/r qd		DRV/r bid		
Baseline factor	N	% response	N	% response	Difference in response (95% CI)
HIV-1 RNA (as stratified) (copies/mL)					
≤50,000	222	78.4	224	76.8	1.6 (-6.2, 9.4)
>50,000	72	52.8	72	52.8	0.0 (-16.4, 16.4)
CD4 count (cells/mm^3)					
<50	13	53.8	3	100	-46.2 (-109.6, 17.3)
50-<100	36	58.3	35	57.1	1.2 (-22.2, 24.6)
100-<200	76	77.6	77	67.5	10.1 (-4.1, 24.3)
200-<350	108	72.2	107	74.8	-2.5 (-14.4, 9.3)
≥350	61	77.0	74	74.3	2.7 (-12.0, 17.4)
Gender					
Female	115	69.6	98	69.4	0.2 (-12.3, 12.7)
Male	179	73.7	198	71.7	2.0 (-7.0, 11.1)
Age (years)					
≤30	35	71.4	35	60.0	11.4 (-11.0, 33.9)
30-≤45	180	75.6	169	72.8	2.8 (-6.4, 12)
45-≤55	64	60.9	72	72.2	-11.3 (-27.2, 4.6)
55-≤65	14	78.6	18	66.7	11.9 (-20.6, 44.4)
>65	1	100	2	100	0 (0, 0)
Race					
Black	83	62.7	72	65.3	-2.6 (-17.9, 12.7)
Caucasian	102	71.6	110	69.1	2.5 (-9.9, 14.9)
Hispanic	47	72.3	59	67.8	4.5 (-13.2, 22.3)
Asian	48	89.6	41	87.8	1.8 (-11.6, 15.1)
Other	14	71.4	14	78.6	-7.1 (-40.7, 26.4)
Clade					
B	179	70.4	199	64.3	6.4 (-3.4, 15.6)
Non-B	115	74.8	97	84.5	-9.8 (-20.7,1.2)

resistance-associated mutations at screening. We evaluated the effect of demographic and baseline (BL) disease parameters on virological response (VR) of qd vs bid DRV/r at Week 48.
Methods: Week 48 VR (HIV-1 RNA <50 copies/mL; ITT-TLOVR) was analysed by subgroups including gender, age, race, HIV clade, BL HIV-1 RNA and CD4 count.
Results: Week 48 VR was 72.1% for DRV/r qd vs 70.9% for bid (95% CI = -6.1 to 8.5%). Week 48 VR by gender, age, race, HIV clade, BL CD4 count and HIV-1 RNA is reported (Table 1).
Conclusions: VR was comparable with DRV/r qd and bid regardless of subgroup analysed. As the trial was not powered for treatment comparisons in subgroups, and as numbers were small for some subgroups, these exploratory findings should be interpreted with caution.

P26

Health-related quality of life (HRQoL) assessment with once- and twice-daily darunavir/ritonavir (DRV/r) in the ODIN trial

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Background: The open-label, Phase III, ODIN trial randomised treatment-experienced HIV-1-infected patients with no DRV resistance-associated mutations (RAMs) to receive DRV/r 800/100mg qd or DRV/r 600/100mg bid, plus an optimised background regimen (≥2 NRTIs). Non-inferiority in the primary endpoint of virological response at Week 48 was demonstrated with DRV/r qd versus bid dosing: 72.1% vs 70.9% of patients, respectively, achieved HIV-1 RNA <50 copies/mL (95% CI: -6.1, 8.5; p<0.001; ITT-TLOVR). The current analysis explores patient-reported HRQoL.
Methods: Treatment-experienced patients with no DRV RAMs at screening and HIV-1 RNA >1,000 copies/mL were randomised. Patient-reported HRQoL was measured with the Functional Assessment of HIV-infection (FAHI) questionnaire at baseline and at Weeks 4, 12, 24 and 48 (or withdrawal visit). FAHI score at Week 48 was modelled by means of an ANCOVA, and the evolution of the FAHI score over time by means of a longitudinal mixed model, each with treatment as a factor and CD4 and baseline HIV-1 RNA as a regressor. FAHI response was defined as the proportion of patients with a clinically meaningful difference (relative increase of 10%) in total FAHI imputed score versus baseline.
Results: HRQoL data were available for 262/294 DRV/r qd and 268/296 DRV/r bid patients. The baseline total FAHI imputed score was relatively high (124.1 and 121.2 for DRV/r qd and bid, respectively), leaving limited room for improvement. Mean (SE) increase in total FAHI score from baseline (ITT-LOCF) at Week 48 was comparable with DRV/r qd and bid dosing (table 1). A mean increase in total FAHI score from baseline was observed in both treatment groups at all timepoints. No relevant between-group differences were noted either by ANCOVA (p=0.761) or longitudinal mixed model (p=0.995). There were no relevant differences between arms at any time in the proportion of FAHI responders (p=0.957).
Conclusions: DRV/r qd and bid dosing was comparable with respect to the increase in mean total FAHI score from baseline at Week 48 and in the proportion of patients achieving a clinically meaningful difference in total FAHI score at Week 48.

Table 1 (abstract P26)

	DRV/r 800/100mg qd (n=262)	DRV/r 600/100mg bid (n=268)
Mean (SE) change in total FAHI score from baseline (ITT-LOCF)		
Baseline value	124.1 (1.78)	121.2 (1.73)
Week 4	0.4 (1.10)	1.3 (1.08)
Week 12	3.2 (1.18)	1.7 (1.28)
Week 24	2.8 (1.27)	2.5 (1.26)
Week 48	2.7 (1.36)	3.1 (1.40)
FAHI responders (LOCF) at Week 48, %	27.5	29.5

P27

Darunavir in experienced patients

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Purpose of the study: This study aims to assess the performance of DRV in clinical practice, as part of salvage therapy strategies.
Methods: We did retrospective assessment of HIV+ patients who received DRV at our institution, prescribed as part of a salvage regimen since 2006. Liver, metabolic and renal profile were assessed at baseline, after 1 month and every 3 months. 52 HIV1+ patients have been enrolled; mean age was 48 (IQR 44-54) years, male 82%, IDUs 29%, MSM 37%, heterosexuals 33%; 15 patients were HCV or HBV co-infected. All but one were subtype B. Median CD4 nadir was 82 (IQR 27-234). Thirty-one patients had AIDS history. Mean time on ARVs was 15 (IQR14-17) years; major mutations were: 8 for NRTI, 2 for NNRTI and 5 for PI.
Results: Median follow-up was 104 weeks (IQR 60—139). Two patients died: one following a car accident, the other one due to disseminated Kaposi's sarcoma. Four patients stopped DRV: one lost to follow-up, one developed decompensated diabetes, one rash, one virological failure. Companion drugs with DRV were NRTI (71%), etravirine (14%), maraviroc (33%), raltegravir (RAL) (33%), enfuvirtide (ENF) (33%). Seventeen patients had changes in therapy during follow up, four patients stopped NRTIs, among 13 patients who stopped ENF, 5 replaced with RAL. Mean CD4 and HIV-RNA values at baseline were 251 cells/mm^3 and 4.3 log$_{10}$ copies/ml, respectively; CD4 median monthly increase was 9 (IQR 5.1-14.5) cells/mm^3. After 1 month, 49 % had HIV-RNA <50 copies/ml; after 12, 24 and 33 months 91% of patients were still undetectable. No statistically significant modification were seen in transaminases, creatinine, glucose, triglycerides values.
Conclusions: Darunavir was highly effective and well tolerated in most of patients and showed good metabolic, renal and liver profile in our cohort where the rate of co-infected patients was high.

P28

Efficacy and tolerability of darunavir/r 600/100 mg bid in treatment-experienced patients: 48-week data from a German outpatient cohort

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Background: Darunavir/Ritonavir (DRV/r) dosed 600/100 mg bid has shown good efficacy and tolerability in treatment-experienced patients in clinical trials (POWER, TITAN). To assess whether these results can be transferred to clinical practice and a more diverse patient population this prospective non-interventional Janssen-sponsored cohort study was established.
Methods: Between August 2007 and March 2009, 340 HIV-1 infected antiretroviral-experienced patients from 62 German centers enrolled in this non-interventional cohort. All patients received DRV/r 600/100 mg bid as part of their HAART. Virological and immunological response was monitored every 3 months. Patients were followed for up to 48 weeks.
Results: 296/340 (87%) patients were male with a mean age of 47 years (SD 9.9); median time since HIV diagnosis was 12 years. At baseline, mean viral load (VL) was 4.7 log$_{10}$ copies/mL (SD 5.44) with a mean CD4 count of 392 cells/mm^3 (SD 251); 213 (63%) patients started therapy with CD4 < 200 cells/mm^3. Patients had been pretreated with NRTIs (94%), PIs (88%), NNRTIs (63%), FI (11%), INI (5%) and/or CCR5 (3%). No data is available for 17 patients. At baseline, only 138 patients received DRV/r in combination with 2 NRTIs; the majority (202/340) of patients received DRV/r in different combinations based on the individual pretreatment situation. Of note, 116 patients received a combination containing DRV/r, RAL + other antiretrovirals. ETR and DRV/r plus other ARVs were used in 23 patients. 51 patients received an NRTI-sparing regimen. At the time of this analysis, 32 patients had discontinued prematurely and 251/340 patients had reached week 48. VL and CD4 measurements at week 48 are

available for 186 patients, 80.6% patients achieved a VL < 50 copies/ml (VL < 400 copies/ml: 94.6%), mean CD4 count in these patients (n=185) increased from 402 at baseline to 476 cells/ mm^3 (SD: 262; p <0.001). 10 patients (2.9%) discontinued DRV/r due to adverse events. Virological failure (VL >50 copies/mL at 2 visits) was documented in 10 patients (2.9%). 3 patients were genotyped; primary PI mutations were detected in all 3 patients, DRV-RAMs in none of them.
Conclusions: Overall, Darunavir/r, dosed at 600/100 mg bid in combination with other antiretrovirals, showed good efficacy and safety in treatment-experienced patients in clinical practice.

P29

Week 48 efficacy of 900/100 mg daily of darunavir/ritonavir in treatment-experienced HIV-1 patients with virological success: DARDAR study

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Background: Simplification of antitretroviral treatment (ARV) is particularly important. If darunavir/ritonavir (DRV/r) can be used at a 800/100mg once a day (q.d.) on patients with a wild-type virus, it is recommended at a 600/100mg twice a day (b.i.d.) on pre-treated patients. POWER study suggests the similarity of efficiency of the 800/100 mg q.d. and 600/100 mg b.i.d. in patients with a minimal number of DRV resistance mutations.
Objectives: Evaluate the capacity of DRV/r(900/100mg) q.d. to maintain viral load(VL) indetectability at W24, after switch from DRV/r 600/100mg bid, in virologically supressed pre-treated HIV-1 patients.
Methodology: This observational study included 45 patients if they had a VL<50copies/ml and a steady treatment associating DRV/r 600/100 mg b.i.d. with INTI and/or INNTI. A genotypic test was perform on the plasmatic HIV-1 RNA, on the last detectable VL (>50cp/ml) before starting DRV, and in case of virological failure. The follow up is done at D0, W4/W12/W24/W36 and W48 including VL measure, CD4 cells count, residual plasmatic concentrations of darunavir and ritonavir. Virological failure was defined as two consecutives VL >50cp/ml at a minimal 15 days interval. The primary endpoint was the proportion of patients with a VL <50cp/ml at W24.
Results: Between 02/2008 and 02/2009, 45 patients were included with an anterior ARV treatment of 13[1,20] years, with exposure to 3 ARV classes among 34(75%) patients and a previous failure ≥ 2 PI for 20(44%) patients. CD4 cell count was 478/mm^3 [317-560]; nadir CD4: 93/mm^3 [39-165]. They were treated by DRV/r b.i.d. since 10[3;44] months. DRV/r was associated with: 2 INTI (76%), 3 INTI (8%), 2 INTI/1INNTI(5%). 93% plasmatic RNA genotypic tests were amplified. Five patients had ≥ 3 DRV impacting resistance mutations, six patients 2 mutations, and nine patients 1 mutation. The proportion of patients with VL<50cp/mL[IC95] at W24 was 93%[81-98] and 91%[78-97] at W48, in ITT and PP analysis.
Three virological failures were observed at W12 and one at W48. For 1 patient, 2 primary PI mutations (I50V and L33F) were observed.
Conclusion: This study suggests that DRV/r can be used once a day even for patients with a previous IP failure. This approach is particularly important for the once daily use of combination INTI. It also enables a reduction of the ritonavir dose.

P30

Efficacy and safety of lopinavir/ritonavir (LPV/r) in antiretroviral-experienced subjects infected with different subtypes of HIV-1

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Purpose: There are three classes of HIV-1 based on diversity of the viral envelope: M (major), O (outlying) and N (new). The M group is subclassified into nine major subtypes including A—D, F—H, J and K, as well as several recombinant forms. There is a growing need to evaluate antiretroviral (ARV) treatment in these diverse subtypes.
Methods: M06-802 was an open-label, global, 48-week phase III trial. 599 ARV-experienced, HIV-1-infected subjects were randomized 1:1 to receive LPV/r 800/200mg QD or 400/100mg BID with ≥2 investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors. Classification of

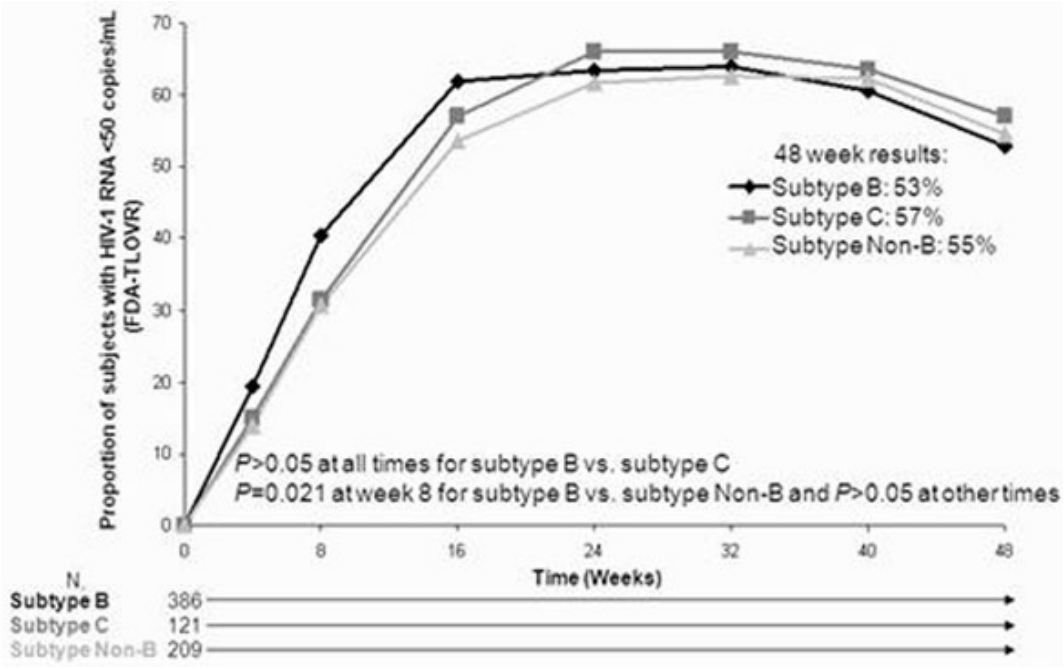

Figure 1 (abstract P30) Percent of subjects infected with different subtypes that have plasma HIV-1 RNA <50 copies/mL, FDA-TLOVR analysis

HIV-1 viruses by subtype was determined by analyzing sequences of the *env* gene for this post hoc analysis.
Results: Of the 595 subjects with available sequence data, 386 (65%) were infected with subtype B, 121 (20%) were infected with subtype C, 88 (15%) were infected with another subtype. Subjects infected with subtype B were more likely to be male (75%), white (56%), and living in North America (N.A.) (52%), while subjects infected with subtype C were more likely to be female (56%), black (83%), and living outside of N.A. or Western Europe (W.E.) (99%). Subjects infected with other subtypes were more likely to be male (56%), white (88%) and living outside of N.A. or W.E. (82%). The proportion of subjects with subtype B responding to treatment at week 48 as analyzed using the FDA-TLOVR method (53%) was similar to that of subtype C subjects (57%, P=0.465) and non-B subtype subjects (55%, P=0.731) (Figure 1). The prevalence of moderate/severe treatment-related adverse events was similar across subtypes. There was a nonsignificant trend to more frequent emergence of new protease resistance mutations in subtype B (18%) vs. subtype C (8%, P=0.277) or non-B (7%, P=0.088) subjects; however, subtype B subjects were more likely to have previously been treated with PIs.
Conclusion: LPV/r demonstrated similar efficacy and safety among subjects infected with different HIV-1 subtypes.

P31

Long-term efficacy and safety of atazanavir/ritonavir treatment in a real-life cohort of treatment-experienced HIV patients

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Purpose of the study: Atazanavir (ATV)-based regimens have demonstrated efficacy and safety in both ARV-naïve and -experienced patients. However, few reports have assessed effectiveness beyond 2 years. The aim of this study was to describe the long-term outcomes of ATV/r containing regimens in ARV-experienced patients in a clinical setting.
Methods: Non-comparative, retrospective, observational study which collected data from 3 European databases (France-DatAids, Germany-KompNet, Sweden-InfCare). Clinical data for ARV-experienced adult patients who started an ATV/r-based regimen between October, 2004 and March, 2007 were extracted every 6-months (maximum follow-up 5 years). Primary endpoint was the proportion of patients remaining on ATV treatment by baseline HIV-1 RNA (< 500 or ≥ 500 c/mL). Secondary endpoints included virologic response and reason for discontinuation. The duration of treatment and time to virologic failure were analyzed using the Kaplan-Meier method.
Summary of results: Data for 1294 ARV-experienced patients (prior ARV exposure: mean, 5.70 years) were analyzed. Patients were predominantly male (74%); median age 43 years (min, max: 18, 85); 75% had prior exposure to PIs (mean: 3.5 years). At baseline (BL), 56% of patients had HIV-1 RNA < 500 c/mL and 37% had < 50 c/mL. The estimated proportion of patients remaining on ATV during the follow-up period was 52% (median duration of treatment: 3.7 years); 54% for patients with BL HIV-1 RNA < 500 c/mL and 50% for those with BL HIV-1 RNA > 500 c/mL. The estimated probability of discontinuation was 21% during the first year and decreased at each subsequent 1-year treatment interval. Time to virologic failure is presented in Figure 1.
The most frequent reasons for discontinuation were "unknown" (32%), adverse events (25%), patient withdrew consent (13%) and lack of efficacy (11%). Hyperbilirubinemia was reported as reason for discontinuation in 12 patients. No unexpected changes in metabolic parameters were observed and renal AEs were reported rarely (1.9/100 patient-years).
Conclusions: In real life setting, ATV/r-based regimen demonstrated sustained virological efficacy in an ARV-experienced population including patients with previous virological failure. After long-term treatment a high proportion of patients remained on an ATV regimen and no unexpected AEs were observed.

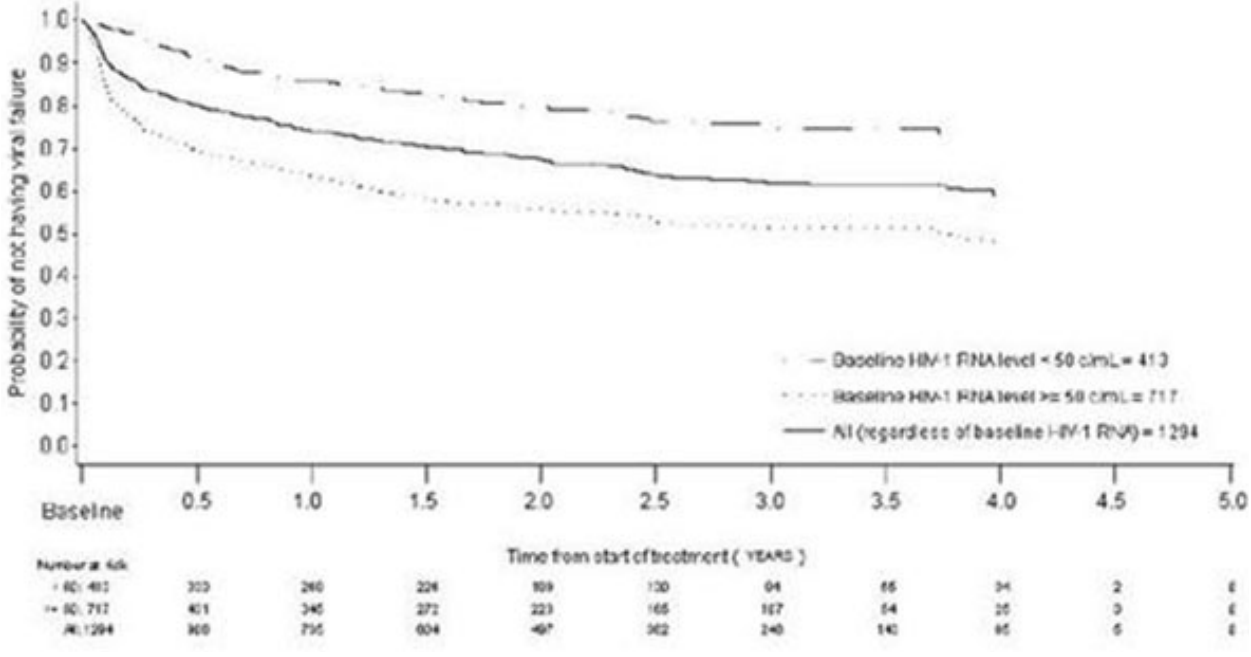

Figure 1 (abstract P31) Time to virologic failure (two consecutive HIV-1 RNA ≥ 50 c/mL or one HIV-1 RNA ≥ 50 c/mL followed by discontinuation)

P32

Integrase inhibitor-based treatment in clinical practice

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Background: Raltegravir (RAL) is a the first compound of a novel class: integrase inhibitors. Aim of our study was to evaluate efficacy and safety of RAL based regimen.
Materials and methods: We proceeded to retrospective analysis from patients(pts) referring to our service. We searched our databases for epidemiological, clinical, immunological and virological issues. Moreover we recorded HCV and HBV status. We focused our attention on the reason of ARV switching, duration of ARV before RAL introduction, immunological gain, virological suppression and tolerability of the prescribed regimen. We followed side effects in order to define safety of prescribed regimen.
Results: We enrolled 70 pts. (male 53:female 17), according to CDC 1993 they were classified as A(12); B(32);C(26). Median age was 49 years, 42 pts were HCV-positive and only 4 presented an active HBV coinfection. Risk factors for HIV infection resulted: injective drug abuse(33) homosexual(20) and heterosexual(17)exposition. They were switched to RAL therapy for drug resistance(39)(DRR); regimen simplification(7) or drug toxicity (24). Most of patients presented multiple drug failures to ARV therapy (almost two different classes resistance). Median follow up was with RAL is 9 months and median extent of ARV before RAL was 9 years. Among DRR. 29 were coming from a PI failure whereas 9 from NNRTI based regimen and one from 3TC monotherapy. The most represented drug associated in new ARV regimen was DRV/rtv (42) followed by etravirine (12) and maraviroc (10).
We collected data of immune and virological response after 3 and 6 months, so at 6 months 59 pts. (84.3%; 71.8% in DRR) presented undetectable(<20) viral load and a medium CD4 gain of 89 cc/ml(90 cc/ml in DRR). No relevant side effects were observed.
Conclusions: Pts. treated with RAL based therapy presented a good outcome, most of them achieve (after 6 months) virological suppression and immunological recovery. In our case list, darunavir/rtv and RAL obtained the best results with no relevant side effects. So more studies are needed to confirm that RAL based ARV could be very efficacious and safe even in long term follow up period.

P33

Switching to a 'nuke-sparing' raltegravir/atazanavir combination: an individualised approach

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Introduction: The success of HIV treatment is limited by tolerability/toxicity of ARVs and patient adherence remains paramount to achieve viral suppression. Several small studies have investigated the combination Raltegravir and Atazanavir. This is particularly attractive to exclude NRTIs and ritonavir in metabolic toxicity. Optimum dosing has yet to be decided however recent data from SPARTAN suggests once daily regimens are associated with raltegravir resistance.
Objectives: To assess HIV virologic control in patients switched to RAL/ATZ. To compare metabolic parameters before and after switch.
Methods: We retrospectively identified patients RAL/ATZ from pharmacy database. Using medical notes and lab results system, we recorded the HIV-1 VL and lipid profiles pre- and post- switch. TDM, hepatitis status, drug resistance and treatment experience were also recorded.
Results: We identified 11 patients on RAL/ATZ, 9 male. At switch, 1 patient had a detectable VL (582 copies/mL), all other patients were undetectable. At the most recent appointment all patients had an undetectable viral load. The mean number of previous regimens was 5; no patient commenced the regimen with known PI resistance. In 5 patients other ARVs were included, and in 6 RAL/ATZ were used alone. Therapeutic drug levels of raltegravir and atazanavir were measured in 9/11 patients and the predicted trough levels for both raltegravir and atazanavir were greater than the minimum recommended concentration. There was a reduction in total cholesterol and triglycerides post switch and a trend towards reduction in LDL-cholesterol and total cholesterol: HDL ratio. Two patients were lost to follow up and three patients discontinued the combination. The reasons for discontinuation: to avoid drug interactions pre-renal transplant, to aid adherence (once daily regimen) and presumed raltegravir intolerance (anxiety and sleep disturbance).
Conclusions: A switch was made when 10/11 patients were suppressed and required therapy change because of another reason. All patients maintained a viral load of less than 50 copies/ml (7-102 weeks). The combination was well tolerated and there was a trend towards improved lipid parameters observed. In the absence of resistance, this combination shows promise in terms of prolonged virologic efficacy, tolerability and an improved metabolic profile.

P34

Portuguese cohort: raltegravir with optimized background therapy (OBT) in multiple-experienced HIV1- and HIV2-infected patients

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Purpose: The efficacy and safety profile of raltegravir in the clinical setting were evaluated retrospectively in HIV Portuguese pts treated with raltegravir since the implementation of Early Access and Compassionate Use Program.
Methods: Pts from 11 Hospitals were enrolled between Mar07-Dec08. Three different subgroups of pts were analyzed (Group1-Pts multi-experienced HIV-1 at virologic failure, Group2-Pts virologically suppressed who needed to change ARV due to toxicity, including T20 replacement and Group3-HIV2 infected pts with failing therapy). OBT was selected based on previous resistance test and prior treatment history. Demographics, co-infections, no. of previous ARV regimens, OBT, adverse reactions and discontinuations were analysed. Immunologic and virological responses were evaluated at baseline, weeks 24 and 48. The primary efficacy endpoint was the proportion of pts with RNA<50 cop/mL and change in TCD4 at weeks 24 and 48. Statistical analysis was performed by SPSS®v18.0.
Results: A total of 151 pts were eligible for the analysis (107 in Group1, 24 in Group2 and 20 in Group3), 76% were male with a mean age of 47 years, median TCD4 count of 180.0 cells and RNA of 4.3 log10cop/mL. Fifty-one (34%) pts were HCV/HBV co-infected. Median no. of previous ARV treatments was 5. The proportion of pts with RNA<50 cop/mL at week24 (week48) was 70% (69%) in Group1, 100% (100%) in Group2 and 85% (80%) in Group3. Overall median increase in TCD4 count at week24 was 72.0 cells (83.5 in Group1, 31.5 in Group2 and 66.0 in Group3) and at week48 was 99.0 cells (124.5 in Group1, 63.0 in Group2 and 50.0 in Group3). In Group1, 80 pts had PIs in OBT and 76% of these obtained RNA<50 cop/mL vs. 48% without PIs (p=0.006), at week48. In Group3, 13 pts had PIs in OBT and 69% of these obtained RNA<50 cop/mL vs. 100% without PIs, at week48. Adverse reactions occurred in 11 pts but none led to discontinuation. 18 pts discontinued:13 therapeutic failures, 2 lost follow-up and 3 deaths (not therapy related). In pts with hepatic abnormalities (AST/ALT) co-infected presented a lower percentage of G3 than no co-infected (67% vs. 83%)/(75% vs. 83%).
Conclusions: In multiple experienced HIV-infected pts with limited treatment options, raltegravir+OBT has good efficacy as demonstrated in obtaining RNA<50 cop/mL and increasing median TCD4 cell count with a "clean" safety profile namely in co-infected pts. Contrary to HIV1 pts, in HIV2 pts the inclusion of PIs in OBT did not reveal better efficacy.

P35

Reasons for using and efficacy of raltegravir in salvage regimens without protease inhibitors in clinical practice

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Purpose of the study: The efficacy of raltegravir (RAL) in salvage regimens without protease inhibitors (PI) has not been evaluated in randomized trials, and information about its efficacy and reasons for its initiation in cohort studies has received scant attention. In some particular scenarios physicians may be forced to use RAL without PI due to advanced protease resistance, toxicity or patient refusal.
Methods: Systematic multicenter search of databases in University-affiliated hospitals in Spain to identify all pre-treated patients with limited options due to resistance or intolerance to multiple antiretrovirals, starting a regimen including raltegravir and not a PI for any given reason, with a baseline plasma HIV-1 viral load (VL) >500 copies/mL. Primary endpoint: proportion achieving a VL<50 c/mL at 48 weeks.
Results: We identified 55 patients, 69% male, with a median age of 45,8 y., 40% IVDU, 45% with chronic hepatitis C, 40% in stage CDC C. Fourteen (25%) were diagnosed of dyslipidemia. 19/20 (95%) patients with results available had a CCR5 tropism. The main reasons for initiating a regimen with RAL and without PI were advanced protease resistance (44%), toxicity (15%), pharmacokinetic interactions (11%), and patient refusal (7%). The most frequently used drugs on board were tenofovir in 43 (78%) patients, maraviroc in 16 (29%) patients, and etravirine in 11 (20%). Eight (14%) patients did not use any nucleoside analogue, all of them due to complete resistance or toxicity. At 48 weeks, 66% of them had an HIV-1 VL < 50 c/mL. There was a significant increase in the median CD4 cell count from 257 cells/<micro>L at baseline to 415 cells/μL at 48 weeks (p=0.01), with only 19% of patients remaining with <200 CD4 cells/μL at 48 weeks. Virological failure was documented in 4 (7%) patients. There were no unexpected adverse events related to RAL when used without PI.
Conclusions: Salvage regimens including RAL but not PI may be used in selected patients mainly due to advanced protease resistance, toxicity, pharmacokinetic interactions or patient refusal to PI. The efficacy of raltegravir when used with a background regimen without a protease inhibitor is high, but the inclusion of 2 further active drugs must be strongly pursued. This cohort analysis supports further study of RAL with novel combinations in this difficult-to-treat population.

P36

Use of once-daily raltegravir-based HAART in HIV-infected injection drug users

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Purpose: Within a prospective observational study, we measured adjustment of methadone doses and responses to treatment after once-daily raltegravir (RGV)-based highly active antiretroviral therapy (HAART) was initiated in injection drug users (IDUs).
Methods: We evaluated HIV-infected IDUs attending an inner city clinic in Vancouver who were receiving RGV-based HAART and methadone within a directly observed therapy program. Follow-up was according to clinical standards, with changes in methadone dose being made as required to achieve clinical stabilization within the first month of HAART. The change in methadone dosing associated with the initiation of HAART was calculated as the difference between the post- and pre-HAART methadone doses. The most recent on treatment CD4 cell count and HIV plasma viral load were used to evaluate HAART efficacy after initiation of therapy.
Results: The study included 34 subjects (9 female) with a median follow-up period of 16.5 months. All patients were treatment experienced and co-infected with hepatitis C virus. Most patients received RGV-based HAART along with emtricitabine and tenofovir (n=16) or lamivudine and abacavir (n=9). At baseline, the mean methadone dose, mean CD4 cell count and median plasma viral load were 97.4 mg/day, 286 cells/mm^3 and 243 copies/mL, respectively. At month 3, the mean methadone dose was 97.9 mg/day with the observed mean methadone dose change from baseline being 0.4 mg/day (p=NS). In these patients, 7 (21%) required increases, 8 (24%) required decreases, while 19 (56%) required no change in daily methadone dose from baseline. At most recent follow-up, the mean CD4 cell count was 355 cells/mm^3 while virologic suppression (HIV RNA <50 and <400 copies/mL) was achieved in 23 (68%) and 31 (91%) of patients receiving RGV-based therapy.
Conclusions: Lack of drug interactions with methadone and improved immunologic and virologic responses support the use of once-daily RGV-based HAART in this vulnerable population.

P37

Temporal trend of the first prescription of nevirapine: the ANRS CO3 Aquitaine Cohort, 1997-2008

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Purpose: Nevirapine (NVP) is commonly prescribed in antiretroviral therapy (ART). We aimed at describing the evolving characteristics of the patients receiving a first prescription of NVP over 12 years in the ANRS CO3 Aquitaine Cohort, a French hospital-based HIV1-infected cohort.
Methods: All HIV1-positive patients of the participating clinic wards, aged over 13 and giving informed consent are included in the cohort. Patients receiving a first prescription of NVP between 1997 and 2008 are described at baseline and during follow-up according to their treatment status, ART-naïve or not. Chi-square test, signed rank Wilcoxon test, Mc Nemar test and log-rank test are used for comparisons.
Results: Among 5,566 cohort participants, 1,775 received a first NVP-based regimen during the study period, and 277 (16%) of them were naïve of ART at the time of NVP introduction. Pre-treated patients received ART prior to NVP for a median duration of 47 months (IQR: 27-76). The ratio pre-treated: naïve patients increased from 4.7:1 in 1997-1999 to 14.5:1 in 2006-2008, whereas, respectively 476 and 47 patients on average initiated NVP each year in these periods.
At the time of NVP initiation, the median age of the ART-naïve group was 36 years, vs 39 years in the pre-treated one (p<0.001). Women accounted for 29% of both groups. The naïve patients were rarely at the AIDS stage 4.7% vs 23.4% in the pre-treated group (p<0.001). The median CD4 cell counts in the naïve and pre-treated groups were 365 and 390 cells/mm^3, respectively (p=0.32), and the median plasma HIV RNA loads were 19,000 and 2,200 copies/mL in naïve and pre-treated patients, respectively (p<0.001).
Pre-treated patients were more likely to interrupt the NVP-based treatment (p<0.001). Within 6 months after NVP initiation, 61 (22%) ART-naïve patients and 394 (26%) pre-treated patients interrupted NVP. After one year these proportions were 32% and 41%, respectively. Clinical or viro-immunological failure represented 40% of the causes of NVP interruption in pre-treated patients and 18% in naïve patients. Drug toxicity represented respectively 21% and 25% of the causes of NVP interruption in these groups.
Conclusion: The number of annual initiation of NVP based ART has decreased in the Aquitaine Cohort until 2005, and is stable since then. After one year of treatment, 40% of the patients had interrupted the NVP-based regimen. The main causes of discontinuation were clinical or viro-immunological failure and drug toxicity.

P38

Long-term follow-up of HIV-infected patients in salvage therapy with raltegravir plus optimized background regimens: a multicentre Italian experience

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Background: Raltegravir is the first integrase inhibitor to get into the clinic and the MK-0518 Expanded Access Program (EAP) started in Italy in 2007, so that most patients now have an observation period of two years. Up to date a few studies have described the durability of raltegravir-containing regimen with a follow up of 96 weeks [1].
Methods: Patients from the MK0518 EAP were followed-up prospectively since enrolment in the study. Clinical and laboratory data were collected every 2 - 4 months after commercial availability.
Results: Out of 250 patients enrolled in the MK0518 EAP in our centres, 229 are still on the same regimen. The mean follow up was 80 weeks. At the time of present analysis (96 weeks) 133 patients were evaluated. Eighty-nine% of these had HIV-RNA < 50 Cp/mmc. Two patients temporarily stopped therapy, one developing the integrase 72I mutation plus 2 additional RT mutations, and both stably resuppressed the virus with the same regimen. Seven patients discontinued therapy due to virological failure: primary mutations for integrases were detected in all the samples (155H/N, 148H+140S, 143R) in addition to other mutations (157Q, 72I, 73V, 165I, 97A, 163R). Four patients with non-primary mutations detected continued the same therapy maintaining viral replication below 4000 copies/ml, with 1.9 log decrease in HIV-RNA. One patient was lost to follow up, four discontinued due gastrointestinal AEs and one for CK elevation, while eight died during the observation period, 4 of non-Hodgkin's lymphoma (NHL), 1 of acute myocardial infarction, 2 of end stage liver disease and 1 post-transplantation for HCV-related cirrhosis. The immunological gain of the patients who remained on therapy is good in a salvage setting: +230 CD4/mmc.
Conclusions: The MK0518 EAP seems to have contributed in a relevant measure to obtain full viral suppression for two years in most of our salvage patients, with an important immunologic gain and very few adverse events, in a situation were active companion drugs were really difficult to find out (the overall mean GSS was <2). The number of deaths (including NHL that represented the cause of death for 50% of the cases) has not been related to the drug regimen, but more likely to the advanced stage of HIV infection.

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P39

Immunologic impact of maraviroc in clinical practice of a university hospital

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Purpose of the study: Maraviroc (MVC) is one of newest antiretrovirals. Several studies have assessed the impact of MVC on CD4 count, although few have analyzed it in clinical practice. We assessed the immunological impact of MVC in clinical practice in a university hospital.
Methods: Observational, retrospective, and cohort study in adult outpatients taking antiretroviral therapy. We selected two cohorts: the MVC cohort (MVCC), comprising patients who had switched to MVC between 01/05/2008 and 31/07/2009, and the last-generation antiretroviral cohort (LGAC), comprising patients who had switched to darunavir, etravirine, and/or raltegravir during the same period. The primary endpoint was the increase in CD4 count at 48 weeks.
Results: The MVCC included 21 patients and the LGAC 56. Only 18 of the 21 patients were finally analyzed, as 3 patients stopped MVC and did not reach 48 weeks. There were no differences in age (median MVCC, 46.93 years; LGAC, 45.43 years) or sex (MVCC, 66.1% men; LGAC, 61.9% men) between the cohorts. HIV was multidrug-resistant (genotypic resistance to drugs of ≥2 classic families and/or extensive experience with 3 classic families) in 73.2% of LGAC and 95.2% of MVCC (p=0.094). Adherence during the previous year of treatment with MVC was >90% in 85.7% of MVCC and 76.6% in LGAC. There were no significant differences between the cohorts. Raltegravir was included in the regimen in 86% of the MVCC and in 89% of the LGAC. At baseline, viral load was undetectable (defined as <50 copies/ml) in 19% of the MVCC and 51.8% of the LGAC (p=0.02). At the end of follow-up (48 weeks), viral load was undetectable in 90.5% of the MVCC and in 85.7% of the LGAC (p=0.86). At baseline, the mean CD4 count was 362.67 in the MVCC and 365.64 in the LGAC (p=0.96); at the end of follow-up, these values were 507.24 (95% CI, 377.40-637.08) and 462.07 (95% CI, 367.14-556.99) for MVCC and LGAC, respectively, with a mean difference of 45 cells (95% CI, "C126.80 to 217.14). The mean increase in CD4 count was 145 cells (95% CI, 126.80 to 296.17) vs. 96 cells (95% CI, 30.44 to 223.30)
Conclusions: An increase in the immune response was observed in both cohorts at 48 weeks of follow-up. Although the increase in CD4 count was higher in the MVCC, significant differences were not found.

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Short-course intensification with enfuvirtide in virologic failure: impact on intracellular HIV reservoir and on viral tropism (INNOVE study)

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Background: Overall, studies of ART intensification in suppressed patients showed no reduction in HIV reservoir, as assessed by proviral DNA. Limited data about impact of ART intensification are available for failing patients harbouring multidrug resistant viruses. We studied the effects of intensification with enfuvirtide (ENF) on intracellular HIV reservoir and tropism evolution under treatment selective pressure in this clinical setting.
Methods: Innove is a prospective, open-label multicenter study in pretreated patients harboring viruses still susceptible to at least 2 active compounds on genotypic resistance test performed at pre-inclusion. Patients with confirmed virologic failure were randomized to optimized regimen (OBR) plus 12-week short-course intensification with ENF n=14 or only OBR n=15. Genotypic tropism and quantification of HIV-1 intracellular-DNA were determined in total peripheral blood mononuclear cells (PBMC) obtained at baseline, W4, W12 and W24. HIV intracellular-DNA was quantified by a real-time PCR assay (Biocentrics). V3 env sequences were amplified from PBMC HIV-1 DNA and interpreted according to Geno2pheno (10% false positivity).
Results: At inclusion, median plasma HIV-RNA was 4 $\log_{10}$ cp/mL, median CD4 346 cells/mm^3 and patients harbored viruses with a median of 4 INTI-associated resistance mutations (RM), 1 INNTI-associated RM and 9 PI-associated RM. Median HIV-DNA ($\log_{10}$/106 PBMC) was 5.05 at baseline, 4.91 at W24 (4.96 log in OBR and 4.81 log

in ENF+OBR). The decrease being not significant overall nor between groups: median change from baseline to W4 was -0.19 and -0.19 and to W24; -0.09 and -0.29 in OBR and ENF+OBR groups, respectively . At baseline, predominant variants were DM/X4 in 10 patients and R5 in 17 patients. At W24, tropism switches were observed in 6 patients: 1 from DM/X4 to R5 and 5 from R5 to DM/X4. Among these 5 patients with R5-X4 switch, plasma HIV-RNA was <50 cp/ml at W24 in 5/5, none received maraviroc, and 4/5 were randomised in ENF+OBR group.
Conclusion: In patients with therapeutic failure and harboring resistant viruses with a GSS≥2, a 12-week short-course intensification with enfuvirtide did not yield any impact on intracellular reservoir. In this intracellular compartment, R5-X4 switch can occur despite achievement of maximal virologic suppression with enfuvirtide-containing regimen.

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Efficacy of once daily darunavir/ritonavir 800/100 mg in PI/r-experienced HIV-1 infected patients with suppressed HIV-1 replication: the RADAR study

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Background: Once-daily darunavir/ritonavir 800/100 mg is licensed for first-line treatment and data are available in treatment-experienced patients with no resistance-associated mutations to darunavir. We designed an investigator study to evaluate the switch to once-daily darunavir/ritonavir 800/100 mg in treatment-experienced patients with suppressed HIV-1 replication on a twice-daily ritonavir-boosted protease-inhibitor (bid PI/r) containing regimen, i.e. in a setting where genotypic resistance test cannot be performed.
Methods: In this open-label, noncomparative, multicenter study, patients on a bid PI/r-containing triple combination, with suppressed viral replication, were switched to once-daily darunavir/r 800/100 mg containing triple combination. The primary endpoint was the proportion of patients with plasma HIV-RNA< 50 cp/ml 24 weeks after the switch. Detailed darunavir pharmacokinetic evaluation was performed at Week 4 (W4) and measurement of HIV-RNA in seminal plasma at baseline and W48 in a subset of patients.
Results: 85 patients were enrolled. All had HIV-RNA<50 cp/ml at screening with a median of 478 CD4/mm3 (range 40-1559) and pre-exposure to a median of 2 PI (1-5). 61 patients were currently on lopinavir/r, 18 on fosamprenavir/r, 4 on saquinavir/r and 2 on indinavir/r. At baseline, 15/16 patients had a seminal HIV-RNA< 100 cp/ml and 125 cp/ml for the remaining one. By intent-to-treat analysis (missing=failure), 78/85 patients (92%, CI95 [83;96]) maintained an HIV-RNA<50 cp/ml at W24. 7 patients experienced protocol-defined treatment failure between baseline and W24: 2 had confirmed viral rebound (88 and 70 cp/ml), 1 discontinued study treatment at W4 for adverse event, 3 withdrew their consent and 1 was lost to follow-up. By on-treatment analysis, 78/80 patients (97%, CI95 [91;99]) maintained an HIV-RNA<50 cp/ml at W24. At W4, the median area under the darunavir plasma concentration-time curve measured in 11 patients was 61 380 ng.h/ml (IQR 25-75% 42 094-97 313), darunavir median trough concentration 1340 ng/ml (907-1830) and darunavir half-life was 12.2 h (8.3-13.7). Tolerability of once-daily darunavir/r 800/100 mg was excellent.
Conclusion: In PI/r-experienced patients with suppressed viral replication on a bid PI/r-containing regimen, switching to once-daily darunavir/r 800/100 mg containing regimen was able to maintain suppression of viral replication and was safe in this setting where genotypic resistance test could not be performed.

P42

Switching to Atripla (EFV/FTC/TDF) from Kivexa (ABC/3TC) plus EFV leads to improved perceptions of treatment: results from the ROCKET 1 study

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Purpose of the study: The aim of this analysis was to examine the impact of switching to ATR from KVX+EFV on patients perceptions of treatment including the following: treatment intrusiveness, treatment satisfaction and HIV/HAART related symptom experiences; self-reported adherence was also assessed.
Methods: Data was collected as part of ROCKET 1, a Phase 4, open-label, randomised, UK, multicentre, controlled study. At baseline 159 subjects stable on KVX+EFV with raised cholesterol were randomized 1:1 to one of two treatment groups: Treatment Group 1 (TG1): switch to ATR; Treatment Group 2 (TG2): continuation of previous stable regimen of KVX+EFV. At week 12, subjects in TG2 were switched to ATR. Treatment in both groups continued to study week 24. Subjects completed questionnaires assessing treatment intrusiveness, satisfaction with treatment, and symptom experiences at baseline and at weeks 4, 12, 16, and 24. Adherence over the preceding 30 days was measured using a visual analogue scale.
Summary of results: Following the switch to ATR, 69% of subjects in TG1 indicated that they preferred their current regimen to their previous antiretroviral regimen. At week 12, between group comparisons showed those who switched to ATR perceived their treatment to be more convenient ($p<0.05$) and tolerable ($p<0.05$), reported fewer symptoms ($p<0.0001$) and were less bothered by side-effects ($p<0.005$) than those who remained on KVX+EFV. There was no difference between groups in reported adherence: 87% of those who switched to ATR and 86% of those who remained on KVX+EFV reported taking at least 95% of their antiretroviral medicines over the past 30 days ($p>0.05$). Those who switched to ATR were more likely than those who remained on KVX+EFV to experience a reduction in symptoms ($p<0.0001$) and treatment intrusiveness ($p<0.05$) between baseline and week 12.
Conclusions: These findings indicate that switching to ATR from KVX+EFV leads to improved perceptions of treatment among people who have raised cholesterol. These findings complement those from the primary analysis of ROCKET 1 showing improvements in lipid profiles among subjects who switched from KVX+EFV to ATR.

P43

Long-term outcomes of switching to fixed-dose abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC): 3-year results of the BICOMBO study

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Background: Once-daily fixed-dose combinations ABC/3TC and TDF/FTC are the preferred backbones in Europe [1]. Long-term (>2 years) efficacy and safety of these compounds in simplification strategies are unknown.
Methods: 333 HIV-1-infected adults on 3TC-containing triple regimens with <200 copies/mL for at least 6 months had their NRTI backbone randomly switched to either ABC/3TC or TDF/FTC. Pre-planned results at 1 year have been already published [2]. Treatment failure (defined as

virological failure, discontinuation of study therapy, withdrawal of consent, lost to follow-up, progression to AIDS, or death), virological failure (defined as confirmed plasma HIV-1 RNA >200 copies/mL), adverse events, and changes in CD4 cells, fasting plasma lipids, glomerular filtration rate (GFR) (Cockcroft-Gault), and transaminases at 3 years were compared between arms.

Results: Treatment failure increased from 32 (19%) to 58 (35%) patients on ABC/3TC and from 22 (13%) to 61 (37%) patients on TDF/FTC at 1 and 3 years, respectively (HR for ABC/3TC treatment failure at 3 years 0.99, 95% CI 0.69-1.41). The most common reasons for treatment failure at 3 years in both arms were lost to follow-up/withdrawal of consent (68 patients, 20%) or discontinuation of study drugs for reasons other than adverse events (15 patients, 5%). Total discontinuations due to adverse events increased from 17 at 1-year to 18 patients at 3-years on ABC/3TC and from 9 at 1-year to 10 patients at 3-years on TDF/FTC. Total virological failures increased from 4 at 1-year to 6 patients at 3-years on ABC/3TC while no patient on TDF/FTC developed virological failure at 1-year and through 3-years (HR for ABC/3TC virological failure at 3 years 3.59, 95% CI 0.77-6.42). Change from baseline (mg/dL) in triglycerides (+1 vs -29, P=0.008), total cholesterol (+12 vs -12, P<0.001), LDL-cholesterol (+1 vs -1, P<0.001), and HDL-cholesterol (+3 vs -2, P<0.001) were increased in patients on ABC/3TC compared with decreases in patients on TDF/FTC, although total-to-HDL cholesterol ratio remained almost identical in both arms. There were no significant changes in GFR or transaminases in each arm at 3-years.

Conclusion: From the 1-year analysis, we observed two additional virological failures in patients on ABC/3TC; there were no virological failures in patients on TDF/FTC over 3 years. Through 3 years long-term safety/tolerability was very good. Differential lipid effects between arms were maintained at 3 years.

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P44

Tolerance and durability of abacavir/lamivudine (ABC/3TC)-containing regimens: results from a large prospective French cohort

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Methods: Patients (pts) were selected from the Dat'AIDS French prospective cohort if they were prescribed an ABC/3TC containing regimen for the first time between 01/01/2004 and 31/12/2007 and were still actively followed on 31/05/2008 as to ensure sufficient follow-up. All causes of treatment discontinuation were recorded, as well as immuno-virological data and cardiovascular events (CE) during follow-up.

Results: Among the 1704 pts included in the study (male 70%, mean age 43 years, HBV or HCV co-infection 24.1%) 407 (24%) were antiretroviral (ARV) naïve, 696 (41%) were virologically controlled on ARV treatment (switch), and 601 (35%) were on treatment with detectable VL (failure) at time of ABC/3TC initiation. Previous treatment with 3TC was noted in 92% of the pretreated pts. With a median duration of follow-up of 496 days, the population represents 2636 pts-year.

Overall 565pts (33%) discontinued ABC/3TC combination during follow-up (36%, 24%, and 42% of the naive, switch and failure groups, respectively). Reasons for discontinuation were poor tolerance in 41% of the cases, including suspected hypersensitivity (HSR) in 4% of the overall population, treatment failure in 20%, and other causes in 39%. This distribution was not different if pts received either a NNRTI (20% of the pts) or a boosted protease inhibitor (46%) in their regimen. Median time to discontinuation was 4.3 years overall and less than one month in case of suspected HSR. Discontinuation for bad tolerance was observed in 38%, 54%, and 35% of the naïve, switch and failure populations respectively, whereas treatment failure was responsible for discontinuation in 15%, 10%, and 29% of the same populations. Major CE were reported in 21 cases (0.08% py). Death was recorded in 27 cases, 9 deaths being AIDS related, 6 related to liver diseases, 6 to cancer, 2 to vascular accidents (1 cardiac, 1 neurological), 1 accidental, and 3 unknown. At M24, probability of still receiving ABC/3TC was 62%, 77%, and 60% respectively for the defined groups, and VL on treatment was below detection for 86%, 90%, and 71% of them, respectively.

Conclusion: In this population of pts who received ABC/3TC containing regimens before HLA screening was routinely available, treatment was maintained with virological success for more than 2 years. Poor tolerance was the main reason for early discontinuation, and was not different if the pts received either NNRTI or boosted PI in their regimen. CE were rare.

P45

48-week efficacy and safety of transitioning virologically stable HIV-1 patients from nevirapine IR 200 mg BID to nevirapine XR 400 mg QD (TRANxITION)

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Background: Wk 24 TRANxITION study data showed patients transitioned from immediate release nevirapine (NVP IR) twice daily (BID) to NVP extended release (NVP XR) once-daily (QD) demonstrated non-inferior efficacy to patients continuing on IR NVP BID [1]. Similar safety was reported for NVP XR and NVP IR in the VERxVE study [2][2]. Wk 48 efficacy/safety data from TRANxITION study are presented here.

Methods: Open label, randomized (2:1), non-inferiority, parallel group study comparing NVP XR 400 mg QD with NVP IR 200 mg BID in HIV-1 patients >18 years receiving IR NVP plus one of three NRTI combinations, with viral load (VL) <50 copies/mL. Patients remained on their previous background therapy for treatment duration. Sustained virologic response (VL <50 copies/mL) was assessed at Wk 48 using a time-to-loss of virologic response (TLOVR) algorithm.

Table 1 (abstract P45)

Parameter	NVP XR QD (N=295)	IR NVP BID (N=148)	Difference (95% CI)
Virologic response (VL <50 copies/mL, TLOVR-FAS), n (%)	261 (88.5)	130 (87.8)	0.6 (-5.9, 7.1)*
CD4+ count cells/mm3 (LOCF), mean (SD)	52.1 (140.5)	81.6 (138.2)	-
AEs, n (%)	255 (86.4%)	108 (73.0%)	-
DAIDS Grade 3-4	19 (6.4%)	9 (6.1%)	-
SAEs, n (%)†	30 (10.2%)	12 (8.1%)	-

*Based on Cochran's statistic †None drug related, FAS = full analysis set; AE = adverse event; SAE = Serious adverse event

AEs were mostly mild-moderate in both groups with a higher reported rate of gastrointestinal AEs in XR. The proportion of patients with DAIDS Grade 3/4 AEs was similar in the XR and IR groups.

Results: 426 patients completed 48 wks of treatment. 94.9% of NVP XR and 91.9% of NVP IR patients. Mean baseline CD4+ counts: 557.7 cells/mm^3 and 569.7 cells/mm^3, respectively. 48 Wk data are reported in Table 1. Non-inferiority of virologic suppression was achieved using a TLOVR and snapshot analysis.
Conclusions: At Wk 48, non-inferiority between the NVP XR 400 mg QD and NVP IR 200 mg BID groups was sustained. No unexpected AEs were observed at Wk 48. These data support transition from NVP IR to NVP XR in patients stable on the former formulation.

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P46

Lopinavir to atazanavir or darunavir switch in HIV-1-infected patients with dyslipidemia: an observational study

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Background: Antiretroviral therapies including lopinavir (LPV) are frequently associated with dyslipidemia. Atazanavir (ATZ) and darunavir (DRV), currently recommended new boosted protease inhibitor, seems to have a better lipid profile than LPV, respectively in the Castle and Artemis study.
Purpose of study: An observational study was conducted to evaluate the benefit of switching LPV to ATZ or DRV on the lipid results, and to compare the potency of DRV and ATZ to enhance the lipid profiles.
Methods: Patients treated with LPV with undetectable viral load since 6 months were switched to ATZ or DRV if they have low density lipoprotein (LDL)>1.6 g/l with no other cardiovascular risk, LDL>1.3g/l with at least 1 cardiovascular risk, or high density lipoprotein (HDL)<0.35mmo/l. None of the patients had an additional lipid-lowering treatment since 3 months, and others antiretroviral treatment wasn't modified.
Results: Forty two patients were included (12 females and 30 males), mean age 45.7 years (25-65). At baseline mean (SD) triglyceride (TG) level was 2.50g/l (1.64), total cholesterol (TC) 2.14g/l (0.51), LDL 1.23g/l (0.42) and HDL 0.48g/l (0.17). The two groups (26 ATZ and 16 DRV) were not different at baseline for weight, body mass index, CD4, TG, TC, LDL and HDL. At month 12, none of the 42 patients had virological failure but 1 patient in the DRV group had his treatment switched to Atripla® for simplification. There was a significant decrease in TG and TC, -0.54g/l (1.06) ($p<0.01$) and -0.15g/l (0.41)($p<0.05$) respectively [mean (SD)]. In ATZ and DRV group, the variation was respectively -0.33g/l (1.11) and -0.91g/l (0.89) for TG ($p=0.08$), -0.17g/l (0.45) and -0.12g/l (0.36) for TC ($p=0.75$), -0.08g/l (0.37) and +0.04g/l (0.41) for LDL ($p=0.47$), +0.01g/l (0.11) and +0.03g/l (0.10) for HDL.
Conclusion: In this observational study, switching LPV for ATZ or DRV enhance the lipid profile. DRV has a trend to reduce TG level more than ATZ.

P47

Switch to once or twice daily unboosted atazanavir in a cohort of stable HIV patients: strong differences in drug exposure and virological outcome

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Purpose of the study: Switch to once daily unboosted (u) atazanavir (ATV) is an attractive option for HIV-infected patients with undetectable viral load, due to its convenience and favorable metabolic profile. However, due to a large interindividual variability, increased risk of inadequate ATV plasma concentrations (ATVc) and virological failure (VF) may be observed. Dividing the daily dose in a twice a day (BID) regimen could increase ATVc and improve virological success.
Methods: In a prospective observational cohort of HIV-infected patients, all individuals with undetectable viral load who were switched to uATV during at least one month were retrospectively selected. ATVc were measured by a validated HPLC in all patients at least two weeks after the initiation of ATV. ATVc was considered inadequate when trough concentration was below 0,150 mg/L. Patients with once (400 mg QD) versus twice daily (200 mg BID) uATV were compared.
Summary of results: From 2002 to 2009, 58 patients who received a total of 69 uATV based-regimens (27 QD and 42 BID regimens) were included. At the start of uATV, patients received a median duration of 9 years (IQR 4-11) of antiretroviral therapy. The mean exposure time of uATV was 16 months. Clinical characteristics and comedications (including tenofovir) were similar in the two groups. ATVc was inadequate in 17 (63%) patients in the QD group versus 4 (9%) patients in the BID group ($p<0.001$). During the follow up, VF happened significantly more frequently in the QD group than in the BID group (6 [22%] versus 1 [2%]; $p=0.012$). VF or low ATVc lead to treatment discontinuation in 10 (37%) QD regimens versus 4 (9%) BID regimens ($p=0,06$). No other significant differences were detected in the two groups.
Conclusions: Despite possible bias due to the observational study design, strong differences were detected in plasma drug exposure and virological outcome in our study. When a switch to uATV is proposed in HIV-controlled patients, BID would be preferred to QD.

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Analysis of determinants of long-term efficacy of unboosted atazanavir-based regimens in the clinical setting

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Background: Switch to unboosted atazanavir (ATV 400 mg qd), although not licensed in Europe, is an attractive off-label option due to convenience and tolerability. However there is a substantial lack of data concerning efficacy of ATV 400 mg-based regimens outside the trial setting. Our aim was to perform a retrospective study of determinants of long term efficacy in 2 Italian large HIV clinics.
Materials and methods: A retrospective analysis of virological (responder = last viral load < 50 copies/ml) and PK data of patients (pts) administered with ATV 400 mg QD + 2 N(Nt)RTIs for at least 3 months was performed. Genotypic Sensitivity Score (GSS) and ATV resistance associated mutations (RAMs) were calculated according to Stanford database using cumulative genotype. ATV Ctrough was measured by a validated HPLC method.
Results: 246 patients [65% male, mean age 47.5 years (±9), mean BMI 23.8 Kg/m^2 (±3,4)] were considered. 40.7% and 6.6% were HCV- or HBV-coinfected, respectively, of whom 23 (9.3% of total) were cirrhotic. 32,9% and 17.9% of pts showed previous virological failure to NNRTIs and to PIs, respectively. Switch to ATV was mainly (48,4%) due to toxicity [dyslipidemia (21,5%) and gastrointestinal side effects (9,7%)] and to simplification (28,5%); last regimen was boosted PI-based in 178 patients (72.3%, 48% of whom ATV/r) and NNRTI-based in 24 (9.8%). At baseline CD4+ cell count was 428 cell/mm3 (±223) and 58,1% showed undetectable viral load. 212 (86.5%) patients had previous genotype available: backbone GSS was < 2 in 36,9% of patients and 6,7% had at least 1 ATV-RAM. Mean (±SD) follow-up was 120 weeks (± 64), and 235 (95.5%) pts were responders (74.4% still on treatment) while 11 (4.5%) showed a virological failure (3 showed selection of ATV-RAMs). ATV Ctrough (available in 84 patients) was higher in responders (median value 130 vs. 70 ng/ml), although this was not statistically significant ($p>0.05$). At multivariate analysis, GSS<2, ATV-RAMs ≥1 and self-reported non-adherence were associated with failure. ATV was stopped only in 4 patients (1.6%) for side effects.

Conclusions: Over a mean follow up of more than 2 years, unboosted ATV showed high efficacy with good tolerability even in a clinical cohort including moderately experienced pts. However, due to the impact of GSS of backbone and presence of ATV-RAMs on the risk of failure, pts need to be accurately selected. The role of ATV plasma exposure deserves to be clarified on a larger sample size.

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Switching from tipranavir (TPV) 500/ritonavir (RTV) 200 mg to TPV 500/RTV 100 mg in treatment-experienced patients (pts) with HIV RNA <50 copies/mL

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Background: The administration of 200 mg of RTV to boost TPV plasma levels is associated with poor tolerance and toxicity. Some studies have shown that 100 mg of RTV could be enough to reach plasma levels of TPV that inhibit most HIV strains. This clinical trial was designed to show the efficacy and tolerability of switching to TPV 500/RTV 100 in patients with suppressed viremia receiving TPV 500/RTV 200.
Methods: Open, randomized, multicenter clinical trial. Pts who were receiving TPV 500/RTV 200 with an HIV RNA<50 copies/mL for at least 6 months and with a genotypic sensitivity score showing activity of TPV were randomized to continue on the same dose or to switch to TPV 500/RTV 100 mg. The efficacy endpoint was the proportion of pts with HIV RNA<50 copies/mL at 48 weeks in an ITT analysis. Discontinuation due to intolerance, liver toxicity and lipid abnormalities were also evaluated. TPV plasma trough levels were measure in all the patients.
Results: 35 pts were randomized: 16 pts continued on TPV 500/RTV 200 mg while 19 pts were switched to the lower TPV 500/RTV 100 mg dose. At baseline, 48% had AIDS, and mean CD4 count was 515 cells/mm^3. Coinfection with HCV was more frequent in pts who continued on the 200 mg RTV group (44%) than in those that switched to the 100 mg RTV group (11%)(p=0.02). Pts had received a median of 10 drugs (including 3.6 PI), and mean duration of TPV therapy was 32 months. Mean number of accompanying drugs was 3.4 in the two groups. Mutations in RT and PRO before initiating therapy with TPV were found in 31% and 20% pts, respectively. After 48 weeks, HIV RNA remained below 50 copies/mL in 89.5% pts in the RTV100 group and in 75% in the RTV200 group [ITT, difference 14.5% (95%CI -10.5, 39.5%)]. Mean CD4 count change was +24 in the RTV100 group, and -33 in the RTV200 group (p=0.5). A greater decrease in GPT, total cholesterol, and triglycerides was observed in the RTV100 group. One pt on the lower dose developed grade 2 increase in total cholesterol, while 3 pts developed grade 2-4 toxicities in the higher dose group (grade 2 and 4 hypertriglyceridemia, grade 2 hypertransaminemia). Median TPV trough levels at 48 weeks were 38854 ng/mL and 25465 ng/mL in the RTV 200 and RTV 100 groups, respectively.
Conclusions: Switching from TPV 500/RTV 200 mg to TPV 500/RTV 100 mg in treatment-experienced patients with HIV RNA <50 copies/mL maintains virological suppression, while improving liver and lipid abnormalities.

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Lopinavir/ritonavir monotherapy in clinical practice

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Purpose of the study: To assess the usefulness of monotherapy with lopinavir/ritonavir (LPV/r) as an option for antiretroviral treatment in clinical practice.
Methods: Seventy-seven subjects (56 men, median age 44.5 years) with HIV-1 RNA <50 copies/mL for at least 6 months, were switched to LPV/r as single antiretroviral agent. Reason for changes were simplification strategy (36.4%) or toxicity (63.6%) either mitochondrial toxicity (55.8%) or other (7.8%). Treatment with LPV/r was maintained for at least 3 months.
Summary of results: The average time from HIV-1 diagnosis to starting HAART was 54 months. Patients had received a median of 7 antiretroviral drugs (range 3-14). The previous antiretroviral regimen included LPV/r in 55 (71.4%) patients. After a mean (±SD) follow-up of 25 (±16) months (median 22 months), viral load remained undetectable in 68 patients (90.7%) (9 of them after reintroduction of triple therapy for reasons other than virological failure), and virological failure was detected in 9 (11.7%), due to poor adherence in 7 (77.8%). The median time of undetectable viral load prior to initiating LPV/r monotherapy was 36 months. The mean CD4+ T cell count at the time of beginning LPV/r was 518.9 cells/mm^3 (range 33–1433) and the end of follow-up 634.5 cells/mm3 (range 99–1547), with an increase of 115.6 cells/mm^3. In 8 patients, 13 blips were detected (viral loads > 50 copies/mL and < 500 copies/mL), which did not warrant a change in therapy. Differences between patients with and without virological failure during LPV/r monotherapy included: older age at HIV-1 diagnosis (40.2 vs 30.7 years, P < 0.049), time of undetectable viral load prior to starting monotherapy (29 vs 45 months, P = 0.05), and CDC category C (77.8% vs 42.6%, P = 0.074). On the other hand, there were no significant differences according to sex, risk group, previous failure to PIs(9 patients), nadir CD4+ T cell count, or reasons to change to monotherapy. In the Cox regression analysis, age was independently associated with virological failure.
Conclusions: LPV/r monotherapy has been an effective alternative in clinical practice either as a simplification strategy or in patients in which toxicity reduces the selection of antiretroviral drugs. Poor adherence and greater age were related to a higher rate of therapeutic failure.

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Switching to dual therapy with darunavir/ritonavir and etravirine: a simplification strategy

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Background: Long term maintenance with NRTI-sparing regimens may be preferable for patients with NRTI toxicities, and may offer potential cost savings. Dual ART with once daily darunavir/r and etravirine may be preferable to previous PI/r/NNRTI combinations due to its theoretical higher genetic barrier to resistance and good PK profile. We looked at the use of this regimen within our HIV cohort.
Methods: Patients prescribed dual ART with darunavir/ritonavir 800 mg/100 mg QD with etravirine 400 mg/day (DRV/r/ETR) until January 2010 were identified by our virtual clinic database. Reason for switch, HIV resistance, viral outcomes were identified.
Results: 21 patients were switched to DRV/r/ETR with median time on regimen of 51.5 weeks (IQR 33-69 wks). 85% (18/21) where given ETR 400 mg QD. 62% (13/21) switched from dual PI/r regimens, 10 combined with efavirenz or nevirapine. 28% (6/21) switched from conventional cART (2 NRTI + PI/r or NNRTI). Patients had a median exposure to 9 ARV drugs prior to switch (IQR 4-11), with 90% (19/21) having previous NNRTI exposure, 7 of which had CNS toxicity with efavirenz. At switch, 57% (12/21) had no previous resistance, 19% (4/21) NRTI mutations only, and 19% (4/21) had NNRTI mutations (K103N (2), Y181C combined with NRTI K65R, M184V mutations (1), prior NNRTI failure (2)). 90% (19/21) had VL<50cps/ml at switch, with 95% (20/21) achieving/maintaining VL<50cps/ml on regimen. Four patients discontinued the regimen, 2 switching to darunavir/r monotherapy, one switching to kivexa/darunavir/r due to non-adherence, and one switching back to previous regimen after 4 weeks. One patient was lost to follow up. Median virological follow of patients remaining on therapy was up 40.8 wks

(IQR 32-58 wks). Median CD4 change for the 17/21 who remained on therapy was +101 cells/mm^3 (IQR -50-138) with median 39 wks follow up (IQR 31-58 wks). Indications for switch were desire for simplification (9) (typically from dual PI), and need for NRTI-sparing regimen (12), including previous renal toxicity with tenofovir (4), lipoatrophy (7), peripheral neuropathy (1) and lactic acidosis (2).
Conclusions: For patients with VL<50cps/ml, simplification to dual therapy with darunavir/r 800/100mg QD plus etravirine 400mg QD maintains viral suppression and immune reconstitution.

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Changes in cerebral function parameters in HIV-1 infected subjects undergoing a treatment simplification to darunavir/ritonavir

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Purpose of study: Concerns exist regarding the central nervous system (CNS) penetration and cognitive sequelae when utilising novel, nucleoside-sparing treatment strategies such as protease-inhibitor monotherapy.
Methods: The aim of this study was to assess changes to cerebral function parameters in HIV-1 infected subjects, stable on antiretroviral therapy with a plasma HIV RNA<50 copies/mL, randomised to commence on a one to one basis, either darunavir/ritonavir (800/100 mg one daily) alone (DRVmono) or with nucleoside analogues (DRVnrti), within the MONET study. Cerebral function was assessed via a detailed, validated, computerised neurocognitive function assessment (CogState™) and cerebral metabolites measured via cerebral proton spectroscopy in three anatomical locations (frontal grey and white matter and right basal ganglia (RBG)), at baseline and after 48 weeks. Associations between cerebral function parameters and study treatment arms were evaluated using linear regression.
Results: 6 subjects were enrolled (3 assigned to each treatment arm) with a mean age of 44 years (SD 4.5) and 83% male. Mean baseline plasma CD4+ cell count was 503 cells/uL (SD 173). Over 48 weeks, mean score improvements were observed in 6 of 8 neurocognitive tasks assessed including speed domains (2.5% increase identification speed), accuracy domains (4.6% increase non-visual learning) and executive function (30% reduction in errors). Reductions in cerebral metabolite markers of cerebral inflammation (choline:creatine (Cr) and myo-inositol: Cr ratios) were also observed in all cerebral locations assessed (maximum reduction of 28% myo-inositol:Cr ratio in frontal grey matter). No associations between study treatment arm and these improvements in cerebral function parameters were observed (p>0.06 all values).
Conclusion: On detailed assessment of cerebral function, overall improvements were observed over 48 weeks in subjects allocated to either DRVmono or DRVnrti. Despite very small numbers, our study highlights future tools which can practically be utilised to assess cerebral function in HIV-treatment programmes.

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Epidemiological description of the demographic and HIV disease characteristics of HIV patients who are in care but not on treatment in Spain

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Background: It is estimated that around 15% of HIV infected patients are being followed in HIV units for disease evolution and need of treatment. Data on the demographics and HIV disease status of these patients are scarce.
Methods: Cross sectional analysis within 12 HIV units in Spain with the aim of describing the characteristics of patients in care but not on treatment. We collected data on demographics, HIV disease status as well as the prevalence of non-HIV co-morbidities that could qualify for antiretroviral treatment initiation regardless immunological status according to current Spanish treatment guidelines.
Results: Data from 865 patients naïve to ARV treatment were collected. Mean age 37 y, most of them were male (83%) and Caucasian (85%). Predominant HIV risk factor was MSM (56%). Median time from HIV diagnosis 2.3 y (IQR 1.0 to 5.1). Current median CD4 cell count was 602 /mm^3 (IQR 422 to 729) and mean HIV-1 RNA levels were 4.6 log.
The prevalence of key HIV and non-HIV features according to different CD4 strata can be seen in Table 1.
Conclusions: In our cohort of patients who are under care but not on treatment, a considerable amount of them could benefit from treatment initiation according to current guidelines. When monitoring to what extent treatment guidelines are being followed, non HIV comorbidities should also be taken into account. Among these patients, HCV coinfection is the most prevalent comorbidity. Some of these patients could also benefit from generalisation of cardiovascular risk evaluation in HIV units.

Table 1 (abstract P53)

	CD4<350 (n=112)	CD4 350 - 500 (n=261)	CD4>500 (n=492)
>55 years of age	1.8%	3.1%	2.6%
HIV RNA >100,000 cop/mL	20.5%	13.4%	8.1%
CD4 percentage < 14%	19.6%	3.1%	1.2%
HCV coinfection	25.0%	14.2%	14.0%
HBV coinfection requiring treatment†	0%	0.4%	0%
Liver cirrhosis	4.5%	1.1%	1.6%
HIV associated nephropaty	0%	0.8%	0%
10 y CHD>20% (Framinghan score)‡	Not available	Not available	0.8%

†: According to Spanish guidelines ‡: Data not available for 30% of the subjects

P54

Treatment of HIV-2 infection: a retrospective study from a Portuguese center

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Purpose of the study: Tailoring of antiretroviral therapy (ART) in HIV-2 remains unclear, therefore therapeutic experience in this population is presented.
Methods: Retrospective analysis of HIV-2 infected patients (pts) on ART followed at a single Portuguese center, between 1988 and 2010.
Summary of results: 37 pts were included; 19 (51%) female and 28 (76%) Caucasian. Mean ages were: 46 years [18-77] at HIV-2 diagnosis and 48 years [20-81] at the beginning of ART. The majority (54%; 20) was probably infected in West Africa through heterosexual intercourse (75%, 28). The average T CD4+ nadir was 137 cells/mm^3 [3-586] and mean TCD4+ count prior to ART initiation was 205 cells/mm^3. The main reason for starting ART was immunological deterioration (87%; 32) followed by pregnancy (8%; 3). Ten pts (27%) had an AIDS defining illness prior to ART initiation and 4 (11%) developed it while on ART. The mean value of the last TCD4+ count was 305/mm^3. Overall the median number of regimens received per patient (pt) was 3 [1-7]; 12 (32%) pts took just one regimen. Mean length of ART was 61 months [1-228] and mean duration

of the last prescribed regimen was 23 months [0.25-125]. Viral load ("in house" assay) was always undetectable in 19 (51%) pts. Switch of ART occurred in 21 (57%) pts with 1.4 reasons/pt. The main cause for switching was GI intolerance (57%; 12), followed by failure (38%; 8), toxicity (29%; 6) and simplification (19%; 4).
The last prescribed regimens were as follows:
a) 73% (27): 2 NRTIs + 1 PI [NRTIs: TDF/FTC (9), AZT/3TC (7), TDF/3TC (6), others (5); PIs: LPV/r (13); SQV/r (8); IDV/r (3); others (3)];
b) 19% (7): 2NRTIs (FTC/TDF) + 1 PI (DRV/r) + 1 INSTIs (RAL);
c) 8% (3): dual/triple NRTIs.
Only one pt on RAL was ART naïve. After a median follow-up of 11 months [4-24] on RAL based regimens, 3 pts had undetectable viral load (the remaining had it from the beginning). Median length of previous ART was 77 months with an average of 2.4 regimens/pt. The median gain of T CD4+ with RAL regimen was +94 cells/mm^3 [3-239]. Currently: 21 (57%) pts are kept on follow up, 19 (90%) of whom on ART; 9 (24%)pts died (4 with AIDS related deaths) and 7 (19%)were lost to follow-up.
Conclusions: This population had a fairly good T CD4 cell recovery while on therapy which is the best approach to assess treatment response together with clinical improvement. NRTIs/PI/INSTI containing regimens appears to be effective, although longer term outcomes are needed.

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The prognosis of patients with dissociated virological and immunological responses to HAART

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Background: While HAART allows for the reconstitution of immune functions in most treated HIV patients, failure to achieve a significant increase in circulating CD4+ T cells despite undetectable viremia occurs.
Methods: A retrospective study was conducted to evaluate the treatment outcome in a subgroup of 232 patients who after 3.1 years of treatment had not achieved desirable immune reconstitution despite a good virological response to HAART.
Results: After a further 3.5±2.7 years of HAART, 41 (17.7%) patients achieved immune reconstitution (681.4±172.7 CD4 cells/μL), while 191 (82.3%) patients did not (306.6±109.16 cells/μL); the difference in the achieved CD4 counts between these subgroups was significant (P<0.01). One patient experienced treatment failure. Eleven patients died to the end of follow-up, of which ten with a continuously dissociated response. Factors associated with immune recovery included, usage of PIs and of drugs from all three classes (OR 2.1, 95% CI 1.0-4.2, P=0.037 and OR 5.1, 95% CI 1.4-18.7, P=0.013, respectively), and a rise in CD4 count to over 200 cell/μL after the first 3.1 years of treatment (OR 2.8, 95% CI 1.1-6.6, P=0.019). Achievement of a rise in CD4 count to over 200 cell/μL after the first 3.1 years of treatment, and usage of all three drug classes were independent predictor of immune reconstitution in the following period.
Conclusions: If patients on HAART reach CD4 cell counts of above 200 cells/μL in the first three years, immune recovery is possible after at least six years of treatment, particularly if treated with drugs from all three classes.

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Prediction of virological failure in HIV-infected individuals treated with cART in Suriname

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Purpose: In Suriname, a South American country with 500.000 inhabitants and an estimated prevalence of HIV infection of 4%, virological monitoring of combination antiretroviral therapy (cART) is uncommon. Therefore, the virological response to cART is poorly known. The objective of this study is to determine the virological response and to identify risk factors for virological failure among HIV-infected patients in Suriname. An additional aim is to develop and validate a prediction model that could be used to identify patients at risk for virological failure.
Methods: 100 HIV-infected individuals, treated with cART participated in this study. Patients were selected from 2 major hospitals and 4 general medicine practices in Paramaribo, Suriname. Patients were eligible for this study if they were prescribed cART for 6 months or more, their last drug pick-up date was no longer than 9 months before inclusion and if they were at least 18 years old. To assess risk factors multiple questionnaires were conducted considering HIV stigma (HIV Stigma scale), Social Support (based on the Norbeck Social Support Questionnaire), Depression (CES-D scale), Quality of life (based on the HIV questionnaire of the Medical Outcomes Study) and Beliefs about Medications (Beliefs about Medication Questionnaire). In addition, HIV RNA concentrations were measured in dried blood spots. A detectable viral load (HIV RNA > 300 copies/mm^3) was considered as virological failure.
Results: 19% of all participants had a detectable viral load (range 463-319815). A significant correlation was found between virological failure and a lower level of social support (r = -0.0357, p = 0.00), younger age (r = -0.245, p = 0.014), and higher perceived personalized HIV stigma (r = 0.206, p = 0.039). A prediction model was formed consisting of three variables: age, social support and personalized HIV stigma. This model has a discriminatory power of 0.7993 (receiver operating characteristic) and an explained variance of 0.252 (R^2).
Conclusions: In this Surinamese cohort, 19% of patients treated with cART are demonstrating virological failure. A prediction model consisting of age, social support en personalized stigma scales can predict for almost 80% whether a viral load will be detectable or not. This prediction model could assist in identifying patients at risk for virological failure, especially in situations where virological monitoring is unavailable.

P57

British HIV and ageing study. HIV and ageing: older people with HIV, who are they?

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Objectives: The life expectancy of HIV positive individuals has improved dramatically with the advent of HAART. The cohort of older people living with HIV is steadily increasing in size. Both advancing age and HIV are associated with an increased likelihood of comorbidities and polypharmacy independently, but little is known about their combined impact and how this will shape the care required from HIV physicians. This study was designed to gain insight into the characteristics of patients aged 60 or over living with HIV.
Methods: Data was collected from 5 centres across England and Wales. All patients currently aged 60 or over were included. A questionnaire format was used to collect information on demographics, risk factors for infection, co-morbidities, co-infections, all medicine use including HAART and resistance patterns.
Results: There were 66 patients in total. 79% of these patients were male. Half of the patients were MSM. 76% were Caucasian, 12% Black African, 8% Black Caribbean and 3% Asian. The current age range was 60 to 79 years, with a mode and median age of 62 and 64 years respectively. The age of diagnosis ranged from 39 to 71, with a median age of 59 years. Almost half of the patients were diagnosed at age 60 or over. The duration of HIV infection ranged from 2 months to 22 years with 48% of patients having been diagnosed within the last 5 years. This supports a combination of patients living to older ages with HIV and acquisition of HIV in later life. 53% had a CD4 count of less than 200 at diagnosis. 38% had had an AIDS defining condition. Only 7% had a CD4 count of <200cells/mm^3 in 2010. 84% had one or more comorbidity. 31% had 3 or more comorbidities. 92% of patients were on HAART. Of those on

treatment, 86% had current viral loads of <50 copies/ml. Of the 5 patients who were not on treatment, all were between the age of 60 and 65 currently, diagnosed within the last 4 years and had CD4 counts over 450cells/mm^3. 89% of patients were on 1 or more prescribed medication, in addition to HAART or septrin. 23% were on 5 or more medications.
Conclusions: This data provides an insight into an ever growing cohort of older people with HIV, in whom there is a paucity of information. It gives some information on the risk factors, comorbidities, stage of infection at diagnosis and response to treatment. In this cohort, despite the complexities associated with managing HIV in older patients, the majority of patients were fully suppressed with good CD4 counts.

P58

A comparison of the FDA TLOVR and FDA Snapshot algorithms based on studies evaluating once-daily vs. twice daily lopinavir/ritonavir (LPV/r) regimens

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P58

Purpose: The FDA TLOVR algorithm has been commonly used to assess virologic response to antiretroviral (ARV) regimens. The FDA Snapshot algorithm has been proposed to replace the TLOVR algorithm, as it is simpler and is expected to yield similar results. Multiple studies determined that efficacy of LPV/r dosed once-daily (QD) + nucleoside reverse transcriptase inhibitors (NRTIs) was statistically similar to LPV/r dosed twice-daily (BID) + NRTIs using the FDA TLOVR algorithm. The purpose of the analyses presented here is to compare the TLOVR and Snapshot algorithms in the context of studies evaluating QD vs. BID LPV/r-based regimens.
Methods: Three studies comparing LPV/r QD + NRTIs vs. LPV/r BID + NRTIs in ARV-naïve (Study 418, n=190; Study 730, n=664) or ARV-experienced (Study 802, n=599) subjects were analyzed. Study results through 48 and 96 weeks were compared using the FDA TLOVR and FDA Snapshot algorithms. The Snapshot algorithm differs from the TLOVR algorithm primarily in its focus only on the visit of interest: a subject is a responder if and only if the subject has an HIV-1 RNA level <50 copies/mL at the visit of interest.
Results: In the comparison of the FDA TLOVR algorithm to the FDA Snapshot algorithm, 59/1453 (4%) subjects had discordant results (responder by one algorithm but not the other) at week 48, as did 28/854 (3%) at week 96. In each study, LPV/r QD-based regimens provided similar virologic response rates to LPV/r BID-based regimens for each analysis algorithm at each visit (Table 1).
Conclusions: The FDA Snapshot analysis is easier to understand, simpler to calculate, and gives similar results compared to the FDA TLOVR algorithm. Efficacy was similar for LPV/r QD-based vs. BID-based regimens in ARV-naïve subjects as well as ARV-experienced subjects, irrespective of timepoint or analysis algorithm.

Table 1(abstract P58) Percent of subjects with HIV-1 RNA <50 copies/mL using FDA TLOVR and Snapshot algorithms

Week	Analysis Algorithm	Study 418		Study 730		Study 802	
		QD (n=115)	BID (n=75)	QD (n=333)	BID (n=331)	QD (n=300)	BID (n=299)
48	TLOVR	71%	65%	78%	77%	55%	52%
48	Snapshot	70%	64%	80%	78%	57%	54%
96	TLOVR	57%	55%	63%	64%	n/a	n/a
96	Snapshot	57%	55%	65%	69%	n/a	n/a

n/a not available, 48-week study

P>0.05 for all QD vs. BID comparisons within each study, analysis algorithm, and timepoint

P59

Abstract withdrawn

Journal of the International AIDS Society 2010, **13(Suppl 4)**:P59

P60

Long-term efficacy and safety of low-dose ritonavir-boosted atazanavir (ATV/r) 200/100 mg in HIV-infected Thai patients

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P60

Purpose of the study: Atazanavir is a good but expensive regimen in resource limited settings (RLS). A previous HIV-NAT study showed that a low dose of ATV/r 200/100mg once daily (QD) provided adequate atazanavir plasma concentrations in HIV-infected Thai adults. Reducing the dose would make atazanavir more accessible to those patients in need in RLS. We aimed to evaluate long term efficacy of lower dose ATV/r 200/100 mg in HIV-infected Thai adults.
Methods: HIV infected patients commencing ATV/r 200/100 mg QD in a prospective long term cohort at HIV-NAT, Bangkok, Thailand were analysed. CD4, HIV RNA, and safety parameters are performed every 6 months as part of the cohort.
Summary of results: A total of 84 (51% men) subjects with median age of 40 years and median body weight of 57.6 kg were included in this analysis. The median time of taking lower dose was 63 (IQR 39-82, range 2-237) weeks. 11/84 subjects had HIV RNA > 50 copies/mL at time of ATV/r lower dose initiation. These patients mainly were NNRTI based treatment failure. 79% used tenofovir as backbone. High ATV Ctrough (32%), hyperbilirubinemia (32%), and clinically jaundice (22%) were the main reason for using the lower dose. At time of analysis, 72/74 (97%) patients with availability of at least 1 HIV RNA at 6 months interval, had HIV RNA <50 copies/mL. The median CD4 count was significantly increased from 394 to 456 cells/mm^3 (P =0.010). The median change in fasting cholesterol, triglyceride, LDL and HDL were -6 , -11, 13.8 and 4 mg/dL, respectively. However, the changes were not statistically significant exception for HDL (p=0.006). In patients previously used standard dose of ATV/r 300/100 QD, the median of bilirubin was 1.9 (range 0.1-7.7) mg/dl and it improved significantly after dose reduction (p = 0.003). Majority of the patients well tolerated to the treatment, only 9 patients, ATV/r 200/100 mg QD was discontinued due to ran out of stock (4 patients), hepatitis (2 patients), hyperbilirubinemia (1), nephrotic syndrome (1), and non-adherence (1). ATV Ctrough concentrations of ATV/r 200/100 were available in only 51 cases, all had ATV Ctrough concentrations >0.15mg/L.
Conclusions: Regimens with ATV/r 200mg/100mg provided adequate ATV plasma concentrations, were effective and well tolerated in HIV-infected Thai adult patients. A randomized controlled trial should be conducted to confirm our findings. This data will be benefit to a million of HIV infected in RLS.

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P61

Immune impairment and adaptive response in relation to antiretroviral therapy of HIV-infection

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Purpose of the study: In Moscow Regional HIV Living Cohort we have recently defined the groups with progressive HIV infection and those

with temporary and permanently no progressive disease. The aim of the study was to find major features of progressive HIV infection in relation to antiretroviral treatment.

Methods: In the study 615 progressors were compared with 1311 and 345 temporary and permanently non progressors. Additionally 208 late presenters (with CD4 counts less than 100 cells/mm^3) were compared with the sample from the whole population of people leaving with HIV (2271 patient). In blood specimens HIV virus load (PCR m2000rt Abbott, 'RealTime HIV-1') and major subpopulation of T-lymphocytes were analyzed (flow cytometer BD FACSCount, sets ÑD3/CD4/CD8/CD45).

Summary of results: The most distinct feature allocating groups was the response to the elevation of viral load. In the progressive group the number of CD8 cells among individuals decreased with the elevation of viral load. This was due to the T-cell depression including CD8+, CD4+ and CD3+CD4-CD8- T-lymphocytes.

Contrary to this no progressive groups demonstrated elevation of CD8 population with the increase of viral load. The elevation was more expressed in permanently no progressive group. This resulted in preservation of CD4 T-lymphocyte subset and CD3+CD4-CD8- T-lymphocytes were significantly elevated. Figure 1.

Demonstrated "pathologic process" and "adaptive response" allows better understanding of the HAART efficacy. HAART affects the viral replication thus restoring the proportion between the cytotoxic lymphocytes and virus infected cells. This causes HIV viral load reduction. Immune reconstitution appears to be a host property which depends on the severity of the previous immune impairment.

Among the studied late presenters two groups were defined. Table 1

Though both groups had pronounced CD4 loss and high burden of the viral load, the amount of CD8+ and CD3+CD4-CD8- depletion was different between the groups and more profound in the first group compared with the second. For the first group with severe breakage of immunity combination regiments of HAART with boosted protease inhibitors, fusion and/or integration inhibitors are recommended even in the first line of therapy to obtain better results.

Conclusions: Depletion of different T-cell branches is the major pathological process in HIV-infection, diagnosis of the level of immune impairment is needed to prescribe appropriate treatment.

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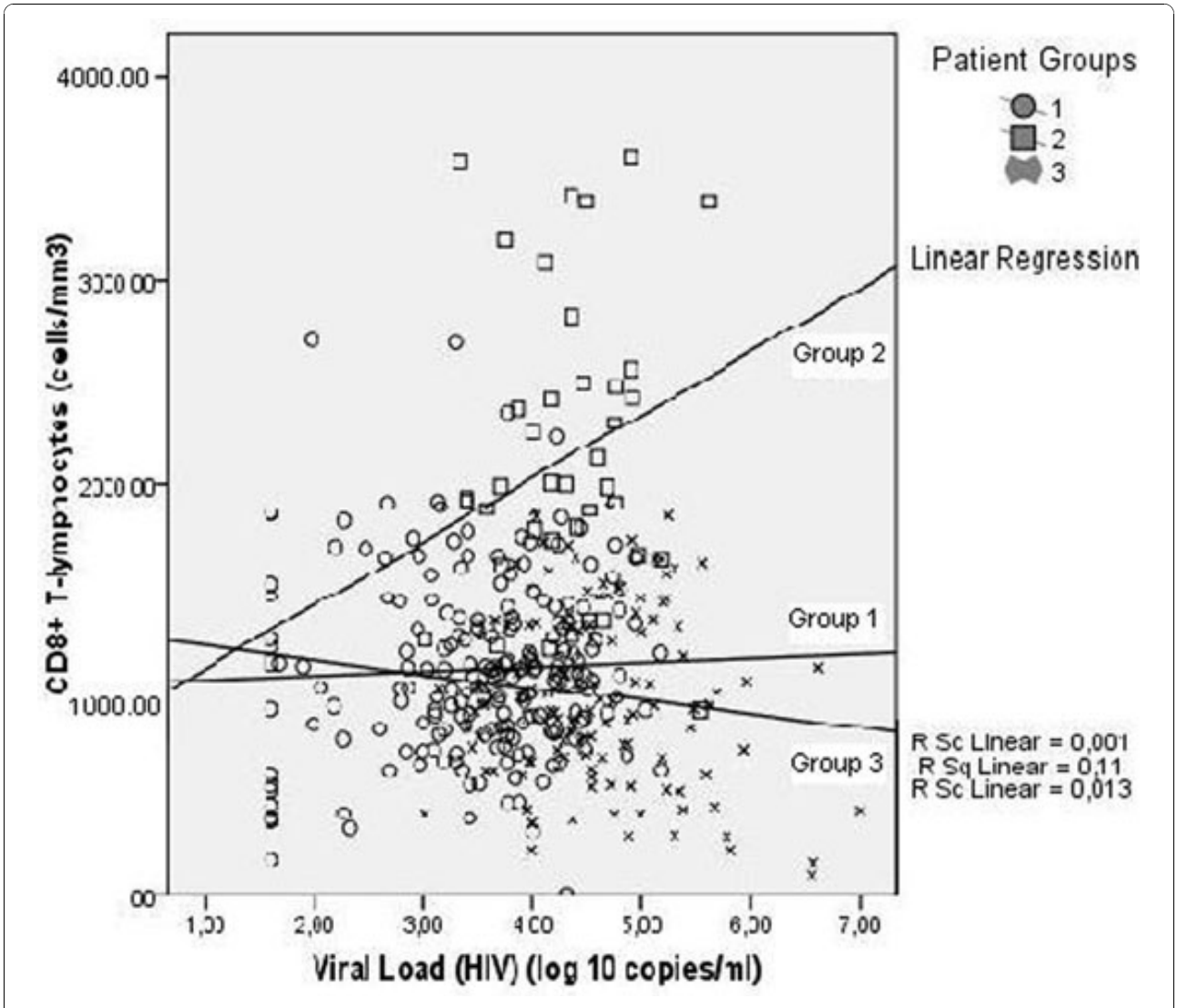

Figure 1 (abstract P61)

Table 1 (abstract P61)

	CD3+ (cells/mm^3)	CD4+ (cells/mm^3)	CD8+ (cells/mm^3)	Viral Load (HIV) (log_{10} copies/ml)	CD3+ CD4-CD8- (cells/mm^3)
Late Presenters First Group	225	38	289	5,47	19
Late Presenters Second Group	552	26	380	6,09	179
HIV Living Cohort	2363	589	1195	3,80	394

ADVERSE EFFECTS

P62

Role of platelet activation in the cardiovascular complications associated with HIV infection: differential effect of abacavir versus tenofovir

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Purpose: Abacavir use has been associated with an increased risk of ischemic cardiovascular events in several cohort studies, but the pathogenic mechanisms are still unknown. Recently Martinez et al. observed no differences in markers of inflammation, endothelial dysfunction, insulin resistance or hypercoagulability in HIV infected persons treated with either abacavir or tenofovir. While several studies have shown endothelial dysfunction in HIV-infected patients, only a few data are available on the involvement of platelets. Aim of our study was to evaluate markers of platelet activation and endothelial dysfunction in HIV infection comparing patients treated with abacavir or tenofovir.
Methods: In a retrospective, case-control study, the time course of some endothelial (MCP-1, sVCAM-1) and platelet activation markers (sPLA2, sGPV, sP-sel) was examined in 62 HIV-infected patients, before starting HAART and after 6-12 months of therapy with either Abacavir (n=31) or Tenofovir (n=31). Data were compared with those from 20 untreated HIV-infected patients at diagnosis and after 6 months and 10 healthy matched controls.
Results: Soluble P-selectin (sP-sel), sPLA2, soluble vascular cell adhesion molecule-1 (sVCAM-1) and monocyte chemoattractant protein-1 (MCP-1) were significantly higher in HIV-infected patients than in healthy controls. During 6-12 months of follow-up, we found no significant differences between abacavir and tenofovir-treatment for endothelial markers, while sPLA2 (2113.6±39.5 vs 2742.5±29.7pg/ml, p<0.05) and sPsel (524±53.2 vs 713.47±20.3ng/ml, p<0.05) increased significantly in the abacavir group as compared with the tenofovir-treated group. sGPV, the platelet glycoprotein V major fragment released upon thrombin cleavage, was increased after 6-12 months as compared to baseline in both treatment groups (Abacavir: 89.7±13.7 vs 118.64±15.3 ng/ml Tenofovir: 133.5±10.7 vs 157.36±11.2, p<0.05). In naïve patients, not treated with HAART, significantly increased plasma markers of endothelial dysfunction sPsel and sPLA2 were confirmed at diagnosis, as compared with healthy controls, with no changes upon follow-up.
Conclusions: Our results confirm that chronic HIV infection induces endothelial dysfunction but indicate that a short-term treatment with abacavir enhances also some parameters of platelet activation, suggesting a role of platelets too in the increased incidence of ischemic cardiovascular events in HIV-infected patients treated with abacavir.

P63

Platelet activity in HIV-infected patients on abacavir-containing antiretroviral therapy

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Background: Recent studies have shown an increase in the incidence of coronary heart disease in HIV-infected patients on treatment with abacavir (ABC), and platelet hyper-reactivity induced by this drug has been suggested as a possible cause.
Objective: To assess platelet activity in HIV-infected patients with and without antiretroviral therapy (ART), analysing the influence of the presence or absence of ABC in the ART regimen.
Patients and methods: Observational, cross-sectional, pilot study. Among HIV-infected patients on regular follow-up in our Centre, we selected 30 asymptomatic patients: 20 on ART for at least 24 weeks and with undetectable HIV viral load, 10 on ABC, and 10 on tenofovir (TDF), and 10 naïve patients, in addition to a control group of 10 HIV-negative subjects from the same hospital area. No subject was receiving drugs with antiagregant activity. Platelet activity was assessed by measuring time-dependent platelet aggregometry (electrical impedance on fasting whole blood), induced by ADP (1,25 y 2,5 μM), collagen (0.5 y 1 μg/mL), arachidonic acid (100 y 200 μM), and U46619 (receptor agonist of the tromboxano A_2) (1.25 y 2.5 μM). A bivariate analysis by t student, anova and chi-square, and multivariate by linear regression were performed. Statistic program: SPSS, 16.0.
Results: Demographic and anthropometric data, prevalence of cardiovascular risk factors, lipid profile and fasting glycemia were similar in all groups, but older age and longer time of HIV infection in the ABC group (50.4 vs 36.1, 34.2 and 42.7 years, respectively; p<0.05, and 140.3 vs 88.1 and 48.3 months in the two other groups of HIV patients; p< 0.05). Mean CD4 cells count in HIV-patients was 564/mm^3. Platelet aggregation with exposure to U46619 was higher in the ABC group compared with the TDF group (11.1 vs 4.4%; p=0.007), naïve patients (11.1 vs 5.7%; p=0.014), and the HIV-negative group (11.1 vs 6.5%; p=0.04). These differences remained significant when controlled for age and time of HIV infection.
Conclusions: ABC increases platelet aggregability possibly in relation with the receptor of tromboxano. Wider studies are needed to confirm this hypothesis.

P64

Cardiovascular risk in patients visiting the Hadassah AIDS Center, Jerusalem

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Objective: To evaluate cardiovascular risk (CVR) in patients visiting Hadassah AIDS Center & to characterize clinical parameters of patients with high CVR.
Materials and methods: A cross-sectional study. CVR was calculated using Framingham risk score (FRS). Metabolic syndrome (MS) and LDL-cholesterol optimal levels were defined using National Cholesterol Education Program criteria. Adherence to ART was evaluated using the self-reported Visual Analogue Scale.
Results: *We* analyzed data of 150/350 clinic consecutive patients (median age 41 years, range 24-79; 60% males). Sub-Saharan Africans comprised 51% of patients, mainly immigrants from Ethiopia. Most patients (90%) were on ART, 62% were treated with PIs. Median time for ART and PI exposure were 7 and 4 years, respectively. Most patients (88%) defined adherence to ART>90%. High adherence correlated with viral suppression (p=0.039), but not with increase in CD4. Analyzing traditional CVRs, we observed higher rate of hypertension (HTN) among HIV+ patients compared to the general Israeli population (20% vs. 15%, respectively). In 16% of Ethiopians HTN was

likewise observed. HTN rates were 20% among ART-experienced patients, 22% in PI-exposed patients, and 16% among ART-naïve patients. The prevalence of diabetes was 5.7%, similar to the general Israeli population. It was higher among Ethiopians (8%). The rate of smoking was 25% in HIV+ patients, similar to general population (24%) and lower in Ethiopians (8%). Overall increased CVR was observed in 21% of all patients (FRS ≥10%). In 13% the MS was diagnosed. Lower rate of increased CVR (11% only) was observed among HIV+ Ethiopians. Increased CVR was correlated with increased age (p<0.05), male gender (p=0.034), HTN (p=0.002), but not with smoking (p=0.53), change of CD4 (p=0.7) or viral suppression (p=0.64). Increased duration of HIV infection and longer exposure to ART were noted in patients with increased FRS (p=0.059 and p=0.06, respectively), but not so for PI exposure (p=0.1). In 17% of patients LDL-cholesterol levels were higher than optimal goal, as set for CVR factors, especially in the group with increased FRS (p<0.05). Including HIV infection & ART per se as independent CVR, led to LDL goal above target in 30% of the patients in this cohort.
Conclusions: High rate of HTN and increased CVR were seen in this, mostly ART experienced cohort in Jerusalem. High diabetes prevalence, but lower overall rate of increased CVR were observed among Ethiopian HIV+ patients.

P65

Incidence of ischemic cardiovascular events in the maraviroc clinical development program

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Purpose of the study: Maraviroc (MVC), a CCR5 antagonist, does not appear to adversely affect serum lipids and may decrease LDL cholesterol in dyslipidemic subjects. The CCR5-del32 polymorphism, resulting in reduced (heterozygous) or absent (homozygous) CCR5 expression, is associated with reduced risk of cardiovascular disease. An early imbalance of cardiovascular adverse events was noted in the MVC phase 2b development program at 24 weeks. We investigated the longer term risk of cardiovascular events in MVC recipients in the development program. The D:A:D study and other cohorts have reported an incidence of 3.6/1000 PY for myocardial infarction (MI) among patients on HAART.
Methods: Ischemic cardiovascular adverse events among patients treated in MERIT (MVC versus efavirenz [EFV] in treatment-naïve [TN] patients), MOTIVATE (MVC versus placebo [PBO] in treatment-experienced [TE] patients), and study 1029 (MVC versus PBO in non-R5, TE patients) were prospectively collected. Incidence rates and exposure-adjusted incidence rates (/100PY) were compared to those of comparator regimens or existing cohort data.
Summary of results:
Conclusions: Rates of ischemic cardiovascular events were similar in TN patients treated with either MVC or EFV. In TE patients, the rate in the MVC arm was low and there were no events in the PBO arm. However, exposure to maraviroc was much greater than PBO in the TE population, and most events occurred in individuals with known cardiovascular risk factors. There were no additional patients with MI beyond the first 24 weeks among TE patients. Rates of MI in the TE population (1.0/1000PY) were consistent with published rates from prospective cohort studies.

P66

Low serum phosphate levels are related to increased cardiovascular risk in HIV-1 infected patients

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Purpose of the study: Hypophosphatemia may contribute directly to the development of obesity, hypertension and dyslipidemia. Hyperglycemia, insulin resistance, hyperlipidemia and hypertension, which are components of metabolic syndrome, are also recognized as strong risk factors for cardiovascular disease [1]. This study was performed to determine whether serum phosphate levels are associated with increased risk for cardiovascular events.
Methods: We enrolled 125 consecutive HIV-1-infected patients in a cross-sectional study. All patients were receiving highly active antiretroviral

Ischemic Cardiovascular Events in MVC Phase 2b/3 Trials

		MOTIVATE (TE)		MERIT (TN)		A4001029 (non-R5)	
		MVC*	PBO	MVC*	EFV	MVC*	PBO
Number of patients		840	209	534	361	125	61
Person-years (PY)of exposure (median exposure in weeks)		1428.9 (108)	159.8 (20)	1126.6 (139)	768.4 (139)	133.5 (22)	36.1 (18)
Event type							
Overall†	n	11		4	5	2	
	%	(1.3)		(0.7)	(1.4)	(0.8)	
	rate (100PY)	**0.8**	**0**	**0.4**	**0.7**	**0.8**	**0**
Myocardial infarction (MI)‡	n	2		2	2	2	
	%	(0.2)		(0.4)	(0.6)	(0.8)	
	rate (100PY)	**0.1**	**0**	**0.2**	**0.3**	**0.8**	**0**
Unstable angina	n	2		2	1		
	%	(0.4)		(0.4)	(0.3)		
	rate (100PY)	**0.1**	**0**	**0.2**	**0.1**	**0**	**0**
Angina pectoris	n	7			1		
	%	(0.8)			(0.3)		
	rate (100PY)	**0.5**	**0**	**0**	**0.1**	**0**	**0**
Myocardial ischemia	n	2			1		
	%	(0.2)			(0.3)		
	rate (100PY)	**0.1**	**0**	**0**	**0.1**	**0**	**0**

PBO = placebo, EFV = efavirenz, TN = Treatment-naïve, TE = Treatment-experienced;
*Includes MVC BID and QD recipients; †Patients counted once in each applicable category; ‡Includes MI and acute MI.

Figure 1 (abstract P65)

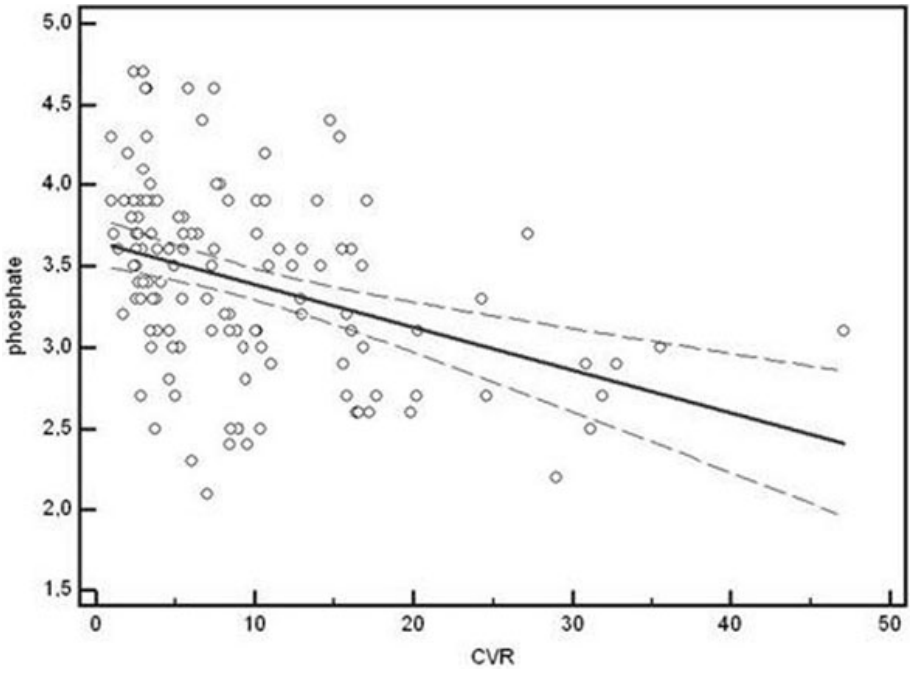

Figure 1 (abstract P66)

therapy (HAART) for more than six months. Fasting phosphate, lipids (cholesterol, HDL, triglycerides), Homeostasis Model Assessment (HOMA), blood pressure were evaluated. Framingham 10 years risk of general cardiovascular disease was used to assess three cardiovascular risk (CVR) categories (low CVR < 10%, medium CVR between 10 and 20%, high CVR > 20%).

Summary of results: We observed a statistically significant decrease in serum phosphate levels in the three different CVR groups (low risk: 3.5 mg/dl; medium risk: 3.3 mg/dl; high risk: 2.9 mg/dl; p=0.001). There was a strong negative correlation between Framingham score and phosphate levels (r:-0.37, p<0.0001). Figure 1

Multiple regression analysis, including age, months of HAART, CD4 cells count, cholesterol, HDL, HOMA, systolic pressure, months of Tenofovir use, showed that only HOMA (r:-0.30, p<0.01) and age (r:-0.3, p<0.01) were the most important determinants of serum phosphate values.

Conclusions: We found that lower phosphate level is correlated with cardiovascular risk and insulin resistance. Therefore, when serum phosphate levels are too low the patients is at risk for cardiovascular events and/or metabolic syndrome.

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P67

Prevalence of cardiovascular risk factors in Spanish HIV-1-infected male inmates

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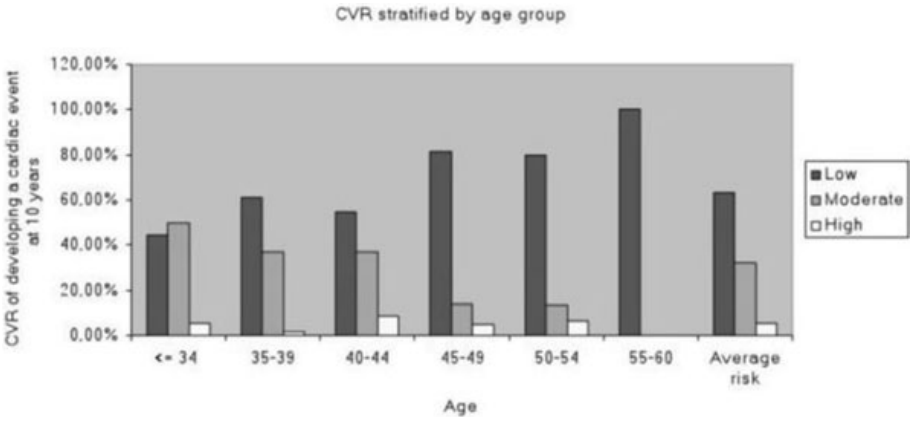

Figure 1 (abstract P67) CVR stratified by age group.

Table 1(abstract P67) Cardiovascular risk factors prevalence stratified by age group

Age	Smokers	Diabetes	Hypertension	Tot Chol > 200	HDL Chol <39
<34	99,44%	0,00%	8,33%	13,89%	72,22%
35-39	100%	3,23%	8,07%	8,07%	43,55%
40-44	100%	3,60%	12,50%	23,20%	51,80%
45-49	100%	0,00%	4,65%	9,31%	60,00%
50-54	100%	26,67%	20%	13,34%	46,00%
55-60	100%	0,00%	75%	100%	0,00%
Overall prevalence	99,07%	3,70%	10,60%	15,27%	53,24%
P	0,455	0,029	0,023	0,001	0,029

Purpose of the study: HIV-1-infected inmates have an increased prevalence of some particular comorbidities. However, the cardiovascular risk(CVR) of this population has rarely been evaluated.
Methods: Cross-sectional study carried out among 216 male HIV-1 patients in prison. Patients were stratified according to age(<34, 35-39, 40-44, 45-49, 50-54 and >55 years old, respectively) and their CVR was assessed by Framingham(FRAM) equation. The prevalence of some further risk factors was also evaluated: time on antiretroviral therapy, nadir CD4 count, maximum viral load(VL), time on undetectable VL, HCV-coinfection, and cocaine use.
Results: Patients median age was 41 years(36-46), their median CD4 count was 386(240-549)cells, 68% had an undetectable(<50 c/mL)VL, median nadir CD4 count was 207(104-315)cells, and 48% of them had a nadir CD4 count <200 cells. HCV-coinfection prevalence was 94%, cocaine consumption prevalence was 93.1%, and 54.2% of them were intravenous cocaine users. The FRAM 10-years CVR score among subjects studied was 5.88%. Figure 1 and Table 1.
Age (p<0.001), total cholesterol (p<0.001), HDL cholesterol (p = 0.029), diabetes mellitus (p = 0.029), hypertension (p = 0.023), and nadir CD4 <200 cells (p = 0.04) were significantly associated with an increased CVR. Smoking, chronic HCV-hepatitis, cocaine use, and the HIV-1 VL were not significantly associated with an increased CVR. There is a trend towards an increased prevalence of hypercholesterolemia and hypertension paralleling the aging.
Conclusions: Using the FRAM scores, the median CVR of developing a cardiac event at 10 years in a population of Spanish HIV-1-infected inmate males is 5.88%. Of them, 5.1% have a high CVR, and are evenly distributed among age groups. The smoking prevalence is significantly higher than in non-inmate HIV-1 infected individuals, and is so high that it does not allow CVR differences among age groups. HCV-coinfection, cocaine use, and parenteral cocaine consumption were not associated with an increased CVR in our population. On the other hand, a lower nadir CD4 count was associated with high rates of CVR, thus supporting an earlier initiation of ARV therapy in HIV-1 infected males in the prison environment.

P68

Nitric oxide protects against HIV gp120 endothelial injury

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Purpose: The SMART study demonstrated that an higher number of cardiovascular events had occurred in patients receiving an intermittent therapy, suggesting HIV itself could contribute to the increased cardiovascular risk. Moreover vascular dysfunctions in HIV-1 patients have long been documented before era HAART. In addition to an indirect damage caused by pro-inflammatory cytokines, it is increasingly recognized the HIV infection might injury endothelial cells by both a direct damaging activity linked to cell invasion and virus replication and an indirect effect depending on viral proteins, such as TAT and gp120. Previous studies have demonstrated NO effectively protects endothelial cells from apoptosis and inflammation caused by a variety of noxious agents, but its efficacy against gp120 injury is unknown. In order to achieve new insights in NO activity in the endothelial injury by HIV we have investigated whether, in an in vitro model, NO ± aspirin protects against endothelial apoptosis induced by the HIV gp120.
Methods: Human umbilical cells (HUVEC) supplemented with human epithelial growth factor were used. Cells were cultured with 100 μM DETA-NO alone or in combination with aspirin 100 μM, in the presence of GP-120 1 μg/ml. The detection of nitrite/nitrate, mitochondrial membrane potential, the cytochrome c release into the cytosol and of caspase activities were performed.
Results: We observed:
1) HIV-1 gp120 has apoptotic activities in HUVEC cells.
2) DETA-NO, which slowly and continuously release NO, decreases the induced apoptosis induced by gp 120.
3) HIV-1 gp120 causes mitochondrial depolarization, releases of cytochrome c into the cytosol and increases caspase 9 activity.
4) NO prevents the gp120-induced mitochondrial depolarization and protects against cytochrome c translocation into the cytosol and the increased caspase activity.
5) These protective activities were not reproduced by aspirin.
Conclusions: These data provide further support the notion the HIV itself might promote endothelial injury and lead to increased cardiovascular complications. Moreover, this study grounds the basis to development of NO-based strategies for cardiovascular protection of HIV infected persons.

P69

Higher red blood cell distribution width is associated with a worse virologic and clinical situation in HIV-infected patients

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Background: A high level of red blood cell distribution width (RDW) is a novel prognostic marker that may reflect an underlying inflammatory state. It has recently shown that when increased, it is related to cardiovascular disease, mortality, and metabolic syndrome (MetS) in the general population.
Objectives: To analyse the potential relation between high levels of RDW and cardiovascular risk (CVR) and MetS in HIV-patients.
Patients and methods: Observational, cross-sectional study of a series of HIV-outpatients attended in our Hospital. Demographic, anthropometric, clinical, and fasting lab data were recorded in all cases. CVR at 10 years was evaluated by Framingham equation, and MetS diagnosed according to the National Cholesterol Education Program criteria. Statistic program: SPSS 17.0.
Results: 666 patients were included, 79.3% were men, and mean age was 44.7 years. Mean CD4 count was 506 cells/mm^3, 87.5% of the patients were on antiretroviral therapy, and 85.3% had undetectable HIV viral load. Mean RDW was 13.07% (range: 7.7-33.6%; 75th percentile 14,1%), with a prevalence of MetS of 15.7, 9.3, 18.8 and 16.6% first through fourth RDW quartile, and of patients with CVR >20% of 8.4, 4.0, 4.4 and 6.4%, respectively (p>0,05). The highest quartile of RDW (>14.1%) was associated with AIDS (OR 1.6, 95%CI 1.0-2.4; p 0.02), detectable HIV viral load (OR 1.5, 95%CI 1.01-2.4; p 0.04), and hypertension (OR 2.3, 95%CI 1.4-4.0; p 0.001).
Conclusions: In HIV-infected outpatients, higher RDW is related with detectable HIV viral load and with AIDS. Although it was associated with a traditional CVR factor as hypertension, we found no relation with MetS nor with higher CVR.
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P70

Alexithymia, an impairment of emotional cognitive processing, is a candidate risk factor for carotid artery plaque formation in HIV-infected patients

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Purpose of the study: Vascular aging is now one major concern in the care of HIV infected patients, as many factors may contribute to its faster progression in comparison with the general population. We investigated several psychological factors including Alexithymia, Type D personality, Mental and Physical Components (MCS and PCS) of Quality of Life (QoL) and Depression in a single Italian HIV cohort, well characterized for traditional cardiovascular (CV) risk factors and intima-media thickness of carotid arteries.
Methods: HIV infected patients followed at our Institution were consecutively enrolled from February to June, 2010. Carotid Intima-Media Thickness and the presence of plaque(s) were investigated by B-mode ultrasonography. Alexithymia was assessed with the 20-item Toronto-Alexithymia-Scale (TAS-20, positive score ≥ 49), Type D personality with the DS14 Distress Scale, depression symptoms with the Beck Depression Inventory (BDI, positive score ≥ 15) and QoL with the SF12 questionnaire. All statistical analyses were carried out using Stata 9.0 package.
Summary of results: We enrolled 93 HIV infected patients, 75.3% males, aged 45.4±9.8y (r. 21-69), 65.6% infected through heterosexual (39,8%) or homosexual (25,8%) exposure, 32.3% because of drug abuse or transfusion (2,1%). Coinfected patients were 29.0%, smokers 69.8%. As to HAART, 12.9% of patients were untreated, 51.6% on a PI-based and 35.5% on a NNRTI-based regimen, 67.7% of patients with undetectable HIV RNA. Carotid plaques (CP) were found in 40.9% of patients, in 15.0% bilaterally. Patients with CP were significantly older (50.6±8.7 vs 41.8±8.9, p<0.0001) and with lower nadir CD4 counts (p=0.04); CP were more frequent in hypertensive (p=0.02) and lipodystrophic (p=0.02) patients. Non significant differences were found between sexes (p=0.8), as well as in smokers (p=0.08), diabetics (p=0.2) and hypercholesterolemic patients (p=0.2). Patients with the Alexithymia trait had significantly more CP (p=0.002) or bilateral CP (p=0.008). Other psychological factors were not associated with CP. Stepwise multivariate logistic regressions confirmed only age (p=0.004) and Alexithymia (p=0.04) as independently associated with the presence of CP.
Conclusions: Alexithymia in our series appeared as more tightly associated with CP than most traditional CV risk factors. If this correlation will be confirmed, diagnosis of Alexithymia may allow psychological intervention programs to reduce CV risk in HIV patients.
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P71

Lipodystrophy and metabolic syndrome in Romanian HIV-infected adults

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Background: Lipoatrophy (LA), lipohypertrophy (LH) and mixed features of lipodystrophy (LD) are variable observed in human immunodeficiency virus (HIV)-infected patients. Dyslipidaemia is frequently reported as the overlap disorder of HIV related LD and metabolic syndrome (MS). Moreover, waist circumference could be a common measure of LH and MS criteria.
Objective: To assess the connection between LD and MS on HIV adult patients.
Methods: 76 HIV patients were retrospective evaluated, according to the Adult Treatment Panel III criteria for metabolic syndrome, Carr's clinical and biochemical criteria for LD, immunologic and ART status.
Results: The prevalence of MB was 18.42% (14/76). LD was found on 57.89% (44/76) as atrophy (22%), hypertrophy (20%) or mixed (16%). Characteristics of the patients are: av. age=32 [22;59] years old , sex ratio M/F=31/45, smokers: 27/49, av. length of HIV diagnostic 5.52 [20;1] years, av. LCD4 nadir=264/mm^3, av. LCD4 end-point=605.78/mm^3, ART: 15 naïve, 19 first line INNRT regimen, 43 first line IP regimen. Neither LH nor LA are related to 3/5 criteria of MS: hyperglycemia (p<0.001; OR=54), hypertrigliceridemia (p=0.014; OR=6), arterial hypertension (p<0.001; OR=24.75). Male sex influences development of LA (p=0.01; OR=2.57) and MS (p=0.04; OR=3.27), while LH is more frequent on females (p=0.05; OR=5.83) . Only LA is influenced by young age (p=0.03), low LDC4 nadir (p<0.001) and PI—ART regimen (p=0.03). The length of HIV diagnostic is related either LA or LH, but not with MS. Over waist circumference was significantly associated to LH (p<0.001), but not to MS.
Conclusions: 1. The prevalence of LD is higher than MS on HIV adults.
2. Sex differences are recorded both for LD and MS.
3. HIV and ART status are mostly related to LA.
4. MS is an apart condition from LD on Romanian HIV infected adults.
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P72

Mesenteric fat thickness in a group of HIV patients on HAART

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Background: Metabolic complications of HAART are well known. Yet the structural effects are rarely described. We report the baseline carotid artery intima-media thickness (IMT), mesenteric and subcutaneous fat in a pilot study for investigating their changes following treatment with lipid lowering agents in the presence of HAART.
Methods: All subjects were stable HIV positive patients receiving HAART. All have been attending a specialist clinic for monitoring HIV-related metabolic complications. Mesenteric, subcutaneous fat and IMT were measured by ultrasound operated by a specialist ultrasonographer. Fasting lipid was measured on the same day of ultrasound measurement. The relationships between variables were analyzed by non parametric test and univariate analysis of variance (ANOVA) where appropriate.
Results: A total of 27 patients were recruited in the period between June 2008 and June 2009. They have been on HAART for at least 2 years. Majority was male, while. NRTI+PI, NRTI+NNRTI, NRTI+NNRTI+PI were prescribed in 16, 9 and 2 patients respectively. The triple agent group was not included in subsequent analysis because of the small sample size. About 1/5 of patients were on anti-lipid agents. The mean cholesterol, triglyceride, IMT, mesenteric and subcutaneous fat of the NRTI+PI group were 5.4+1.1 mmol/l, 3.59+2.38 mmol/l, 0.069+0.018 mm, 0.58+0.21 cm and 1.24+0.82 cm respectively. The values of NRTI+NNRTI group were 4.88+1.3 mmol/l, 3.21+2.35 mmol/l, 0.069+0.017 mm, 0.97+0.27 mm and 1.94+1.28 mm respectively. Only the mesenteric fat showed significant difference between the 2 groups, p<0.01. There was no significant relationship between lipid and IMT.
Discussion and conclusions: Metabolic complications are commonly seen in HIV patients receiving HARRT. It is known that hyperlipidemia, increased IMT and mesenteric fat are related. However, there are little data on the effects of HAART per se on these parameters. Protease inhibitor is known to affect lipid by a class effect. Our results showed that patients receiving NRTI+NNRTI had a higher mesenteric fat than those on NRTI+PI. However, we failed to show any relationship between other

parameters probably due to small sample size. Larger study would be needed to confirm our finding and whether mesenteric fat is a more sensitive marker to reflect metabolic derangement.

P73

Hypertriglyceridemic waist identifies HIV+ men and women at increased cardiometabolic risk

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Background: Screening for increased waist circumference and hypertriglyceridemia (the hypertriglyceridemic-waist phenotype) is an inexpensive approach to identify patients at risk of coronary artery disease in apparently healthy individuals who may be at increased risk of type 2 diabetes and coronary heart disease because of an excess of intra-abdominal (visceral) fat. We examined the relationship between the hypertriglyceridemic-waist and selected cardiometabolic risk factors in HIV individuals.
Methods: The HW phenotype was defined as a waist circumference of 90 cm or more and a triglyceride level of 2.0 mmol/L or more in men, and a waist circumference of 85 cm or more and a triglyceride level of 1.5 mmol/L or more in women. Using these threshold values a total of 2322 patients (841 women and 1481 men) with HIV aged 18-75 years were divided into 4 groups: Low TG/Low WC, High TG/Low WC, Low TG/High WC, High TG/High WC. Continuous variables were analyzed using ANOVA or Kruskal-Wallis test where appropriate; categorical variables were compared using X2-test. The relationship between the HW and cardiometabolic risk assessed with Framingham risk score (FRS) was analyzed using multivariable logistic regression analyses.
Results: Compared with patients who had a waist circumference and triglyceride level below the threshold values, those with the HW phenotype had higher visceral adipose tissue (P<0.001), higher prevalence of hypertension and the metabolic syndrome (P<0.001), higher levels of total and LDL-cholesterol (P<0.001), lower levels of high-density lipoprotein cholesterol (P<0.001), and higher values of HOMA-insulin resistance (P<0.001) as shown in Table 1.
The FRS (median 10, range 5;16) was also highest in those with the HW phenotype (P<0.001). These observations were true independent of gender and remained significant after statistical control for illicit drug use, insulin resistance, antiretroviral therapy exposure, leg fat, and proteinuria as shown in image 1. Figure 1
Conclusions: Among HIV patients from an Italian monocentric cohort, the HW phenotype was associated with a deteriorated cardiometabolic

Table 1 (abstract P73)

	Low TG/Low WC	High TG/Low WC	Low TG/High WC	High TG/High WC	P value
n (%)	592 (25.50)	856 (36.86)	311 (13.39)	563 (24.25)	-
DEMOGRAPHICS					
Women, n (%)	284 (47.9)	245 (28.62)	145 (46.62)	167 (29.66)	< 0.001
Age mean (± S)	43.3 (6.7)	44.4 (6.6)	45.4 (7.7)	46.9 (7.8)	< 0.001
Physical activity, n (%)	232 (39.19)	282 (32.94)	103 (33.12)	152 (27.00)	< 0.001
Smoke (> 10 cigs/day), n (%)	187 (31.59)	285 (33.29)	73 (23.47)	165 (29.31)	0.010
Alcohol consumption, n (%)	270 (45.61)	363 (42.41)	154 (49.52)	279 (49.56)	0.032
ANTHROPOMETRICS					
BMI mean (± SD)	21.2 (2.2)	21.7 (2.3)	26.3 (3.9)	27.1 (3.8)	< 0.001
VAT cm^3, median (IQR)	75 (49; 103)	100 (67; 138)	136 (101; 194)	172 (125; 236)	< 0.001
Waist Circumference cm, median (IQR)	79 (75; 83)	81 (77; 85)	94 (90; 98)	95 (91; 101)	< 0.001
Hip Circumference cm, median (IQR)	87 (83; 90)	86 (83; 89)	94 (91; 97)	94 (90.5; 98)	< 0.001
Thigh Circumference cm, median (IQR)	45 (42.5; 48)	45 (43; 48)	49 (46; 52)	49 (46; 52)	< 0.001
% of Leg Fat, median (IQR)	12.6 (7.2; 19.9)	7.7 (5.6; 12.7)	18.1 (12.5; 26.2)	14.0 (9.9; 21.1)	< 0.001
HIV history					
IDU n (%)	201 (33.95%)	286 (33.41%)	99 (31.83%)	151 (26.82%)	< 0.001
CD4+ Nadir median (IQR)	181 (78; 260)	154 (59; 260)	189 (90; 290)	171.5 (63; 260)	0.014
CD4+ Current median (IQR)	499.5 (370; 672)	523 (364; 700)	492 (360; 658)	543.5 (375; 737)	0.113
VL undetectable n (%)	363 (61.32)	492 (57.48)	190 (61.09)	329 (58.44)	0.432
Months of PI exposure median (IQR)	24 (0; 60)	35.5 (8; 69.5)	30 (0; 58)	39 (9;7269)	0.005
Months of NNRTI exposure median (IQR)	16 (0; 45)	18 (0; 48)	17 (0; 49)	16 (0; 46)	0.445
CARDIOVASCULAR					
Framingham risk median (IQR)	2 (1; 5)	6 (2; 10)	2 (1; 6)	6 (2; 12)	< 0.001
Hypertension, n (%)	131 (22.13)	302 (35.28)	119 (38.26)	259 (46.00)	< 0.001
Albuminuria, n (%)	38 (6.42)	84 (9.81)	24 (7.72)	59 (10.48)	< 0.001
LIPID METABOLISM					
Triglycerides median (IQR), mmol/L	1.03 (0.81; 1.27)	2.32 (1.87; 3.41)	1.10 (0.89; 1.30)	2.37 (1.85; 3.34)	< 0.001
Total cholesterol mean (± SD), mmol/L	4.43 (1.09)	5.05 (1.22)	4.55 (1.10)	5.17 (1.30)	< 0.001
HDL mean (± SD), mmol/L	1.36 (0.44)	1.05 (0.42)	1.33 (0.41)	1.06 (0.30)	< 0.001
LDL mean (± SD), mmol/L	2.70 (0.84)	3.02 (1.03)	2.83 (0.91)	3.09 (1.01)	< 0.001
ApoA1 mean (± SD), mg/dL	148.7 (32.6)	137.5 (26.8)	149.9 (29.8)	139.7 (27.0)	< 0.001
ApoB mean (± SD), mg/dL	85.6 (23.4)	108.8 (29.0)	90.3 (24.3)	110.3 (27.3)	< 0.001
HOMA-IR median (IQR)	2.25 (1.39; 3.38)	3.07 (2.04; 5.01)	3.26 (2.21; 5.13)	4.31 (2.74; 6.68)	< 0.001

		Univariate analyses			Multivariable analysis		
		OR	95% C.I.	p-value	OR	95% C.I.	p-value
HW phenotypes							
	Low TG/Low WC	1 (Ref.)	-	-	1 (Ref.)	-	-
	High TG/Low WC	12.10	3.75; 39.01	**< 0.001**	5.40	1.20; 24.24	**0.028**
	Low TG/High WC	2.58	0.57; 11.60	0.217	4.68	0.74; 29.69	0.101
	High TG/High WC	6.17	1.80; 21.19	**0.004**	10.26	2.17; 48.58	**0.003**
% of leg fat		0.91	0.87; 0.95	**< 0.001**	0.93	0.87; 0.98	**0.019**
IDU		0.86	0.51; 1.44	0.566	1.22	0.56; 2.64	0.606
HOMA		0.96	0.88; 1.04	0.340	0.93	0.82; 1.06	0.266
Albuminuria		1.23	0.57; 2.67	0.593	0.93	0.34; 2.52	0.886
ART exposure, per 1 month increase		0.99	0.99; 1.00	0.226	0.99	0.98; 1.00	0.272
CD4+ nadir		0.99	0.99; 1.01	0.214	1.00	0.99; 1.00	0.733

Figure 1 (abstract P73) Univariate and multivariable logistic regression anlyses for associated factors with Framingham risk score more than 20%.

risk profile and an increased FRS. It is suggested that the simultaneous measurement and interpretation of waist circumference and fasting triglyceride could also be used among HIV patients as an inexpensive tool to identify patients with excess visceral fat and with related cardiometabolic abnormalities.

P74

Metabolic: week 48 comparison of METABOLIK parameters and biomarkers in subjects receiving darunavir/ritonavir or atazanavir/ritonavir

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Purpose: Protease inhibitors may contribute to metabolic complications and cardiovascular risk associated with HIV infection. Here we investigate metabolic changes following treatment with darunavir/ritonavir (DRV/r)-compared with atazanavir/ritonavir (ATV/r)-based therapy.

Methods: In this 48-week, Phase IV, multicenter, open-label, randomized, exploratory study, HIV-1—infected, antiretroviral naïve adults were given DRV/r 800/100mg once daily (qd) or ATV/r 300/100mg qd, both with tenofovir/emtricitabine 300/200mg qd. Week 48 changes in fasting lipids, glucose, insulin, insulin sensitivity, creatinine clearance, biomarkers (inflammation, coagulation and bacterial translocation), CD4 count, viral load (VL) and safety are reported. Observed values and descriptive statistics are reported through Week 48 for intent-to-treat and lipid evaluable populations.
Results: 34 (median age, 37 years; men, n=29) and 31 (median age, 35 years; men, n=27) subjects were randomized to the DRV/r arm and ATV/r arm, respectively. Of these, 29 DRV/r and 25 ATV/r subjects completed Week 48. At Week 48, changes in fasting lipids and biomarkers were similar between arms. Although rates of adverse events (AEs) and laboratory abnormalities were comparable between arms, ATV/r arm had higher rates of grade 2—4 hyperbilirubinemia (n=27 [87%] vs n=1 [3%]). At Week 48, 77% of DRV/r and 71% of ATV/r subjects had VL <50 copies/mL (confirmed virologic response). Table 1.
Conclusions: Changes from baseline to Week 48 in fasting lipids, glucose, insulin, HOMA-IR, creatinine clearance, biomarkers, CD4 and VL were similar for DRV/r and ATV/r. Given its favorable metabolic profile, which was maintained over 48 weeks, DRV/r provides a valuable therapeutic option for HIV-1—infected subjects.

Table 1 (abstract P74)

Changes in metabolic and efficacy parameters from baseline to Week 48

	DRV/r		ATV/r		Difference in mean change between arms, (95% CI)
	BL	Change from BL at Week 48	BL	Change from BL at Week 48	
Fasting lipid parameters[a]					
TG, mg/dL					
Mean (SD)	114 (57)	26 (69)	114 (84)	10 (74)	16.5 (−25.0, 58.0)
Median (IQR)	87 (77, 153)	11 (−;15, 37)	90 (65, 119)	15 (−24, 54)	
TC, mg/dL					
Mean (SD)	142 (28)	22 (31)	165 (30)	12 (32)	10.5 (−7.7, 28.8)
Median (IQR)	136 (122, 159)	22 (10, 40)	163 (140, 183)	13 (−11, 29)	
LDL, mg/dL					
Mean (SD)	85 (22)	15 (26)	100 (24)	14 (27)	0.8 (−14.6, 16.3)
Median (IQR)	81 (71, 101)	17 (1, 30)	104 (79, 117)	8 (−7, 33)	
HDL, mg/dL					
Mean (SD)	38 (13)	6 (7)	45 (14)	4 (10)	2.3 (−2.8, 7.3)
Median (IQR)	37 (28, 44)	6 (2, 10)	44 (39, 49)	2 (−2, 11)	
TC/HDL ratio					

Table 1 (abstract P74) *(Continued)*

Mean (SD)	4.1 (1.14)	0.1 (1.06)	3.9 (1.02)	−0.1 (0.75)	0.20 (−0.34, 0.75)
Median (IQR)	4.08 (3.41, 4.90)	0.05 (−0.62, 0.67)	3.87 (3.10, 4.24)	−0.08 (−0.54, 0.26)	
Apo A1, mg/dL					
Mean (SD)	115 (26)	12 (16)	128 (22)	3 (19)	9.7 (−0.5, 19.8)
Median (IQR)	112 (96, 127)	11 (−1, 27)	127 (112, 132)	3 (−11, 19)	
Apo B, mg/dL					
Mean (SD)	74.5 (19)	4 (21)	81.7 (18.5)	2 (17)	2.0 (−9.3, 13.4)
Median (IQR)	72 (64, 84)	3 (−3, 15)	81 (66, 95)	4 (−10, 12)	
Apo B/A1 ratio					
Mean (SD)	0.68 (0.20)	0.68 (0.25)	0.65 (0.16)	0.66 (0.17)	−0.02 (−;0.125, 0.079)
Median (IQR)	0.67 (0.55, 0.82)	0.63 (0.51, 0.79)	0.64 (0.56, 0.73)	0.68 (0.54, 0.78)	
Fasting glucose, fasting insulin and HOMA-IR,[b] mean (SD)					
Glucose, mg/dL	89 (12)	3 (9)	90 (11)	6 (22)	−3.6 (−12.8, 5.6)
Insulin, ulU/mL	6 (6)	1 (6)	9 (14)	−3 (17)	3.8 (−3.0, 10.6)
HOMA-IR	1.62 (1.70)	0.04 (2.26)	2.94 (6.02)	−1.24 (8.01)	1.27 (−2.66, 5.20)
Creatinine clearance,[b] mean (SD)					
Creatinine clearance, mL/min	107.6 (28.7)	−0.00 (0.288)	110.9 (27.9)	−0.03 (0.244)	0.03 (−0.12, 0.18)
Biomarkers,[b] mean (SD)					
IL-1 Beta, pg/mL	0.2 (0.3)	0.3 (1.4)	0.3 (0.3)	−0.1 (0.3)	0.40 (−0.22, 1.04)
IL-6, pg/mL	1.9 (1.9)	0.2 (7.3)	1.0 (1.3)	0.3 (0.9)	−0.08 (−3.24, 3.08)
hs-CRP, mg/L	3.1 (5.2)	1.2 (11.2)	2.2 (2.5)	0.6 (5.1)	0.65 (−4.55, 5.85)
TNF-alpha, pg/mL	4207 (1702)	−1384 (1722)	2957 (727)	−442 (722)	−942.1 (−1735.3, −149.0)
LPS, pg/mL	85 (29)	−18 (35)	87 (31)	−17 (51)	−1.4 (−25.6, 22.9)
D-dimer, ng/mL	373 (580)	−192 (587)	189 (111)	−24 (144)	−168.0 (−432.2, 96.2)
Fibrinogen, g/L	3.3 (1.1)	−;0.3 (1.1)	3.2 (0.7)	−0.3 (0.9)	0.02 (−0.60, 0.61)
Efficacy parameters,[b] mean (SD)					
Viral load, $\log_{10}$ copies/mL	5.0 (0.8)	−3.3 (0.8)	4.6 (0.7)	−2.9 (0.7)	−0.4 (−0.8, 0.1)
CD4+ cell count, cells/mm^3	268.3 (144.2)	217.4 (116.8)	326.7 (174.1)	205.3 (153.5)	12.1 (−61.8, 86.1)

[a]Lipid evaluable set; [b]ITT-observed (sample size varies by time point and parameter);
DRV/r, darunavir/ritonavir; ATV/r, atazanavir/ritonavir; BL, baseline; CI, confidence interval; TG, triglycerides;
SD, standard deviation; IQR, interquartile range; TC, total cholesterol; LDL, low-density lipoprotein;
HDL, high-density lipoprotein; Apo, apolipoprotein; HOMA-IR, homeostasis model assessment-estimated insulin resistance;
IL, interleukin; hs-CRP, high-sensitivity c-reactive protein; TNF, tumor necrosis factor; LPS, lipopolysaccharide;
ITT, intent-to-treat

P75

Adiponectin and leptin levels in HIV-infected patients with lipodystrophy in Southern India

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Purpose of the study: Evidence suggests that the level of adipokines (adiponectin and leptin) may be altered in lipodystrophy related to the long-term use of antiretroviral therapy (ART). The purpose of this study was to estimate the levels of adiponectin and leptin in HIV infected patients with lipodystrophy and to correlate them to metabolic parameters.

Methods: In this cross sectional study, consenting 79 HIV+ve patients on antiretroviral therapy (for more than six months) visiting the Namakkal Government Hospital were recruited. Demography, anthropometry and ART regimens were collected. Patients' self-perception of lipodystrophy was determined using standardized questionnaires and clinically confirmed. An overnight fasting blood was drawn to determine serum adiponectin (Ray Biotech ELISA), serum leptin (DRG International ELISA) and insulin. Statistical analysis included analysis of variance and Pearson's correlation.

Summary of results: Men and women on ART with lipodystrophy (60.8%) when compared to those without lipodystrophy (30.2%) had similar mean adiponectin (p=0.842) moderately lower leptin (p=0.133), and higher insulin resistance (p=0.031). Patients with lipodystrophy had lower BMI than those without lipodystrophy (p=0.02) and similar WHR (p=0.174).

Among the total study population stavudine usage was associated with lower adiponectin (p=0.018) but not leptin whereas insulin (p=0.007) and insulin resistance (p=0.00) positively correlated with leptin and not

adiponectin. In lipodystrophic patients, adiponectin had positive correlation with BMI (p=0.014) and had no correlation with insulin (0.304), and insulin resistance (0.250) whereas leptin had positive correlations with insulin (p=0.00) and insulin resistance (p=0.001). Among patients without lipodystrophy, adiponectin levels had negative correlation with stavudine usage (p=0.018) while leptin had no significant correlation.
Conclusions: Patients with lipodystrophy had moderately lower leptin and higher insulin resistance compared to those without lipodystrophy. Leptin seemed to have influence on insulin and insulin resistance while adiponectin did not influence insulin levels in this study population. Stavudine usage influenced adiponectin but not leptin levels.

P76

Nutritional status in HIV-infected patients using Changi's mini nutritional assessment

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Objective: The achievement of an adequate nutritional status is an important goal in the treatment of HIV infection and requires a proper assessment. We studied the nutritional status of a group of HIV-infected patients using biochemical and anthropometric measures.
Materials and methods: We assessed 91 outpatients followed in an urban infectious disease clinic in south Madrid (Spain). In each case age, gender, race, HIV risk group, hepatitis C virus (HCV) infection status, smoking status, degree of immune depression, viral load, presence or absence of an AIDS diagnosis, time since diagnosis of HIV infection, antiretroviral therapy (ART), type of ART, anthropometric measures (weight, waist circumference, BMI, tricipital fold and arm circumference), and blood and biochemical measures (lymphocyte count, CD4+ cell count, albumin, triglycerides, cholesterol).
Results: Median age was 46 years; 69.2% were males, 81.3% Caucasian. Viral load was below 20 copies/ml and mean CD4 count 468 cells/μL Using Changi's mini nutritional assessment, which involves immunological, biochemical and anthropometric parameters, we found malnutrition in 81.1%; it was severe degree in 16.7%. Most patients were classified as caloric malnutrition (67.8%). Serum cholesterol was increased in 24.7% and triglyceride in 33.3%. Serum albumin was normal in 96.6%.
Anthropometric measurements showed diminished fat compartment (decreased tricipital fold in 66.7% of males and 51.9% of females) whereas muscular compartment was preserved (muscular arm circumference was decreased in 34.9% of males and 25.9% of females). Tricipital fold 50th percentile was 8 mm in males and 19.9 mm in women; corresponding values for arm circumference were 26 cm and 22 cm, respectively. Of males, 6.6% were underweight, as were 23.1% of women. Malnutrition was associated with BMI (p=.0001), waist circumference (p=.029) and with HCV infection (p=.037). Caloric malnutrition was associated with BMI (p=.0001), waist circumference (p=.046) and chronic HCV infection (p=.049). It was also related with the degree of immune suppression (<200, 200-500 and >500 CD4+ cells/μL; p=.019).
Conclusions: Despite HAART we found malnutrition, at least of small degree, in more than 80% of patients, mainly caloric malnutrition. Arm fat compartment was most frequently involved. Chronic HCV infection, degree of immune suppression, low BMI and waist circumference are related with the presence of malnutrition.

P77

Dietician-based approach to lipodystrophic syndrome: role of bioelectrical impedance analysis at week 12

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Background: Lipodystrophic syndrome (LS) is the expression of HIV infection chronicity and negatively affect survival, adherence and quality of life. About 30% of patients suffer from LS; among them, 30% need a specific treatment. We developed a multidisciplinary diagnostic and therapeutic program funded by Regione Piemonte. The patient is guided step by step, aimed at working on changeable lifestyles, to reverse metabolic alterations and to cope with the distress related to change in body image.
Methods: The project is carried out in two regional hospitals in Piemonte. The team is formed by specialists in HIV disease, a nutritionist, a dietician, a psychologist, a cardiologist, a plastic surgeon and a kinesiologist. The first step is the metabolic assessment, then the psychological visit and the dietician follow-up. It is based on clinical and educational aspects of dietetic therapy (i.e. dietetic diary and nutritional counseling) and it starts with Bioelectrical Impedance Analysis (BIA). We use the Tanita BC 418 MA® Segmental Body Composition Analyser that prints out a body profile including weight, body fat percentage, body fat mass (BFM), fat free mass, estimated muscle mass and basal metabolic rate. Dietician visits are at time 0,1,3,6,12 months. The patients are also invited to participate in a psychological homogeneous group and in a group of physical activity (Nordic Walking).
Results: At date 99 patients have been enrolled: 40 females, 59 males; mean age 48,9 years; mean age of HIV infection 9,9 years; risk factors for HIV infection: 20 IVUD, 79 sexual intercourse; CDC Classification: 47 A, 27 B, 25 C. At baseline 39 (39%) patients had also metabolic syndrome; 36 (36%) had cardiovascular risk at 10 years ≥10%; 66 (66%) had BMI≥ 25. At date, 10 (10%) patients dropped out after the metabolic assessment; 11 (11%) underwent a cardiological visit. 38 patients were assessed with BIA at baseline and at week 12: 26/38 (69%) significantly decreased their BMI and their BFM and 8/26 (31%) improve plasma lipids, especially triglycerides (TG) (2 of them started pharmacological therapy to decrease TG); 10/38 (26%) had no significant BMI and BFM variation; 2/38 (5%) increased BMI and BFM.
Conclusions: The dietician intervention together with a simple, reliable, repeatable and low cost examination can establish a pattern to observe and improve important metabolic parameters. The follow-up will clarify if early BIA variations are predictive markers of long-term outcome.

P78

Altered phosphate metabolism in HIV-1-infected patients: another feature of metabolic syndrome?

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Purpose of the study: Metabolic syndrome represent a cluster of cardiovascular risk factors that has become a serious problem for HIV-1-infected patients. It was proposed that disturbances in phosphate metabolism may represent a key feature of metabolic syndrome. Because phosphate is involved directly in carbohydrate metabolism, hypophosphatemia can results in impaired utilization of glucose, insulin resistance and hyperinsulinemia. Thus, we undertook the present study to investigate the relationship between phosphate levels and the presence of the characteristics of metabolic syndrome, as well as the mechanism that may be responsible for reduced phosphate levels in patients with this syndrome.
Methods: 130 HIV-1-infected patients were consecutively enrolled in a prospective, cross-sectional, single centre study. All patients were receiving HAART for more than six months. We selected two groups: HIV + patients with metabolic syndrome (group A, n=86) and HIV+ patients without metabolic syndrome (group B, n=44). The diagnosis of metabolic syndrome was based on Adult Treatment Panel III guidelines. Demographic characteristics, metabolic variables, duration of Tenofovir therapy, duration of HAART, CD4 and viral load were collected. Kidney tubular function was examined using tubular resorption of phosphate and normalized renal threshold phosphate concentration.
Summary of results: Patients with metabolic syndrome showed significantly lower phosphate (3.13 mg/dl vs 3.55 mg/dl, p<0.01) and higher insulin (13.2 mg/dl vs 6.9 mg/dl, p<0.01) levels compared with controls. There was a linear significant decrease in phosphate values as

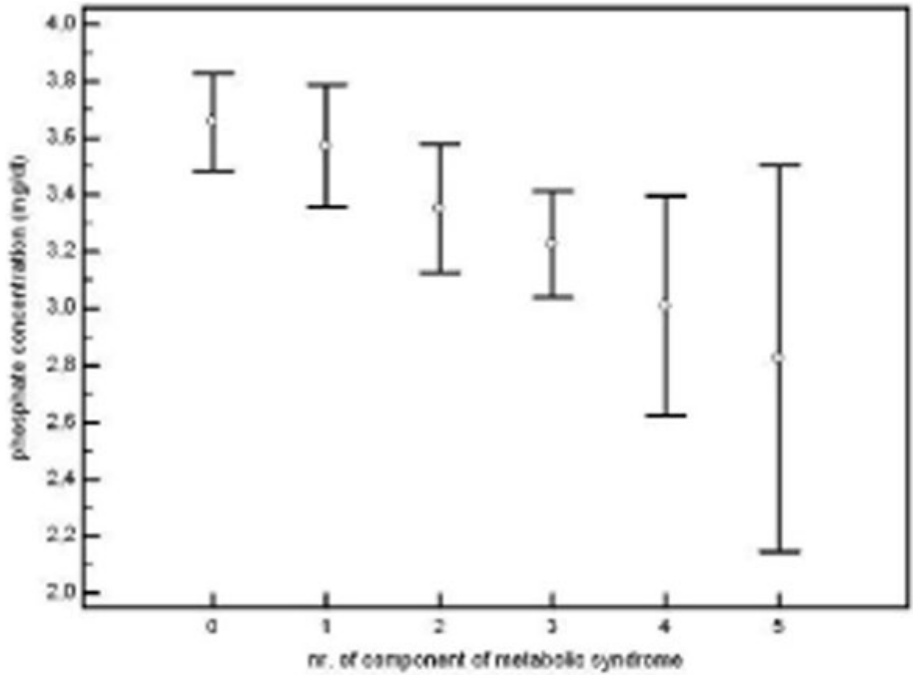

Figure 1 (abstract P78)

the number of components of metabolic syndrome increased (p<0.001). Multiple regression analysis including all 5 components of metabolic syndrome and months of TDF treatment showed that insulin level was the most discriminant of serum phosphate (r=-0.22, p<0.01). Figure 1

Conclusions: Our preliminary data demonstrated that HIV-1-infected patients with metabolic syndrome showed significantly lower phosphate levels compared with HIV-1-infected patients without metabolic syndrome regardless of tenofovir based therapy. The clinical significance of these disturbances, as well as their importance as target for preventive or therapeutic interventions, remains to be established.

P79

Switching to nevirapine (NVP) significantly increases high-density lipoprotein cholesterol (HDL-C) in treatment-experienced patients (NEVICOR study)

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Background: A strong inverse relationship between the plasma concentration of HDL-C and the incidence of coronary heart disease is widely accepted. Few interventions have succeeded to increase plasma HDL levels in HIV-infected pts. NVP has a favorable lipid profile, and clinical trials have suggested that it could have a differential effect on plasma HDL-C levels.

Methods: Prospective, single arm, multicenter study. We included patients on stable antiretroviral therapy with HIV RNA ≤50 copies/mL for at least one year that were switched to a NVP-containing regimen. Patients receiving lipid lowering therapy were excluded. HDL-cholesterol and other lipid parameters at baseline and after 24 weeks of treatment with NVP are compared.

Results: Among 130 pts included in the study, 119 (91%) could be evaluated. BL characteristics: median age 44, female 24%, current smokers 53%. Previous AIDS 29%, CD4 count 502/mm^3. Time on ARV therapy 42 months. Previous therapy: efavirenz 38%, 3 NRTI 12%, PI 50%. Accompanying nucleosides were tenofovir/emtricitabine in 69%, and abacavir/lamivudine in 31%.

Table 1 shows the 24-week results of lipid profile.

At 24 week, the proportion of patients with HDL-C>40 mg/dl were 69.7% (95%CI 60.7-77.8), compared to 52.1% (95%CI 42.8-61.3) before taking NVP (p<0.01). The Framingham risk score decreased from 7.6 to 6.6 (p<0.05) after switching to NVP.

Conclusions: Switching to NVP-containing regimens in patients on stable therapy is associated with a significant increase in HDL-C and decrease in TC/HDL-c, with an overall improvement in the Framingham score.

Table 1 (abstract P79)

		Mean	S. D.	N	p
Triglycerides (mg/dl)	Previous treatment	213.8	178.3	119	
	Nevirapine	154.6	95.3	119	<0.05
TC (mg/dl)	Previous treatment	203.6	48.0	119	
	Nevirapine	198.1	40.5	119	0.108
HDL-C (mg/dl)	Previous treatment	43.8	14.6	119	
	Nevirapine	49.3	16.8	119	<0.05
TC/HDL-C	Previous treatment	5.1	1.9	119	
	Nevirapine	4.3	1.3	119	<0.05
LDL (mg/dl)	Previous treatment	120.2	38.1	107	
	Nevirapine	119.2	32.7	107	0.705
VLDL (mg/dl)	Previous treatment	35.1	19.4	25	
	Nevirapine	23.6	12.6	25	<0.05

P80

Switching from Kivexa + efavirenz to Atripla reduces total cholesterol in hypercholesterolemic subjects: final results of a 24-week, randomized study

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Background: Dyslipidemia in persons with HIV contributes significantly to cardiovascular (CV) risk. Abacavir (ABC) has been shown to increase lipid levels and some cohort studies have suggested an association between ABC use and myocardial infarction (MI). Comparative data suggested Truvada (TDF/FTC) has a lesser effect on lipid parameters than Kivexa [KVX]. We investigated the change in fasting lipid parameters in hypercholesterolemic subjects switching from KVX + Efavirenz [EFV] to Atripla [ATR].
Methods: A 24-week, UK, open-label study in subjects stable on once daily (QD) KVX+EFV, HIV RNA <50 copies/mL for ≥6 months and fasting total cholesterol [TC] ≥5.2 mmol/L at screening, randomized to continue KVX+EFV or switch to QD ATR. The primary endpoint was change from baseline to Week 12 in fasting TC. Changes in fasting lipid parameters and 10 year risk score for coronary heart disease (CHD) were also assessed. At Week 12 subjects continuing on KVX+EFV were switched to ATR (delayed switch to ATR) and all subjects received ATR until Week 24.
Results: 157 randomized subjects received at least 1 dose of study medication; 78 continued KVX+EFV, 79 switched to ATR at baseline; 69 switched to ATR at Week 12. Subjects were well matched for baseline characteristics. Figure 1.
At 12 weeks there was a significant reduction in TC, LDL, HDL and TG in the ATR arm ($p<0.001$) and the ATR vs KVX+EFV between group difference ($p<0.001$), which was confirmed for TC, LDL and HDL in the delayed switch to ATR arm after 12 weeks of switch. The mean (SD) change in 10-year risk for CHD was -0.6 (3.85) ATR vs -0.1 (2.69) KVX+EFV at Week 12 and -0.1 (3.68) in the delayed switch to ATR arm after 12 weeks of switch. There were no protocol defined virologic failures and no study drug related SAEs.
Conclusion: Switching from KVX+EFV to ATR led to a significant, rapid decline in lipid parameters and this may have had a positive impact on calculated CHD risk while maintaining virologic suppression. The full study results showed that the initial 12 week results were replicated in the delayed switch to ATR arm. These results confirm that ATR is a preferred treatment option to a KVX based regimen in hypercholesterolemic patients.

P81

CD4 response, lipid changes and liver outcome in 506 patients receiving nevirapine-based regimens for a median of 9 years

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Purpose of the study: To evaluate long-term outcomes in pts maintaining a NVP-based regimen.
Methods: Retrospective cohort study. Pts received a NVP regimen for at least 5 years and continued up to present. Demographic, clinical, and analytical variables were recorded. A sample size of 506 pts was randomly selected from participating cohorts.

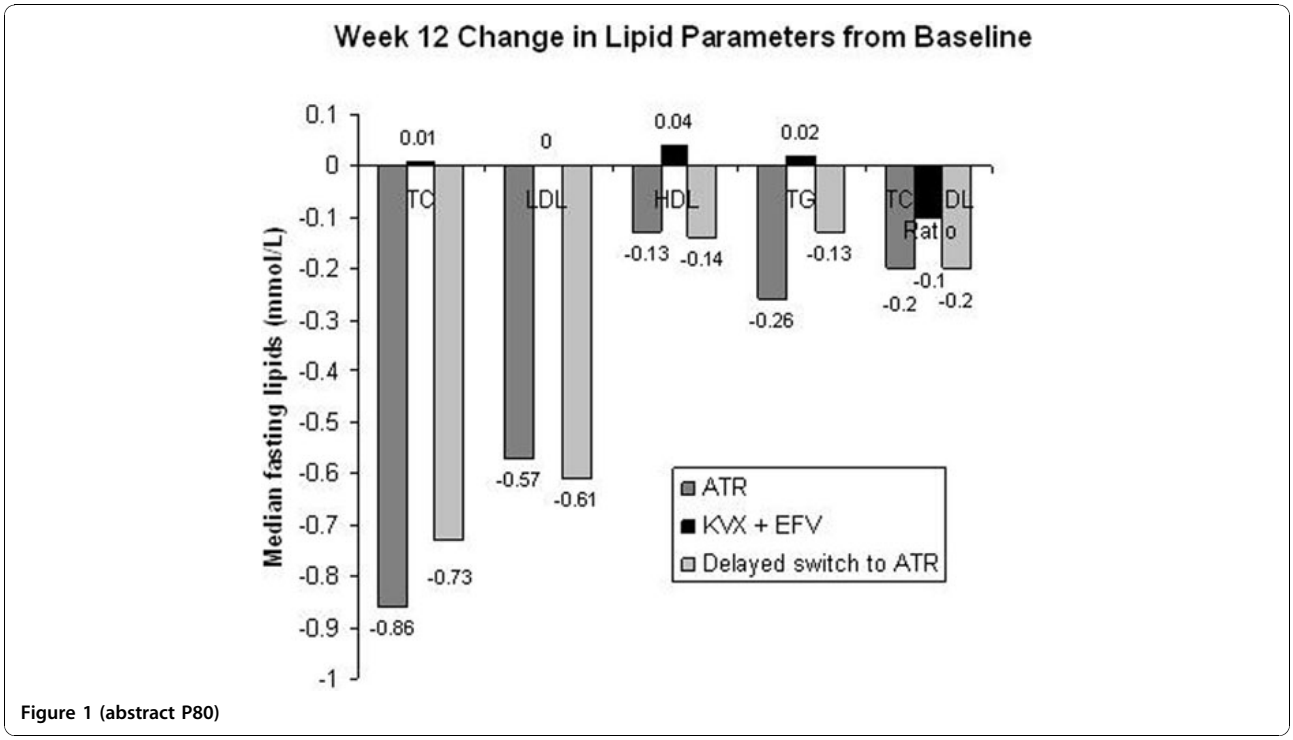

Figure 1 (abstract P80)

Summary of results: Median follow up 8.9 (5.7-11.3) years (506 pts followed ≥ 6 years and 270 ≥ 9 years). At baseline: 74% men, 47 years old, 36% drug users, 40% AIDS, 40% HCV+, 14% alcohol. 45% detectable VL, CD4 395/uL, 19% CD4 < 200/uL, 27% ALT Grade 1-2, 36% AST grade 1-2. 30% ART naïve. 84% received NVP+2 nucleosides (NRTI) during the study period, 17% PI.

Most frequent current combinations were NVP+TDF/FTC in 31%, +ABC/3TC in 24% and +ZDV/3TC in 22%. 97% reached undetectable VL. In pts receiving 2 NRTI+NVP (n=423), regardless of being HCV+ or -, a significant increase was observed in general health status markers: hemoglobin, platelets and albumin (all p<0.001), and +218 and +322 CD4 cells increase after 6 and 9 years (p<0.001). Triglyceride levels decreased 19% and total cholesterol 4% in pretreated pts vs 9% and 12% increase in naive pts. After 6 years, the proportion of pts with lipid levels above (below in HDL) the NCEP thresholds for recommending lipid lowering therapy was 50% for TC, 43% TG, 34% LDL and 14% HDL.

Regarding liver outcomes in the 506 pts, a significant decrease in ALT and AST levels were found in naive (p=0.02, p<0.001) and HCV+ pts (p=0.065, p<0.001), while a strong decrease in alkaline phosphatase (AP) levels (up to -44%) was observed in naive and pretreated pts as well as in HCV+ or — (all p<0.001), regardless of TDF use. GGT levels increased by 78% regardless of the patient status (p<0.001).

This favourable changes in liver function tests occurred despite 53% of 89 pts in whom biopsy or fibroscan was performed after a median of 7.1 years of NVP therapy, fibrosis (≥ F2 and/or 7≥kPa) was detected. In addition, as a consequence of transaminase and platelet changes, Fib-4 index significantly decreased in ARV naive HIV/HCV pts at 9 years (p=0.01).

Conclusions: Patients receiving a long-term NVP-including regimen, show a progressive improvement in general health status and CD4 response, an acceptable lipid profile and favourable changes in liver function tests, even in those with HCV+. The marked decrease in AP levels shown in this large cohort of NVP-treated pts merits further study.

P82

Chronic kidney disease in patients with normal eGFR at baseline: results from EuroSIDA

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Background: Chronic kidney disease (CKD) is an emerging co-morbidity among HIV patients. Recent EuroSIDA analyses identified CKD risk factors including hypertension, diabetes, hepatitis C, age>50, low CD4 count, prior AIDS events and cumulative exposure to certain antiretrovirals (ARVs; tenofovir, indinavir atazanavir and probably lopinavir/ritonavir).

Objectives: We aimed to extend our previous findings by estimating the CKD incidence among patients with normal kidney function at baseline with and without other risk factors, in order to disentangle if ARVs also pose a risk to patients with normal kidney function, and not only to those with pre-existing impairment.

Methods: Cockcroft-Gault equation standardised for body surface was used to estimate Glomerular filtration rate (eGFR, ml/min/1.73m^2). Patients with baseline eGFR> 90 were included. Baseline was defined as the first eGFR assessment after 01.01.2004. CKD was defined as 2 consecutive eGFR<60 (>3 months apart). Follow-up was from baseline until CKD or last eGFR. Unadjusted incidence rates (IR) are presented per 100 PYFU and stratified by cumulative ARV exposure.

Results: 4824 patients had baseline eGFR>90. They were predominantly white (86.4%), male (74.4%) infected via homosexual contact (41.4%). At baseline 17.6% had hypertension, 3.7% diabetes and 24.1% hepatitis C. Median age was 40 (IQR: 34.6-45.1) years, and median CD4 count 446 (300-640) cells/mm^3. During 15391 PYFU and a median follow-up of 41 (IQR 21-56) months, 34 (0.7%) developed CKD (IR 0.22, 95%CI 0.15-0.30). Among patients without traditional risk factors, 7 patients developed CKD during 8076 PYFU (IR 0.09 95%CI 0.04-1.18). In unadjusted analyses CKD incidences increased with increasing cumulative ARV exposure for the ARVs tested (test for trend significant for all drugs investigated) (Figure 1).

Conclusions: This study of almost 5000 patients and a median follow-up >3 years demonstrates that CKD development from normal kidney function was infrequent. The IR was higher in patients with renal risk factors and those cumulative exposed to the ARVs investigated in unadjusted models. This suggests that ARVs might also pose a risk in

ARV	IR (95% CI) per 100 PYFU cumulative exposure to ARVs					Univariate IRR per year exposure (95% CI)	P value (test for trend)
	None	0-1 year	1-2 years	2-3 years	> 3 years		
Tenofovir	**0.11**	**0.28**	**0.52**	**0.25**	**0.48**	**1.33**	**0.0011**
	(0.05 -0.20)	**(0.09-0.67)**	**(0.23-1.03)**	**(0.05-0.72)**	**(0.21-0.94)**	**(1.12-1.57)**	
Events/PYFU	10/ 9186	5/ 1784	8/ 1531	3/ 1209	8/ 1681		
Indinavir	**0.11**	**0.17**	**0.53**	**0.66**	**0.39**	**1.24**	**0.0005**
	(0.05 -0.20)	**(0.04 -0.50)**	**(0.21 -1.09)**	**(0.24- 1.43)**	**(0.17- 0.78)**	**(1.10- 1.39)**	
Events/PYFU	10/ 9385	3/ 1742	7/1323	6/ 915	8/ 2027		
Lopinavir/r	**0.14**	**0.23**	**0.31**	**0.14**	**0.65**	**1.37**	**<0.0001**
	(0.08 -0.23)	**(0.05-0.67)**	**(0.06-0.89)**	**(0.003-0.59)**	**(0.35- 1.11)**	**(1.20 -1.57)**	
Events/ PYFU	14/ 10159	3/ 1304	3/ 984	1/ 950	13/ 1995		
Atazanavir	**0.15**	**0.45**	**0.64**	**0.39**	**0.64**	**1.37**	**0.0032**
	(0.09- .24)	**(0.15-1.06)**	**(0.21-1.49)**	**(0.05-1.34)**	**(0.13-1.88)**	**(1.11- 1.69)**	
Events/PYFU	19/ 12504	5/ 1100	5/ 782	2/ 538	3/ 467		

Figure 1 (abstract P82)

patients with normal kidney function. Adjusted analyses were not possible due to low IR. Future studies with substantially larger size and longer follow up are needed to reproduce the findings in adjusted models, determine the role of cumulative exposure to individual ARVs and investigate the clinical implications.

P83

Kidney tubular function and serum phosphate levels in HIV-1-infected patients treated with tenofovir: preliminary results

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Purpose of the study: There is concern that human immunodeficiency virus (HIV) infection and the use of highly active antiretroviral therapy lead to cumulative toxicity. Tenofovir (TDF) is the first choice for most subjects. Even if it has a safe metabolic profile, much attention has been fixed on kidney tubular function and regulation of phosphate metabolism. We performed this study to evaluate the role of a TDF based regimen has on renal tubular over time.
Methods: Prospective, cross-sectional, single centre study was carried out. 121 HIV-1-infected patients were consecutively enrolled in six groups based on duration of TDF exposition: G0, from 6 to 12 months; G1 from 13 to 24 months; G2 from 25 to 36 months; G3 from 37 to 48 months; G4 more than 48 months and G5 under HAART but never exposed to TDF. Glomerular function was assessed using creatinine clearance (CrCL) calculated by MDRD. Tubular function was assessed using fractional excretion ratio of phosphate and normalized renal threshold phosphate concentration. Demographic, CD4, serum phosphate levels, viral load were collected.
Summary of results: A total of 121 consecutive HIV-1-infected patients were analyzed: 15 in G0, 11 in G1, 14 in G2, 32 in G3, 35 in G4 and 14 in G5. Mean of TDF exposure was 10.26, 21.4, 36.2, 47.3 and 67.4 months in G0, G1, G2, G3 and G4 respectively. There was no statistically significant difference of mean values of FEP(11.2, 10.3, 8.4, 9.8, 11.1 and 10% in G0, G1, G2, G3, G4 and G5 respectively), TmPO4/GFR (3.5, 3.5, 3.6, 3.6, 3.4 and 3.4 mg/dl in G0, G1, G2, G3, G4 and G5 respectively), CrCL (102.2, 94.3, 92.9, 106.5, 103.1 and 101.6 ml/min/1.73m2 in G0, G1, G2, G3, G4 and G5 respectively) and serum phosphate levels (3.4, 3.3, 3.1, 3.5, 3.3 and 3.4 in G0, G1, G2, G3, G4 and G5 respectively) between groups. Moreover, we did not find correlation of FEP (r:0.04, p:0.6) and TmPO4/GFR (r:0.05, p:0.5) with duration of TDF therapy.
Conclusions: Treatment with TDF is not associated with altered kidney tubular function and serum phosphate levels over time.

P84

Smoking, female gender and PI use are associated with decreasing renal function in TDF-containing HAART

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P84

Purpose of the study: Nephrotoxicity of tenofovir (TDF)-containing HAART may be associated to several factors related to treatment or to patient's characteristics. We tried to assess Glomerular Filtration Rate (GFR) changes and their relationship with multiple clinical parameters in an Italian cohort receiving a TDF-containing HAART.

Table 1 (abstract P84)

Variable	CG	p-value	MDRD	p-value	CK-EPI	p-value
Increasing Age	decrease	0.0001	decrease	0.043	decrease	0.0006
Increasing BMI	increase	<0.0001	NA	ns	decrease	0.059
PI/r usage	NA	ns	decrease	0.072	decrease	0.023
Smoking	decrease	0.073	decrease	0.012	decrease	0.05
Female sex	decrease	0.0001	decrease	0.0009	decrease	0.0026

Methods: OSMA-1 (Observational Study on Metabolic Abnormalities), a multicenter Italian study, was designed to evaluate since February 2008 the efficacy and the safety of TDF-based regimen in a real-life clinical setting. HIV infected, therapy naïve subjects were enrolled. GFR was estimated using Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Statistical analyses used a parametric test and a mixed model was used to analysis changes from baseline to 6, 12, and 24 months, with the different variables as fixed effect plus visit (categorical) and baseline value (continuous as covariate).
Summary of results: We consecutively enrolled 172 patients (91.3% Caucasian; 72.2% males; mean age 39.3 yrs; 48.8% heterosexual; 36.6% smokers). At baseline median CD4+ cell count was 225 cells/μL (range 2 - 701), HIVRNA > 100000 copies/mL in 43.6%. Median Body Mass Index (BMI) was 22.6 for males and 21.9 for females. A boosted PI was given in 60.5% of cases. At 6-mos evaluation, Women had greater declines in GFR vs. Men, independently from the GFR equation used (means in W vs. M for CG, MDRD and CK-EPI, respectively: -7.2; -12.1; -10 vs. 0.5; -1.3; -0.3 mL/min/1.73 m2, p=0.0001 to 0.0026). No further decline was documented after 6 months. Factors associated with demography or treatment are shown in Table 1.
Conclusions: Our data suggest that long-term use of TDF is associated with a modest decline in GFR that occurs predominantly at the beginning (in the first 6 months) of therapy in HAART-naive women. However, the decline is small, does not seem to worsen over time, and may not have a relevant clinical effect. A decreasing GFR was also found in elder patients, in smokers and when a boosted PI is used.

P85

A magnifying glass onto renal function and serum lipid evolutions after tenofovir (TDF) and emtricitabine (FTC) in combination with atazanavir/ritonavir (ATV/r) versus efavirenz (EFV) as first-line HAART (the INCA trial)

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P85

Background: Measures of glomerular filtration rate (GFR) showed discordant results. CKD-EPI creatinine formula resulted more accurate than other equations in subjects with normal or mildly decreased renal function in the general population and cystatin C could be even a more sensitive measure. As for lipids, lipoprotein subfractions were suggested to be more informative on the cardiovascular risk than the commonly used cholesterol subfractions, with protection conferred especially by HDLp-small (Baker et al. JID 2010). Prospective evaluation of all these markers upon initiation of standard HAART regimens is lacking. We conducted a small, intensive, randomized study in naïve HIV-infected patients comparing TDF/FTC+ATV/r versus TDF/FTC+EFV as first-line therapy for these novel markers.
Methods: Antiretroviral-naïve HIV-infected patients, recruited from 4 centers in Italy (Brescia, Rome, Ferrara, Bari), were randomized to ATV/r

or EFV standard doses, in combination with fixed-dose TDF/FTC. Patients had to have creatinine clearance>50 ml/min. Outcome measures included serum creatinine and cystatin C levels and derived eGFRs corrected for body surface area. Lipoprotein particle size and concentration were estimated using an NMR spectroscopy method at Jochen-Hunter Lab., Germany.

Results: 91 patients were randomized (48 ATV/r, 43 EFV; 80% males; mean age 43 years; 4 patients class C; mean CD4+ 283/mm^3, SD: 119/mm^3). No significant differences were found between the two arms at baseline, but for some lipids (total cholesterol: mean 173 mg/dL ATV/r vs. 156 mg/dL EFV; p=0.04; HDL-cholesterol: 44 mg/dL vs. 38 mg/dL; p=0.007; HDLp: 36 mg/dL vs. 32 mg/dL; p=0.02). At baseline, a correlation between CKD-EPI creatinine and CKD-EPI cystatine C was found (R2=0.51; p<0.0001). Through CKD-EPI creatinine formula, we detected a significant decrease in eGFR from baseline to week 48 in patients, receiving ATV/r (-4.8233 mL/min/m^2; p=0.002) but not in those receiving EFV. Greater GFR reductions were found with CKD-EPI cystatin C than with CKD-EPI creatinine not only in the ATV/r arm up to week 48 (-15.1388 mL/min/m^2; p<0.0001), but also in the EFV arm from baseline to week 24 (-7.2233 mL/min/m^2; p=0.04). As for lipids, cholesterol subfractions increased more after EFV than after ATV/r: mean increase from baseline to week 48 was 44.15 mg/dL vs. 15.51; p=0.002 for total cholesterol, 32.4 mg/dL vs. 12.47 mg/dL; p=0.007 for LDL cholesterol, 9.31 mg/dL vs. 2.13 mg/dL; p=0.002 for HDL cholesterol. Total/HDL cholesterol ratio remained stable in both arms. As for lipoprotein subfractions, total HDLp increased more after EFV than after ATV/r (11.97 mg/dL vs. 7.97 mg/dL; p=0.03), but HDLp-small increased significantly in both arms, without statistical differences between the two (1.71 mg/dL vs. 1.86 mg/dL).

Conclusions: Patients receiving TDF in combination with ATV/r had greater decline in renal function than those receiving TDF plus EFV, although eGFR decrease was small in both arms. Interestingly, CKD-EPI cystatin C appeared to be a stricter measure. As for lipids, EFV induced greater LDL cholesterol increases but the risk appeared to be counteracted by greater increase of both HDL-cholesterol and HDLp, even though HDLp-small increased similarly in the two arms. We suggest that these novel measures provide additional information so as to better characterize the toxicity profiles of the antiretroviral regimens.

P86

The 10 year safety and efficacy of tenofovir disoproxil fumarate (TDF)-containing once-daily highly active antiretroviral therapy (HAART)

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Background: Study 903 was a Phase III randomized double-blind (DB) 3 year study comparing TDF to stavudine (d4T) each in combination with lamivudine (3TC) and efavirenz (EFV) in HIV-1 infected antiretroviral naïve patients. TDF was associated with durable efficacy and safety (better lipid profile, and less lipodystrophy and peripheral neuropathy). A subset of these patients now provides 10 years of longitudinal efficacy and safety data of TDF-containing once-daily HAART.

Methods: Subjects in Argentina, Brazil, and the Dominican Republic who completed the 3 year DB period of study were eligible to roll-over into an open-label (OL) study (Study 903E) of the once-daily HAART regimen, TDF+3TC+EFV. At DB baseline 86 subjects were randomized to TDF (62% male, 70% white, mean age 33 yrs, mean HIV RNA=4.9 log_{10} c/mL, and mean CD4 count=299 cells/mm^3). At OL baseline, 85 subjects (60% male, 64% white, mean age 37 yrs, median CD4=621 cells/mm^3) switched from d4T to TDF. The results reflect only the period of TDF exposure.

Results: See Table 1

Conclusions: Antiretroviral-naïve subjects who received TDF-containing once-daily HAART for up to 10 years demonstrated sustained virologic and immunologic benefit, improved limb fat, stable renal function, and their BMD remained stable after a clinically insignificant decrease that occurred during the first year of TDF therapy.

Table 1 (abstract P86)

	TDF/TDF$^{\alpha}$ (n=86)	D4T/TDF$^{\alpha}$ (n=85)
Weeks on HAART/TDF	480/480	480/336
HIV RNA < 50 (copies/mL) at Week 480 (ITT, M=F)	63%	64%
HIV RNA < 50 (copies/mL) at Week 480 (ITT, M=E)	92%	96%
Change in Mean (SD) CD4, cells/mm^3	545 (287)	180 (290)
Drug-related Adverse Events (Grades 1-4)	66%	46%
Change in Mean (SD) Creatinine Clearance, mL/min$^{\beta}$	+2.5 (23.4)	-10.7 (22.6)
Median Limb Fat at Year 10, kg	10.4	7.5
Percent Change in Mean (SD) Spine BMD$^{\chi}$	-2.44 (5.08)$^{\delta}$	0.04 (4.72)
Percent Change in Mean (SD) Hip BMD	-2.94 (4.95)$^{\delta}$	-1.86 (4.67)$^{\delta}$
Discontinuations during open-label extension	25 (29.1%)	19 (22.4%)
Adverse event	2 (2.3%)	2 (2.4%)
Suboptimal virologic response	5 (5.8%)	1 (1.2%)
LTFU$^{\varepsilon}$, Nonadherent, Pregnancy, Consent Withdrawn, Death	13 (15.1%)	9 (10.6%)
Other	5 (5.8%)	7 (8.2%)

$^{\alpha}$TDF/TDF results measured from DB BL; d4T/TDF from OL baseline; $^{\beta}$Estimated by Cockcroft-Gault equation; $^{\chi}$Bone mineral density; $^{\delta}$p<0.01 by Wilcoxon Signed Rank Test; $^{\varepsilon}$Lost to follow-up

P87

Intracellular tenofovir-diphosphate accumulation in an HIV-infected patient with Fanconi syndrome and osteomalacia

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We present a patient with tenofovir disoproxil fumarate (TDF)-induced Fanconi syndrome, osteomalacia and concurrent nucleos(t)ide reverse transcriptase inhibitor related CD4 cell decline. Sequentially measured intracellular (ic) tenofovir-diphosphate (TFV-DP) levels were extremely high, with plasma TFV just slightly elevated.

In June 2008 a 53-year-old Caucasian male complained of severe pain in his lower extremities. He was diagnosed with HIV in 1995 and developed some polyneuropathy and severe lipoatrophy after initiation of ART in 1996. In September 2003 TDF 300 mg qd, didanosine (ddI) 250 mg qd and lopinavir-ritonavir (LPV-r) 400/100 mg bid were started. CD4 cells had increased from 136 to 489/mm^3 by December 2007, but then slowly decreased to 181 despite a persistently undetectable HIV-1 RNA. There was 13 kg weight loss when he developed diabetes mellitus in April 2008. In May 2008 blood and urinalysis were compatible with Fanconi syndrome. Creatinine clearance (CCl) had decreased from 76 (2003) to 44 mL/min (GC). Serum 1,25(OH)-vitamin D was low (20 pmol/L), but 25(OH)-vitamin D and PTH were normal. MRI of feet and knees showed patchy bone marrow oedema without fractures, DXA demonstrated osteopenia and bone biopsy confirmed the diagnosis osteomalacia. While CCl decreased, plasma TFV increased only slightly (from 0.23 in July 2004 to 0.36 mg/mL in September 2008), but ic TFV-DP levels were found to be extremely high, 3630 fmol/10^6 cells (mean TFV-DP in patients on LPV-r 233.1 fmol/10^6 cells [1]). Eight weeks after TDF dose reduction and 2 weeks after TDF cessation ic TFV-DP was still high (310 fmol/10^6 cells), but plasma TFV was undetectable, illustrating the long ic half-life. Ic dideoxy adenosine-triphosphate (ddATP) levels were also high, 123 fmol/10^6 cells (n 5.06 fmol/10^6 cells) as were ddI plasma levels (max. 0.304 mg/L). TDF and ddI were replaced by raltegravir/nevirapine and phosphate, calcium and 1,25(OH)2-VitD temporarily supplemented. Two months later symptoms disappeared, CCl improved to

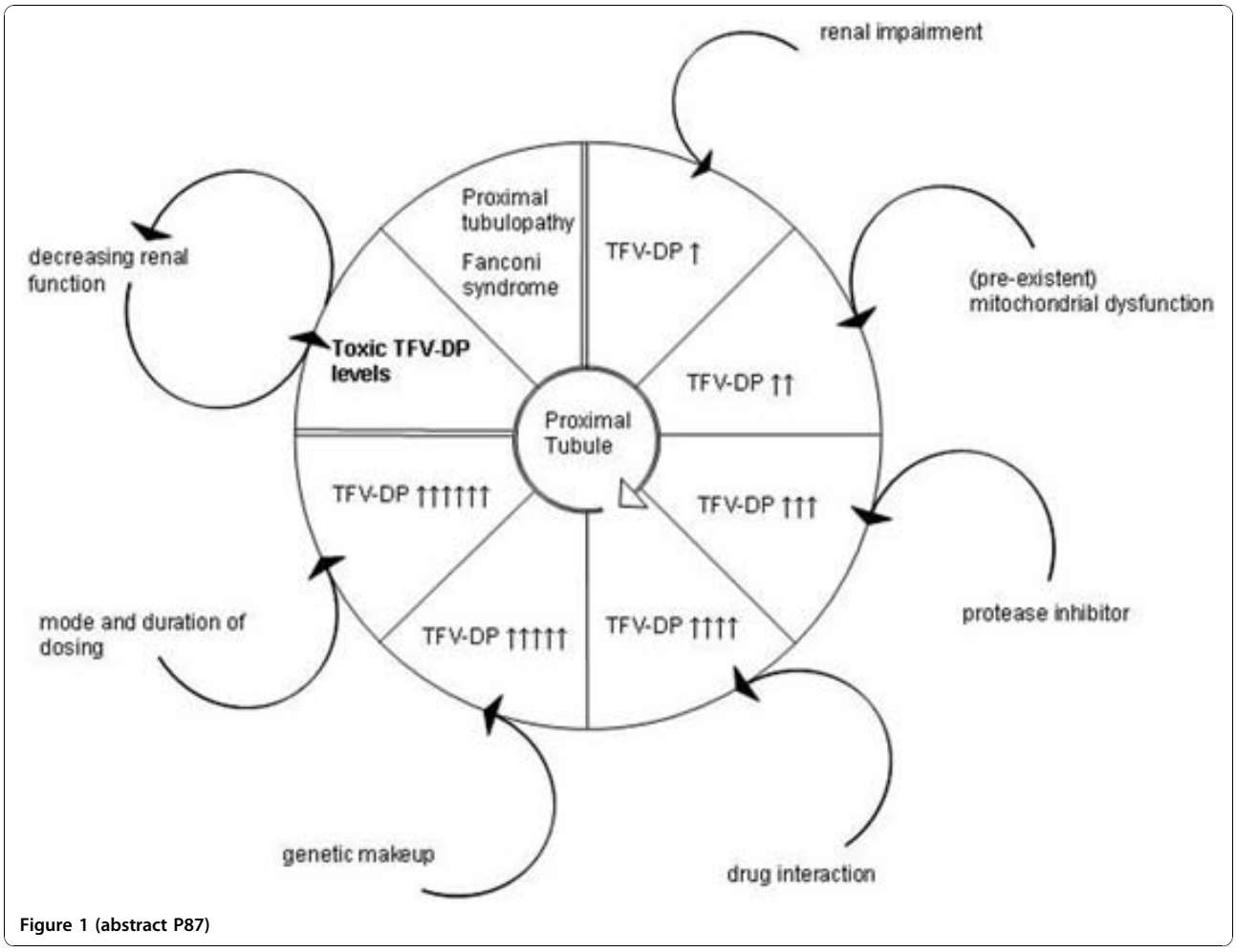

Figure 1 (abstract P87)

62 mL/min, CD4s increased (286 cells/mm^3) and oral antidiabetics could be stopped.

This case illustrates the severe clinical impact of protracted unrecognised TDF-related toxicity and is suggestive of a causal relationship between TDF use, concomitant factors and ic TFV-DP accumulation (fig 1). A significant CD4 cell decline in patients with undetectable HIV-RNA on TDF- and/or ddI-containing ART should alert the physician to investigate for NRTI toxicity.

Reference

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P88

The association between metabolic syndrome and the occurrence of nephrolithiasis in HIV-infected patients

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Introduction: Although HAART therapy has radically changed the prognosis of HIV infected patients, decreasing their morbidity and mortality, the ARV medication produced other clinical manifestations due to their toxicity. For many years there was no data in the literature attesting link between metabolic syndrome and renal disease development. Recent epidemiological studies have found that patients with metabolic syndrome have a high risk of developing chronic kidney disease: chronic renal failure and nephrolithiasis.

Purpose of the study: Evaluation of the relationship between metabolic syndrome and the occurrence of nephrolithiasis in HIV infected patients.

Methods: The study involved 112 patients with known HIV-AIDS infection and metabolic syndrome in the evidence of the Regional HIV Centre Constanta, Romania which were compared with 100 matched control group. The parameters analyzed were: demographic characteristics, weight, height, body mass index, blood pressure, medical history, examination of urine, urea, creatinine, Na, K, Cl, Mg, P, total serum calcium, glucose, serum triglycerides, LDH cholesterol, HDL cholesterol, CD4+ lymphocytes, HIV-RNA. Nephrolithiasis was diagnosed by ultrasound examination. No patient had a history of treatment with Indinavir.

Results: Of the 112 patients studied, 67 patients developed nephrolithiasis (59.82%) in comparison with only 24% in the control group ($p < 0.01$). The age of these patients was between 20 and 67 years, with a mean age of 43.5, sex ratio F:M = 1.09. The predominant form was bilateral (69%) and asymptomatic (58%). The analysis of kidney stones revealed that the major component was uric acid (48%). Ultrasound revealed hydronephrosis in 18 patients (26.8%). Urinary tract infection was diagnosed in 23 patients (34.3%); the most common etiology was E. coli (39%). PCR HIV-RNA was undetectable in 90 patients (80.3%), and 46 patients had a CD4+ cell count > 500 cells/mm^3 and only 10 patients CD4+ < 200 cells/mm^3. The majority of patients (55.3%) received 2INRT and PI/r as ARV treatment.

Conclusions: In HIV infected patients with metabolic syndrome under ARV treatment, nephrolithiasis is 2.5 times more frequent compared to general population. The presence of kidney stones is a risk factor for developing hydronephrosis and urinary tract infection. Because patients with HIV infection and chronic renal failure have a decreased survival, the screening for nephrolithiasis is mandatory in these patients.

P89

Prevalence of chronic renal failure stage 3 or more in HIV-infected patients in Antwerp: an observational study

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The introduction of Highly Active Antiretroviral Therapy has transformed HIV-infection from an inevitably lethal disease to a chronic condition with a life expectancy comparable to that of people with diabetes mellitus.
In recent years it has become evident that people living with HIV/AIDS have an increased risk of developing cardiovascular disease and it is expected that the prevalence of chronic kidney disease will rise accordingly. To investigate the prevalence of chronic kidney disease in patients with HIV we conducted a retrospective observational analysis using the clinical database of a large centre (Institute of Tropical Medicine) in the urban area of Antwerp, Belgium. The prevalence of chronic kidney disease among HIV infected subjects was found to be 3.0%. The development of chronic kidney disease was associated with age above 50 years, lower CD4 cell counts and Caucasian origin. Screening for chronic renal disorders and prevention of evolution toward chronic renal failure is a crucial challenge in the management of people living with HIV/AIDS.

P90

Hepatotoxicity in patients co-infected with HIV and tuberculosis while receiving NNRTI-based antiretroviral regimen and rifampicin

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Objective: To evaluate the rate of and risk factors associated with hepatotoxicity in tuberculosis (TB) and human immunodeficiency virus type 1 (HIV-1) co-infected patients while receiving nonnucleoside reverse transcriptase inhibitors (NNRTI)-based antiretroviral therapy (ART) and rifampicin (RMP)-containing anti-TB regimens.
Methods: We analyzed data from an open label, randomized, comparative trial comparing treatment outcome between 71 TB/HIV-1 co-infected patients receiving efavirenz (EFV)-based and nevirapine (NVP)-based ART and all were receiving RMP containing anti-TB regimens. Demographic data, liver function profile, CD4 cell count, plasma HIV-1 RNA, hepatitis B surface antigen and anti- hepatitis C virus antibody were collected before initiating ART (week 0). Liver enzymes and total bilirubin level were monitored at 6 weeks, 12 weeks and 24 weeks after ART initiation. All patients were followed until TB therapy was completed or 24 weeks after ART initiation if TB therapy was not completed.
Results: Of 134 patients, mean (SD) age was 36.8 ± 8.6 years and 67.2% were male. HCV co-infection was found in 23.9% of patients. Severe hepatotoxicity (grade 3 or 4) developed in 4 (23.9%) patients; 3 patients in NVP group and 1 patient in EFV group (P=0.355). Severe hyperbilirubinemia (grade 3 or 4) occurred in 5 (7.7%) patients in NVP group and 2 (2.9%) patients in EFV group (P=0.264). By univariate analysis, cotrimoxazole use (OR, 2.65; 95%CI, 0.99-7.02) and HCV co-infection (OR, 3.40; 95%CI, 1.49-7.37) were associated with grade 1-4 hepatotoxicity. By multivariate analysis, HCV co-infection (AOR, 3.03; 95% CI, 1.26-7.29) was the only independent risk factor associated with grade 1-4 hepatotoxicity.
Conclusion: Monitoring of hepatotoxicity should be considered in TB/HIV-1 co-infected patients who infected with HCV and receiving NVP.

P91

Liver safety of two nucleoside analogs plus efavirenz, nevirapine or a ritonavir-boosted protease inhibitor in HIV/HCV-coinfected drug-naïve patients

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Purpose of the study: A wide range of hepatotoxicity rates associated with antiretroviral drugs (ARV) has been reported in different studies. Reasons for this include diverse populations, with different prevalence of viral hepatitis coinfection, exposure to diverse ARV and variable criteria to define liver toxicity across studies. The liver safety of regimens including efavirenz (EFV), nevirapine (NVP) or boosted-protease inhibitors (PI/r) has not been compared in a single large cohort of HIV/HCV-coinfected patients with a uniform definition of hepatotoxicity. Because of this, we evaluated the incidence and risk factors for grade 3 or 4 ALT or AST elevations (TE) and grade 4 total bilirubin elevations (TBE) among ARV-naïve HIV/HCV-coinfected patients with an initial regimen including two nucleoside analogs (NRTIs) plus EFV, NVP or a PI/r.
Methods: Retrospective multicenter cohort (January 2000-June 2006) of 745 HIV/HCV-coinfected patients starting their first ARV treatment consisting of two NRTIs plus either EFV, NVP or PI/r. Patients were included if they were exposed to ARV for one week or more and had evaluations within the first three months of follow-up. Definition of grade 3 or 4 TE: 1) Normal baseline ALT or AST levels: ALT or AST elevations ≥5 times above the upper limit of normal (ULN); 2) Baseline ALT or AST levels above the ULN: ALT or AST elevations ≥3.5 times the baseline values Definition of grade 4 TBE: Increases of total bilirubin ≥5 mg/dl.
Summary of results: 323 (43%) patients received EFV, 126 (17%) NVP and 296 (40%) PI/r. Grade 3 or 4 TE were observed in 19 (5.9%) individuals on EFV, 14 (11%) on NVP and 31 (10.5%) on PI/r (global comparison, p=0.068; EFV vs. NVP, p=0.056; EFV vs. PI/r, p=0.036; NVP vs. PI/r, p=0.38). Grade 4 TBE were identified in 7 (2.2%) patients on EFV, 1 (0.8%) on NVP and 11 (3.7%) on PI/r (p=0.19). Severe TBE was detected in 5 (12%) and 15 (2%) patients with and without cirrhosis, respectively (p=0.003). Discontinuations due to hepatotoxicity were: 13 (4%) patients on EFV, 16 (13%) on NVP and 17 (6%) on PI/r (global comparison, p=0.003; EFV vs. NVP, p=0.001; EFV vs. PI/r, p=0.320; NVP vs. PI/r, p=0.015).
Conclusions: Liver tolerability of regimens including EFV, NVP or PI/r is generally good in ARV-naïve HIV/HCV-coinfected patients. Severe TE are less commonly seen with EFV than with NVP or PI/r. Discontinuations due to hepatotoxicity were less frequent for patients receiving EFV than for those treated with NVP.

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Liver fibrosis: concordance analysis between APRI and FIB-4 scores, evolution and predictors in a cohort of HIV patients without HCV and HBV infection

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Purpose of the study: Liver fibrosis (LF) progression is fated to become one of the major long-term complications in HIV patients, even in those without HCV or HBV co-infections (HIV-mono-infected). The aim of this study was to assess LF progression in HIV-mono-infected patients and associated risk factors.

Methods: Observational retrospective study. All HIV naive patients who started HAART from 1996 to 2006 were included. Concordance between FIB-4 and APRI scores was assessed using the weighted kappa coefficient. Rates of transition from lower classes to higher classes were estimated by Kaplan-Meier analysis. Cox regression models were applied to assess possible predictors both at baseline and during the follow-up.
Summary of results: 1,112 naive patients were selected. A moderate concordance between FIB-4 and APRI was demonstrated (K=0.573). For FIB-4, the incidence of transition to higher classes was 0.064 PYFU (95% CI, 0.056-0.072), while for APRI the incidence of transition was 0.099 PYFU (95% CI, 0.089-0.110). Viro-immunological control during HIV infection appeared to reduce the risk of both FIB-4 and APRI transitions. HIV-RNA <500 copies/ml (for FIB-4: HR 2.456 p<0.0001; for APRI: HR 2.084 p<0.0001) and higher CD4 T-cell counts only for FIB-4 (HR 0.881 p=0.0004 for 100 cells higher) during the follow-up were statistically protective. Among baseline variables, for FIB-4 transition, age ≥ 40 years (HR 1.037 p<0.0001) and higher FIB-4 values (HR 1.526 p=0.0038) were associated with increased risk of LF progression, while sexual risk factor for HIV acquisition resulted to be protective (HR 0.524 p=0.0314). For APRI, male gender (HR 1.390 p=0.017), higher GGT values (HR 1.015 p=0.014) and higher APRI values (HR 1.748 p=0.007) were independently associated with APRI transition. A sensitivity analysis demonstrated that DDX drugs (stavudine, didanosine, zalcitabine)as time-dependent covariates were associated with a significant risk of transition with FIB-4 (HR 1.662 p=0.0007) or APRI (HR 1.661 p=0.0001).
Conclusions: Our data suggest that a better viro-immunological control of HIV infection may slow down fibrosis progression provided that DDX are avoided. Moreover our analysis provided a comprehensive feature of the risk factors that should be controlled in clinical practice.

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Clinical significance of hyperbilirubinemia in the CASTLE study

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Purpose of the study: While unconjugated hyperbilirubinemia is associated with the use of ritonavir-boosted atazanavir (ATV/r), the nature of the hyperbilirubinemia over time and its clinical significance has not been well-characterized in controlled studies. The purpose of this study is to describe the patterns and clinical significance of hyperbilirubinemia in patients treated with ATV/r in the CASTLE study.
Methods: CASTLE was a randomized, 96-week study to assess the efficacy and safety of ATV/r vs. lopinavir/r, each with tenofovir/emtricitabine, in treatment-naïve patients. This analysis included only ATV/r patients. The proportions of patients with hyperbilirubinemia (grades 3-4 total bilirubin elevation) were tabulated for each study visit. The impact of hyperbilirubinemia on symptoms (jaundice or scleral icterus), ASL/ALT elevations, quality of life (MOS-HIV physical and mental summary scores), and adherence (MACS adherence questionnaire) were described.
Summary of results: Although the proportion of patients with hyperbilirubinemia at any time throughout the study was 44%, the proportion of ATV/r patients with hyperbilirubinemia at any single visit was between 12.5% and 21.6%. Of patients with hyperbilirubinemia at any time, 11% had grades 2-4 treatment-related jaundice or scleral icterus at any time (0 of patients without hyperbilirubinemia), and 4% had grades 3-4 AST/ALT elevations at any time (3% of patients without hyperbilirubinemia). Quality of life and adherence in patients without and with hyperbilirubinemia. Table 1.
Conclusions: Hyperbilirubinemia, while common in patients on ATV/r at any time through 96 weeks in the CASTLE study, was less frequent at any single time point and not associated with related symptoms in most patients. The presence of hyperbilirubinemia did not affect AST/ALT elevations, quality of life, or adherence. These data suggest that hyperbilirubinemia observed with ATV/r does not impact clinical outcomes.

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A case of nodular regenerative hyperplasia in a patient who had been taking didanosine

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Purpose of study: It is widely recognised that liver disease causes significant morbidity and mortality in HIV positive patients. Many patients are co-infected with hepatitis B and C, have increased alcohol intake or are on hepatotoxic medication e.g. nevirapine, which can cause acute hepatitis or liver cirrhosis. Nodular regenerative hyperplasia (NRH) is characterised by the presence of diffuse, small regenerative nodules in the absence of significant cirrhosis. Prior use of didanosine is associated with NRH. It leads to portal hypertension, oesophageal varices and subsequent gastrointestinal haemorrhage.
Methods: A 53-year-old gentleman presented with a major upper gastrointestinal haematemesis. He was diagnosed with HIV 23 years previously and had been on treatment for the last 13 years, maintaining an undetectable viral load and reasonable CD4 count. He denied significant alcohol and a full liver screen was negative. He was taking zidovudine, didanosine and nevirapine from 1997 to 2005, when he was switched to tenofovir, nevirapine and lamivudine. He continued on this combination until 2009 when his tenofovir and lamivudine were replaced with Truvada.
Summary of results: Liver function tests at the time of admission revealed AST-15, ALT-20, Bilirubin-5, GGT-78. Endoscopy showed bleeding

Table 1 (abstract P93)

		Patients without hyperbilirubinemia	Patients with hyperbilirubinemia
MOS-HIV Physical Summary Score Categories at Week 96			
	Improvement	76/138 (55%)	70/128 (55%)
	No change	35/138 (25%)	29/128 (23%)
	Worsening	27/138 (20%)	29/128 (23%)
MOS-HIV Mental Summary Score Categories at Week 96			
	Improvement	97/138 (70%)	92/128 (72%)
	No change	25/138 (18%)	18/128 (14%)
	Worsening	16/138 (12%)	18/128 (14%)
Adherence Through Week 96			
	To regimen	154/186 (83%)	147/176 (84%)
	To ATV	159/186 (85%)	153/176 (87%)

oesophageal varices, which were treated with variceal band ligation (VBL). Despite this he had two further episodes of bleeding, requiring a transjugular intrahepatic portosystemic shunt (TIPPS). Liver biopsy demonstrated focal nodularity within the parenchyma consistent with NRH but no evidence of fibrosis.
Conclusions: This gentleman had been on didanosine from 1997 to 2005 and it is recognised that this is a risk factor for NRH. It is hypothesised that didanosine, which is a purine analogue, causes destruction of portal veins. Aminotransferases may be normal or elevated. In patients with a previous history of didanosine use, physicians should be aware of the risk of portal hypertension without cirrhosis, which can lead to catastrophic outcomes.

P95

Toxic intracellular anabolite levels of tenofovir and didanosine causing a steep CD4-cell decline

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Introduction: HIV-protease inhibitors may increase tenofovir plasma AUC by 22-37%. Whether this affects tenofovir-diphosphate (TFV-DP) intracellular levels, especially in the presence of didanosine, which is also eliminated through active tubular secretion, is unclear.
Case report: A 52-year-old HIV-1 positive Caucasian male started zidovudine (AZT), lamivudine, nelfinavir in 1999 at a CD4-cell count of 210/μL. In July 2007 treatment was switched because of viral blips to atazanavir, ritonavir, tenofovir, emtricitabine and didanosine (250 mg). Within one year his CD4-cell count declined from 1140 to 140/μL despite complete virological suppression [1]. Renal clearance (Cockgroft-Gault) decreased from 86 to 74 mL/min and renal phosphate threshold to 0.24 mmol/L (n=0.8-1.35), indicative of proximal tubular dysfunction. There was 8 kg weight loss, his serum glucose and lactate were elevated.
In addition, following the ART-switch a thrombocytosis (1355x10^9/L) was noticed. After exclusion of other causes, essential thrombocythemia was diagnosed and hydroxyurea started. Thrombocytes were elevated before initiation of ART (427x10^9/L) and before therapy switch (659x10^9/L), suggesting AZT-related bone marrow suppression may have prevented a further increase in platelet count in the preceding years.
Suspecting NRTI-related mitochondrial and tubular dysfunction, we measured intracellular ddA-TP (didanosine) and TFV-DP (tenofovir) in PBMCs [2]. TFV-DP was 10xULN (1350 fmol/10^6 cells) and ddA-TP 21xULN (105 fmol/10^6 cells). Hydroxyurea may have increased ddA-TP levels, but was used for only 2 weeks. ART was changed to AZT, lamivudine, atazanavir, ritonavir, raltegravir. Two weeks later TFV-DP was still 250 fmol/10^6 cells, demonstrating an intracellular t½ of approximately 140 hrs and ddA-TP 57.4 fmol/10^6cells, t½ 385 hrs, but didanosine and tenofovir plasma levels were undetectable. After switch his CD4-cell count increased again from 140 to 340/μL and his platelet count decreased to 725x10^9/L following re-initiation of AZT.
Conclusions: Elevated TFV-DP and ddA-TP led to tubular dysfunction and mitochondrial toxicity. Inhibition of purine-nucleoside-phosphorylase by TFV-DP and DNA-polymerase-γ by ddA-TP may have caused the steep CD4-cell decline. We believe interactions between tenofovir, didanosine and atazanavir/ritonavir were responsible for this toxicity.

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Lack of association between mitochondrial DNA polymorphisms and didexoxynucleoside-induced hyperlactataemia in black-African, HIV-1-infected patients

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Background: Recent studies have shown some association between specific mitochondrial DNA (mtDNA) polymorphisms and peripheral neuropathy in both white European and black American populations. An association between mtDNA haplogroup H and peripheral lipoatrophy has been reported in white Europeans. Our group has shown a lack of association between mtDNA polymorphisms and the occurrence of HL in white Europeans exposed to dideoxynucleosides, but there have been no studies in black African people.
Methods: mtDNA was extracted from oral mucosa epithelial cells from HIV1-infected active patients seen at Chris Hani Baragwanath Hospital in Johannesburg, South Africa. Cases were defined as confirmed blood lactate >5 mmol/l. Controls were randomly selected from patients who had never developed HL. Sequencing of the hypervariable region 1 (HVS-1) of the mtDNA was performed on all samples and the haplotypes obtained were reported as differences from the Cambridge Reference Sequence. Specific single nucleotide polymorphisms (SNP) were used to predict haplogroup. Logistic regression was used to identify variables associated with case status. An exact test of population differentiation was used to compare HVS-1 haplotype distribution between cases and controls.
Results: mtDNA was obtained from 40 cases and 38 controls. 82.5% of cases and 63.2% of the controls were female (P= 0.05). The ethnicity of the majority of participants were self-defined as Zulu or Sotho (80% of cases and 63% of controls; P=0.184) and all of them were exposed to either d4T (100% of cases and 87% of controls) or AZT (13% of controls). The median blood lactate level in cases at the time of diagnosis was 7.65 mmol/l (IQR 6.65-9.45). The distribution of mtDNA haplotypes was not different between cases and controls (P=0.137) neither were the predicted haplogroups (P=0.429).
After adjusting for haplogroup distribution and ethnicity only factors known to be associated with HL, such as female gender (OR 5.92; 95%CI 1.50-23.42) and CD4 count <200 cell/ml (OR 4.02; 95%CI 1.03-15.68) remained independently associated with case status.
Conclusions: We did not find any association between mtDNA polymorphisms and the occurrence of HL in black African adults exposed to dideoxynucleosides. Contrary to what has been published on other mitochondrial toxicities, our data suggest that mtDNA variability may not explain any predisposition for dideoxynucleoside-associated HL.

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Markers of bone turnover are elevated in patients on antiretrovirals independent of the substance used

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Objectives: Osteoporosis and bone fractures are correlated to antiretroviral treatment. It is not clear, if some substances inherit greater risk of bone loss than others.
Methods: We measured pyridinoline, desoxipyridinoline crosslinks and bone specific alkaline phosphatase in 108 HIV positive patients. We compared patients with and without antiretroviral treatment. We then analysed patients with vs. without tenofovir and patients with PI vs NNRTI use.

Results: Bone specific alk. phosphatase, pyridonoline and desoxipiridinoline crosslinks and were significantly higher in patients with ART compared with patients without ART: 25.17 vs 13.22 pg/L ($p < 0.001$); 83.64 vs 51.23 nmol/mmol ($p < 0.001$) and 16.38 vs 9.68 nmol/mmol ($p<0.001$)respectively. In contrast, no difference was found in patients with vs. without tenofovir 26.25 vs 20.18 pg/l ($p =0.08$); 80.74 vs 85.83 nmol/mmol ($p=0.42$) and 19.36 vs 14.00 nmol/mmol ($p=0.13$) respectively. Comparison between patients with proteinase inhibitor vs non-nucleoside inhibitor yielded no difference either 23.07 vs 26.49pg/l ($p=0.33$); 94.31 vs 80.65 nmol/mmol ($p=0.34$) and 18.18 vs 16.29 nmol/mmol ($p= 0.52$).
Conclusions: Markers for bone turn over are higher in treated vs untreated patients. No difference concerning tenofovir use or proteinase inhibitor vs. non-nucleoside inhibitor use could be found.

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Quantitative ultrasound (QUS) in HIV-infected patients: a reliable and low-cost technique for bone health assessment

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Objective: Bone demineralization is common in HIV-infected subjects. Reliable and low cost methods would be useful in order to identify and monitor bone alterations both in older and younger HIV+ patients. Recent data in normal population suggest that bone mineral quality (BMQ), assessed by a quantitative ultrasound (QUS) technique, could be an early marker of osteopenia/osteoporosis. Therefore, we investigated the usefulness of QUS in order to study bone health assessment in HIV-infected adults.
Methods: 37 HIV-infected patients and 44 HIV-negative controls, matched for sex and age, were enrolled. Bone health was measured using classical dual energy x-ray adsorptiometry (DEXA) of spine and hip and calcaneal QUS. Broadband ultrasound attenuation (BUA) and speed of sound (SOS) and quantitative ultrasound index (QUI)/stiffness index (SI) were assessed by QUS. Data were correlated with CD4+ T-cell count, HIV load, years of disease, immune activation markers (DR+CD38+CD4+ and DR+CD38+CD8+), 25OH vitamin D. Nonparametric Mann-Whitney test and Spearman correlation were used for statistical analysis.
Results: 5 patients were viremic (ARV-naïve), while the remaining subjects were virologically ARV-suppressed. In the latter group, 17 were in treatment with PI and 16 with NNRTI. The mean nadir CD4 was 665/mmc. Comparable QUS parameters were found in HIV+ subjects and controls as well as between NNRTI- and PI-based therapies. No difference was seen in patients treated with TDF. A significant decrease of QUI was found in HIV+ patients aged >48 years ($p=0.012$). A correlation between QUI and age in HIV+ patients was seen ($p=0.047$). No correlation was found between QUS and CD4 nadir, as well as between QUS and immune activation markers. No difference was observed between cases and controls for vitamin D levels which were decreased in both groups. However, a significant correlation between vitamin D level and age was found only in HIV+ population ($p=0.022$), other than between vitamin D and years of infection ($p=0.0142$). Moreover, a strong correlation between QUI and DEXA values was observed ($p=0.001$).
Conclusions: QUS parameters are closely related to the structural and elastic properties of bone and they provide important information about bone quality and strength. Therefore, in HIV+ people QUS might be a simple and inexpensive technique in order to monitor bone health and identify early signs of bone damage, independently from vitamin D levels.

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Fracture risk in HIV and the need for guidelines: the Probono-1 Trial

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Purpose of study: Fragility fractures are a common and increasing cause of morbidity and mortality in the general population; risk factors for fractures are commoner in HIV . This study aims to determine the prevalence and associations of low bone mineral density (BMD) and high fracture risk (FR) in an HIV cohort, suggest screening and management guidelines.
Methods: A cross-sectional study of 223 randomly selected HIV-infected outpatients was undertaken. Recruitment was stratified by gender for age groups 30-39, 40-49 yrs and ≥50 yrs. Osteopenia and osteoporosis were diagnosed according to the WHO criteria. Patients completed a detailed questionnaire including combination HIV drugs (cART) history, & a dual-energy X-ray absorptiometry (DEXA) of Lumbar spine & Left Hip. Investigations included serum Ca, phosphate, 25OH vit D, alkaline phosphatase (Alk P) PTH, albumin, sex hormone binding globulin (SHBG), testosterone, CD4, HIV RNA. BMD risk factors were recorded including previous fractures, smoking, malabsorption, alcohol consumption, BMI, chronic diseases, physical activity index and past medication. FRAX score (10yr probability major fractures), and remaining lifetime fracture probability (RLFP) were calculated. Controls were from the Twin Research Unit at Kings College London. Data were analysed using multivariate logistic regression.
Results: Demographics: 133(60%) were male, 106(48%) were Caucasian, 71(33%) had AIDS at diagnosis. 190(85%) were taking cART, of whom 50 (26%) were on their first line therapy. Osteoporosis/osteopenia were present in 13%/39% of males, 11%/29% females, and was approximately 2.4/3.0 fold greater than age-matched controls. The overall mean 10 yr fracture risk was 3.16%. RLFP exceeded 1.0 in 76% HIV patients, and <20% controls.
Factors associated with low BMD after multivariate analysis: adjusted OR (95 % CI)/p-value BMI 0.90(0.83,0.96), $p<0.001$, Alk P 1.01(1.00,1.02), p 0.05, testosterone 1.04(1.01,1.07), p 0.01, Initiated cART 3.61(1.38,9.42), p 0.01. The lack of association with age is notable, adjusted OR 1.08 (0.92,1.26), p 0.35.
Conclusions: Reduced bone mineral density and subsequent fracture risk is much commoner in patients with HIV compared to controls, especially, and those taking cART, and occurred across the age ranges. Hence screening for BMD and risk factors for fragility fractures is indicated in patients with HIV at a younger age than in the general population, especially if they are on cART.

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Rates of bone fractures in a cohort of HIV-infected adults in the UK

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Purpose of study: With combination antiretroviral therapy (cART), HIV-associated mortality rates have declined substantially in the UK. However HIV-infected adults are living longer to develop co-morbidities, including low bone mineral density (BMD). This study investigates fractures in a UK cohort of HIV-infected adults.
Methods: A cross-sectional survey of 1050 HIV-infected adults from routine HIV clinics was conducted. Subjects completed a questionnaire about demography, lifestyle factors, fracture history and management, exposure to glucocorticoids and other drugs influencing bone metabolism. HIV details (duration and route of infection, disease stage, cART exposure and parameters of viral control) were recorded.

Results: There were 859 useable replies (response rate 82%) from 775 men and 84 women: mean age 43 years (range 19-77 years) and 87% Caucasian. Mean duration of HIV infection was 8 years (range 0-23 years). Co-infection with hepatitis B occurred in 16 subjects and hepatitis C in 11. Overall, 125 (15%) subjects reported 200 fractures: 119 (15%) men and 6 (7%) women. Common fracture sites were forearm (n=65), tibia/fibula (n=29), hand/foot (n=22) and digit (n=19). Hip fractures occurred in 6 subjects and 2 had clinical vertebral fractures. A bimodal distribution of fracture was seen: 114 (57%) fractures occurred in subjects <25 years (peak age 7-12 years) and 33 (17%) fractures in those >40 years, with 8 (24%) in subjects >50 years. Among subjects >40 years with fractures (30 men and 3 women; 32 Caucasian), common fracture sites were forearm (n=6, mean age 48 years) and tibia/fibula (n=4, mean age 49 years); there was 1 hip fracture (age 46 years). 15% of these subjects reported oral glucocorticoid exposure (vs. 9% without fractures (p=ns)) and 79% had ever smoked (vs. 72% without fractures (p=ns)).
Conclusions: This is the first epidemiological study of fractures in HIV-infected adults in the UK. There were 2 peaks of fracture incidence: <25 years and 40-60 years. Forearm fractures were the commonest but fractures at other 'typical' osteoporotic sites (vertebral and hip) were seen. The second peak occurred at a younger age than those reported in HIV-negative subjects. This is consistent with data showing accelerated immune senescence in HIV. Although the clinical importance of low BMD is yet to be fully evaluated, if fracture rates are increased, routine assessment of low BMD and fracture risk may be warranted in this relatively young population.

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Prevalence of vitamin D deficiency: cross-sectional study of a hospital cohort of HIV-1 infected outpatients

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Background: To examine the prevalence and causal factors of vitamin D deficiency among HIV-1 infected patients and specially to assess whether antiretroviral drugs interfere with vitamin D metabolism.
Methods: We performed a cross-sectional study of a hospital cohort (n=147) of HIV-1 infected outpatients followed-up by the same physician. Data were collected between January 2008 and January 2010. We draw samples for the measurement of 25(OH)D3, PTHi, serum calcium, serum phosphate, alkaline phosphatase, CD4+ cell count and viral load. Data on age, sex, VIH infection risk group, weight, height, skin color, time since HIV diagnosis, duration and stage of the infection (according to CDC 1983 staging system), as well as duration of typo of antiretroviral therapy (ART). A nutrition specialist of the same hospital performed a survey of sunlight exposition and daily vitamin D intake. We performed bi- and multivariant analysis to identify risk factor related to vitamin D deficiency (25(OH)D1<20 μg/L).
Results: Median age was 45 years; 67.3% were males and 89.1% Caucasians. CD4+ count was < 200 cells/μL in 15.6 %, and 76.2% had a viral load below 30 copies/ml. Median serum 25(OH)D level was 21.1 μg/L (IQR 12,8-28,3) and 47.6% had 25(OH)D < 20 μg/L. Multivariate analysis of predisposing factor to vitamin D deficiency showed decreasing risk in summer(OR 0.131, 95% CI 0.05-0.336, p=0.0001) and fall (OR 0.021, 95% CI 0.005-0.089, p=0.0001) and increased risk in heterosexual (OR 2.77, 95% CI 1.06-7.21, p=0.036) and with the tenofovir use (OR 2.71, 95% CI 1.14-6.44, p=0.024). In univariate analysis, current nevirapine use was protective against development of vitamin D deficiency (OR 0.42, 95% CI 0.15-0.95, p=0.039). Black race was not a risk factor, but it was underrepresented in our sample.
Conclusions: Despite the low latitude of Spain, moderate vitamin D deficiency in HIV infected patients is more prevalent in our cohort than in the cohorts of Switzerland, Netherlands and Boston. It was related to the season, heterosexual risk group and tenofovir use. Nevirapine use was associated with less risk in univariate analysis.

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The serum level of 25-OH vitamin D and Th1 cytokine pattern in HIV infection versus hepatitis C virus infection and hepatitis B virus infection

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Purpose of the study: To assess the plasma level of 25- hydroxy vitamin D (25-OHD) and its correlations with the immune status in patients infected with Human Immunodeficiency Virus Infection (HIV), Hepatitis C Virus Infection (HCV) and Hepatitis B virus Infection (HBV).
Methods: The study was performed on 54 patients admitted to Matei Bals Institute Bucharest, between January 2010 - July 2010, out of which 30 women and 24 men aged 21-64 years. 14 patients were diagnosed with HIV stage C3(CDC criteria), 11 with HBV and 14 with HCV infection, while 15 were healthy controls. We assessed the plasma level of 25-OHD (nmol/L, Elisa kit, Immunodiagnostic Systems), IFN γ, IL2, IL12(pg/mL, Max Discovery Elisa kit), phosphorus and calcium level, the CD4, CD8 cell count and the CD4/CD8 index. Kruskal-Wallis and ANOVA comparative tests were further used to determine the p value.
Summary of results: HIV patients displayed the lowest plasma concentration of 25-OHD(27.13 nmol/L) despite no statistically significant difference towards controls. No correlation was found between the 25-OHD level and any of the studied parameters. The serum level of IFN γ in HIV patients was similar with the concentration found in controls; a significant positive correlation was found with the CD8 count(p=0.01) and the CD4/CD8 index(p=0.008). The IL2 concentration was decreased and it was correlated with the level of IL12(p=0.000) and the CD4 count(p=0.02). The low level of 25-OHD in HCV patients (28.97 nmol/L), was correlated with the CD4 count(p=0.008) and the CD4/CD8 index (p=0.003); IFN γ displayed a considerable increased level while the concentrations of IL2 and IL12 were within the normal range. 25-OHD was also decreased in HBV patients and its serum level was correlated with the CD4 count (p=0.01), as well as the CD8 count(p=0.06). The serum concentration of IFN γ was increased compared with controls.
Conclusions: The 25-OHD levels were lower in HIV, HCV and HBV patients. Nonetheless a similar insufficiency was also noted in healthy controls. No correlation was further determined between the level of 25-OHD and the immune status in any group of patients. The Th1 cytokine pattern was different in the HIV infection compared with HCV and HBV infection. IL2 and IL12 serum level was significantly decreased in HIV infection; IFN γ exhibits a significant increased serum level in HCV infection. This work was supported by CNCSIS-UEFISCU Grants PNII IDEI code 2508/2008 (project no. 1165)

P103

Prevalence and factors associated with severe vitamin D deficiency in HIV/hepatitis C co-infected patients

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Purpose of study: Vitamin D deficiency (VDD) is associated with elevated risks of cardiovascular disease, malignancies and impaired survival of the general population. In HIV infection VDD is related to anaemia, HIV disease progression and death, and in hepatitis C (HCV) infection impaired treatment responses to interferon. Severe VDD is common in both HIV and HCV mono-infection. The prevalence of VDD in HIV/HCV co-infected patients, and the effect of the severity of liver disease on vitamin D status remains unknown. The aim of this study was to investigate the

prevalence of, and factors linked to severe VDD in HIV/HCV co-infected patients.
Methods: Multi-centre observational study of 309 HIV/Hepatitis C co-infected and 128 HIV mono-infected patients matched for gender and ethnicity. Patients included attended between Sept 09 — July 2010. Severe VDD was defined as 25(OH) vitamin D level <25 nmol/L. Database analysis and case note review was performed. Multivariate logistic regression was used in a model incorporating gender, ethnicity, and season of sample to examine associations between severe VDD, parathyroid hormone (PTH) and HCV status. Patients on vitamin D supplementation were excluded from analysis.
Summary of results: 91% of patients were male, 86% were Caucasian and 18% of HCV had been acquired through intravenous drug use. The prevalence of severe VDD in HIV/HCV co-infected and HIV mono-infected patients was 19% and 6% respectively (p=0.876). The median vitamin D concentration was 29 (range 7-135) and 46 (11-168) nmol/L (p=0.396), and the median PTH concentration was 41 (Range 12-241) and 36 (11-197) units respectively. In HIV/HCV patients, severe VDD was associated with winter season (October to March) (p=0.0001), black ethnicity (p=0.0001), and higher fibroscan score (p=0.05), but not with age, HIV or HIV viral load, HCV genotype, ALT, ALP, platelets or HCV treatment status.
Conclusions: This is the first report on the prevalence of VDD in patients infected with HIV/HCV. Severe VDD deficiency was not associated with HIV/HCV co-infection. In HIV/HCV co-infected patients severe VDD was linked to winter season, black ethnicity and liver fibrosis. Further investigation of the relationship between vitamin D deficiency and liver fibrosis in HIV/HCV co-infection is warranted.

P104

Tenofovir use is associated with low vitamin D levels in a Spanish HIV cohort

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Background: Several studies have shown a high frequency of vitamin D deficiency among HIV patients. Several studies have ascribed these low levels of vitamin D to antiretroviral treatment, especially efavirenz. Tenofovir has been related to changes of bone mineralization in SIV-infected rhesus monkeys and with loss of bone mineral density in children. Adequate vitamin D stores have the potential of an improvement of immune status, lessening of cardiovascular risk and beneficial effects on certain neoplastic disorders.
Methods: Cross-sectional study of 94 adult HIV outpatients in Leganés (Madrid, Spain) performed in 2008. Risk factors for vitamin D deficiency (< 20 μg/L) were examined using logistic regression.
Results: Median age was 44 years (IQR 40 to 48); 69.1% were males, 93,6% whites, 6.4% black race. Mean CD4+ cell count was 446 cells/μL (IQR 312 to 586). Viral load was below 50 copies/mL in 78.7%. Median 25 (OH)D level was 17.7 μg/L (IQR 11.9 TO 24.3). 87.2% of patients had 25 (OH)D < 30 μg/L (suboptimal), 57.4% had 25(OH)D < 20 μg/L (deficient) and 19.1% < 10 μg/L (severely deficient). Factors associated with low levels of 25(OH)D were heterosexual vs. IVDU HIV-risk group (OR 13.3, 95% CI 2.4-74.1, p=0.003), season (spring vs. summer; OR 16.8, 95% CI 3.4-82.1, p=0.0001), age >45 vs < 45 years (OR 10.5, 95% CI 2.4-46.6%, p=0.002), CD4+ cells nadir <200 vs >200 cells/μL (OR 4.1, 95% CI 1.01-17.6, p=0.049), and tenofovir vs. abacavir therapy (OR 12.7, 95% CI 1.8-87.1, p=0.01). Black race is underrepresented to draw conclusions. In this sample, no association of low 25(OH)D with efavirenz was found.
Conclusions: Despite low latitude, low levels of vitamin D are almost universal in our sample of HIV outpatients with satisfactory immunologic and virologic response to ART. Increasing age, less insolation season, heterosexual risk group, and CD4+ nadir were associated with lower levels. Tenofovir use was associated with lower levels of 25(OH)D. Further studies on causality of this association and the need of control bone-mineral density in tenofovir-treated patients seems warranted.

P105

Safety and efficacy of maraviroc (MVC) combined with multiple different therapeutic agents in highly treatment-experienced (TE) patients in Brazil

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Background: MVC is the first-in-class CCR5 antagonist approved for use in treatment of CCR5-tropic (R5) HIV-1 infection; however, there is limited experience with MVC in regimens containing newer PIs and other new agents. This open-label 96-week multi-center study evaluates MVC in a variety of regimens to obtain additional safety and efficacy data in TE patients with limited options due to intolerance or resistance in Brazil.
Methods: Adult TE patients with R5 HIV-1 only (HIV-1 RNA >1000 cp/mL) received MVC 150-600mg (based on concomitant ARV) twice daily, combined with optimized background therapy (OBT). Every 12 weeks, safety parameters (primary endpoint), HIV RNA, and CD4 counts were assessed; we report data at 48 weeks.
Results: Of treated 206 patients, 70% were male (mean age 43 yrs) and 80% Caucasian; 2.9% and 5.8% were seropositive for HBV or HCV infection, respectively. Median baseline HIV-1 RNA and CD4 counts were 4.9 $\log_{10}$ copies/mL and 185 cells/mm^3, respectively. OBT comprised PI+NRTI (67%), PI+NRTI+NNRTI (7.8%), PI+NRTI+other (14.6%), or other regimens (10.2%). The most frequently used NRTIs were TDF (82%), 3TC (76%) and AZT (23%); the most common PIs (most boosted with RTV) were DRV (45%), LPV (41%) and ATV (15%); 16% received RAL. OBTs contained ≤1 drug (1% of patients), 2 drugs (7.3%), 3 drugs (24.3%), 4 drugs (35.4%), 5 drugs (23.8%), or ≥6 drugs (8.2%). Sixty-five patients (31.6%) discontinued; reasons included death (6 patients), adverse events (5), insufficient clinical response (36), lost to follow-up (4), or other (14). There were 238 treatment-related adverse events in 103 patients; 16 treatment-related serious adverse events in 9 subjects; 10 category C

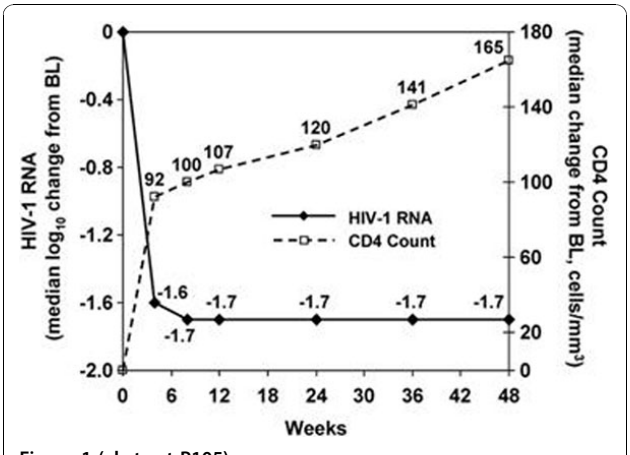

Figure 1 (abstract P105)

events, none treatment-related; and 2 of the 4 malignancies (Hodgkin's disease and intestinal T-cell lymphoma) were considered treatment-related. The most common grade 3/4 lab test abnormalities were GGT elevation (11% of patients), hyperbilirubinemia (11%) and serum amylase elevation (6%). Median CD4 count increased persistently through week 48 (Figure), with similar responses comparing quartiles of baseline CD4; the median increase from baseline at week 48 was 164.5 cells/mm^3. HIV-1 RNA decreases were maintained regardless of baseline viral load; overall 41.1% of patients had HIV-1 RNA <400 copies/mL at week 48.
Conclusions: In highly TE patients, regimens combining MVC with different agents from multiple classes were well tolerated and provided marked antiviral and immunologic responses.

P106

Behaviour and attitudes in HIV (BEAHIV): a national survey study to examine the level of agreement between physicians and patients in symptom reporting

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Background: Management of antiretroviral (ARV)-related symptoms is a major challenge in the treatment of HIV infection, and uncensored reporting by the patient and subsequent acknowledgement by the physician are critical. The primary objective of BEAHIV was to examine the level of agreement between patients and their physicians regarding the presence or absence of 22 symptoms as reported on the HIV Symptoms Distress Module (SDM). P>A non-interventional, observational, cross-sectional survey study was conducted Sept-Nov 2009 across 17 Canadian sites. Data was collected from consenting adult HIV-positive outpatients and their HIV-treating physicians at a single clinic visit. Major inclusion criteria included ability to read and write in English or French.
Results: 1000 patient and corresponding physician surveys were collected. Physician respondents (68% male) had been treating HIV patients for an average of 15 years. 88% of patient respondents were male, 84% were currently on ARVs, 59% had received ARVs >5 years, and 31% had detectable viral load at survey completion. Median age was 46 years, median time since HIV diagnosis was 11 years and median CD4 count was 460 cells/mm^3. Fifty-six percent had comorbid conditions (29.5% mental health issues, 18.7% HBV/HCV co-infection, 18.9% metabolic problems), and 72% were taking non-ARV medications. Median total SDM score (out of 84) was 31.0 reported by patients versus 8.0 by physicians. All symptoms, including those most bothersome to patients, were reported more frequently by patients than physicians; symptoms with the largest discordance were trouble remembering (60.2% vs. 16.4%), sexual problems (59.1% vs. 16.4%) and bloating pain/gas (54.3% vs.12.6%).
Conclusions: This large, Canadian, cross-sectional survey study identified substantial and relevant differences in agreement between HIV patients and their physicians regarding the presence or absence of a defined set of common symptoms associated with HIV and its treatment. Relative to their patients, physicians consistently under-reported patients' symptoms.

P107

Continuing burden of HIV late presenters in the North East of England 2009

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Purpose of the study: To determine whether the pattern of late presentation noted previously in 2007 and 2008 in all patients newly diagnosed with HIV in our regional unit [1] has decreased since the publication of The UK National HIV Testing Guidelines in 2008 [2].
Methods: A retrospective case-note audit was undertaken in the ID/GUM clinics for all patients who were newly diagnosed with HIV in 2009. Patients were characterised as late presenters if they presented with a CD4 count of less than 200 or an AIDS defining illness. Medical records were reviewed to determine whether the patients had previously been diagnosed with a clinical indicator disease as defined by the UK National HIV Testing Guidelines, 2008, which might have facilitated earlier diagnosis of HIV. These 2009 data were compared with previous 2007 and 2008 data.
Results: See table 1.
Conclusions: Significant numbers of patients (53% in ID; 27% in GUM) still present with advanced HIV disease in the North East of England in 2009 despite the publications of the National UK Testing Guidelines in 2008. The numbers of late presenters have not changed as compared to 2007 and 2008. This is despite that a large proportion having had previous indicator diseases that should have prompt clinicians to test for HIV. Further education and awareness of the UK National Testing Guidelines 2008 should be encouraged if this burden of late presenters is to be reduced.

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Table 1 (abstract P107)

Source	ID 2009	GUM 2009	ID 2007	GUM 2007	ID 2008	GUM 2008
No of Patients	32	11	35	26	46	14
Late presenters	17 (53%)	3 (27%)	63%	59%	31%	21%
Male Gender	23 (72%)	11 (100%)	57%	54%	81%	89%
MSM	12 (38%)	10 (91%)	17%	54%	35%	79%
White British	19 (59%)	9 (82%)	37%	65%	54%	79%
Black African	11 (34%)	2 (18%)	49%	15%	43%	14%
Initial CD4 < 200 cells/μl	16*(52%)	3 (27%)	NK	NK	NK	NK
Symptomatic Seroconversion	3 (9%)	1 (9%)	NK	NK	NK	NK
Previous Indicator Diseases	16 (50%)	1 (9%)	50%	50%	35%	29%
AIDS at/prior to diagnosis	8 (25%)	0(0%)	31%	0%	28%	0%
Commenced HAART	21 (66%)	6 (55%)	NK	NK	NK	NK

P108

Drug interactions in the elderly HIV-infected patient

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Elderly HIV-infected patients may present particularities on both disease evolution and morbidity, as compared to younger patients. Moreover, elderly patients are more likely to take numerous medications due to their age-related condition. VISAGE is a French multidisciplinary study group focusing on elderly HIV-infected patients in order to evaluate and improve their therapeutic care. Our study "Visage 1" aimed to analyse potential drug interactions between antiretroviral drugs (ARV) and all other products taken by elderly HIV-infected patients.

This 6-month prospective study involved patients treated for HIV infection and aging more than sixty years at the time of the study. Patients were to fill an anonymous self-questionnaire for reporting their ARV, diseases other than HIV infection, and drugs or products regularly taken other than ARV. Observance has been evaluated using a visual analog scale graduated on 10. Analysis of drug interactions relied on the French drug agency (Afssaps) thesaurus by using the tool available on the website www.theriaque.org.

25 women and 70 men filled 95 questionnaires. Median age was 65.3±5.2 years. Treatment of HIV infection was a combination of three ARV for 85% of patients. Among patients, 94% had concomitant treatment with non-ARV drugs (4.6 ± 3.3 drugs /patient) mainly prescribed for a cardiovascular mean. Most frequently used concomitant drugs were paracetamol, lysine acetyl salicylate, bromazepam, rosuvastatin, and zolpidem. Other products widely used were sexual stimulants and vitamins. Consumption of alcohol, poppers and cannabis occurred in 40, 3, and 2 patients, respectively. Clinically relevant drug interaction occurred in 45% of prescriptions and involved non-ARV drugs but were not in majority classified as serious. Two associations were found contra-indicated: ritonavir+alfusozine and protease inhibitor+simvastatin. Observance reached 9.9 ± 0.4 for antiretroviral drugs, and 9.8 ± 0.6 for the other drugs.

Drug interactions were less frequent and less severe than expected in this population. Physicians' awareness of concomitant drugs taken by the patient is crucial since most clinically and severe interactions occurred between ARV and non-ARV drugs. Observance was extremely high as compared with the rate usually described for the general population of HIV-infected patients and reasons of that high rate need to be further investigated.

P109

Sexual dysfunction and anxiety in HIV-1-infected males in Eastern Sicily

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Purpose of the study: Sexual dysfunctions (SD) in HIV-1 infected individuals have been associated with infection, modification of body image and HAART, mainly PI based treatment. Anxiety is common in HIV+ subjects.

We hypothesized that anxiety could be a cofactor of SDs. A cross sectional analysis was conducted in a cohort of 109 HIV+ males with at least 6 months of continuous exposure to HAART to evaluate the prevalence of anxiety and other factors associated with SDs.

Methods: Sexual evaluation was performed by self-completion questionnaires International Index of Erectile Function (IIEF): a score of <26 was considered diagnostic of erectile dysfunction (ED). Anxiety was evaluated with Self Rating Anxiety State SAS 054, a self-submitted 20 items questionnaire. A z score 45 was considered diagnostic of anxiety.

Results: 109 male patients were enrolled. Median age 46 (IQR 40-52) years, 29% of 50 years old, 25% heterosexuals, 54% MSMs, 22% IVDUs; 45% single. Median time from HIV diagnosis was 11 years (IQR 5-15). 50% CDC A, 20% CDC B, 30% CDC C. Median CD4 cell count 577 (IQR 383-861) cells/µl, 80% had HIV RNA <50 copies/ml. Median length of HAART was 8 years (IQR 4-13): 22% were naïve, 23% on 2nd line, 28% 3rd-4rd line, 27% >4th line of treatment. 61% were on PI based treatment, 38% on NNRTI. Permanence on PI was 74 months (IQR 40-124), on NNRTI 47 months (IQR 18-87). 52 subjects (48%) had a z score of 45 diagnostic of anxiety.

71 subjects (65%) had ED. EDs were more frequent in elderly subjects (>50 yr) (78% vs 60%, OR 2.7, 95% CI 1.01-2.26) and in individuals with anxiety disorders (77% vs 54%, OR 3.04, 95% CI 1.3-7.12). No significant association was seen with actual ARV treatment, length of time on PI or NNRTI, clinical stage, HIV RNA >50 copies/ml.

Conclusions: EDs were highly prevalent and related to elderly age ($P<0.05$) and anxiety ($P<0.01$). We do not show any correlation with actual ARV treatment and with length of exposition time to PI or NNRTI based treatment.

An accurate evaluation and treatment of anxiety should be considered and offered in order to obtain an increase in sexual satisfaction and in quality of life of HIV-1-infected patients.

P110

Raltegravir-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: implications for clinical practice and patient safety

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Introduction: Integrase inhibitor raltegravir is being used increasingly in patients with potential drug interactions [1]. We describe a case of DRESS syndrome in a patient who was switched to raltegravir from a PI based regime.

Case report: A 55 yr old patient was diagnosed with HIV in 2005 with a nadir CD4 30. Virological suppression was achieved on NNRTI based HAART. Following the development of resistance this was later switched to a PI based regime with a good virological response. In order to treat her severe post herpetic neuralgia secondary to multi dermatome herpes zoster, she was given epidural corticosteroid, triamcinolone. Forty one days later she presented with Cushing's syndrome. This was due to the interaction of corticosteroid with PI.

The PI was changed to raltegravir to avoid further interactions; the patient maintained viral suppression. Four weeks after commencing raltegravir she presented with a 2-day history of a rapidly progressive generalized maculopapular rash, pruritis, malaise and pyrexia. Eosinophil count was $1.5x10^9$/l. A clinical diagnosis of DRESS syndrome was made. The timing of raltegravir initiation made it the most likely cause. Dermatologists advised treatment with emollients, topical steroid and prednisolone 30mg daily (a lower dose than usually used for DRESS syndrome, to compensate for the PI interaction). Raltegravir was stopped and PI recommenced. Skin biopsy was consistent with a drug eruption. The rash improved over the subsequent two weeks. The patient continues on a reducing steroid regime. The eosinophil count is declining.

Conclusions: This is the first report of a severe reaction to raltegravir. DRESS syndrome is previously described in other anti retrovirals [2] but not in relation to raltegravir. Clinicians should be aware of this potential adverse event.

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P111

Muscle symptoms and creatine phosphokinase elevations in patients receiving raltegravir in clinical practice: results from a multicenter study

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Purpose of the study: To further investigate CPK increases and muscle symptoms in a cohort of HIV-infected patients receiving raltegravir-based HAART compared with a control cohort with similar characteristics receiving darunavir-based HAART.
Methods: The SCOLTA Project is a prospective, observational, multicenter study created to assess the incidence of adverse events in patients receiving new antiretroviral drugs in clinical practice. Muscle symptoms where classified according to the American Heart Association guidelines and CPK elevations were graded according to the DAIDS table.
Results: A total of 391 HIV-infected patients were included in the study, 258 (66.0%) males. CDC stage was C in 152 (38.9%) patients. Mean age at enrolment was 44.5 ± 9.0 years, mean CD4 cell count 348 ± 260 cell/μL and mean HIV-RNA 3.26 ± 1.54 $\log_{10}$ cp/ml; 135 (35.2%) patients were HCV Ab+ and 155 (39.6%) had a diagnosis of lipodystrophy. Sixteen (4.1%) were naive to antiretrovirals. No statistical difference was observed regarding baseline characteristics when comparing patients receiving raltegravir (n=293) and darunavir-based HAART (n=98). Thirteen patients (5.4%) receiving raltegravir referred muscle pain and 12 (5.0%) muscle weakness compared with 1 (1.1%) and 0 (0%) receiving darunavir (p=0.20 and p=0.04), respectively. Seventeen (5.8%) patients developed muscle pain and/or weakness in the raltegravir cohort in respect of 1 (1.0%) in the darunavir cohort (p=0.05). No statistical difference was observed when considering CPK increases (>200 U/L) that were reported in 26 (8.9%) patients treated with raltegravir and 11 (11.2%) receiving darunavir. No relation emerged between CPK increase and muscle pain/weakness. Of note, no patient discontinued raltegravir due to CPK elevations or worsening muscle symptoms and no cases of rhabdomyolysis were reported.
Conclusions: CPK elevations occurred in >10% of patients receiving both raltegravir and darunavir suggesting a multifactorial aetiology in HIV-infected patients treated with HAART. Raltegravir-treated patients had a significantly higher proportion of muscle symptoms, especially muscle weakness. However, these symptoms did not cause therapy discontinuation, in our cases. Although the limited clinical significance to date, our data suggest the monitoring of muscle symptoms, including both pain and weakness, in patients receiving raltegravir and further diagnostic evaluations if they persist.

P112

Efavirenz use and contraceptive methods in HIV-positive women in a large urban cohort

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Background: Despite increasing reports of successful pregnancies whilst using Efavirenz (EFZ), the drug remains Category C during pregnancy due to concerns around teratogenicity [1]. Additionally, EFZ can render many hormonal methods of contraception less effective. For these reasons, UK guidance suggests that HIV positive women should be informed of these effects before commencing treatment [2]. Following a case in this unit where a young HIV-positive woman had an unplanned pregnancy whilst using Implanon and taking EFZ/Truvada, we examined contraceptive use and advice given to women in our cohort using EFZ, and then instigated changes to improve practice in this area.
Methods: Case-note review of all women taking EFZ in Jan 2008 and again in Feb 2010. Current contraception used, advice on teratogenicity, and advice on efficacy documentation was recorded. Women over 50, with documented menopause or hysterectomy were excluded.
Results: In 2008 we identified 31 females using EFZ in our cohort of 912 patients. Contraceptive choices are shown in Figure 1. 68% were using an 'effective' method of contraception (one not liable to reduced efficacy when using EFZ - condoms, IUS/IUD, sterilisation or recently documented no partner). 36% had documented advice regarding teratogenicity and 75% regarding reduced efficacy of hormonal methods. Following these results we introduced a section for contraception on our clinical review form (which is updated at each HIV clinic review) to act as a prompt for clinicians. After this change was made, we re-examining these data following this in 2010 (See Fig 1) and found 35 females using EFZ. 80% were using an 'effective' method of contraception, 50% had documented advice on teratogenicity and 100% regarding reduced efficacy of hormonal contraception (if appropriate).
Conclusions: Simple changes such as adding contraception to a clinic proforma can help improve sexual and reproductive health outcomes in HIV positive women. However, there are still improvements to be made in documentation of advice given, particularly when using a Category C drug in women who may become pregnant. Additionally, women should be made aware of the potential interaction between antiretrovirals and hormonal contraceptives at the HIV clinic — particularly as some may not disclose their status to Family Planning or GP services and therefore we cannot assume that this advice is being given elsewhere.

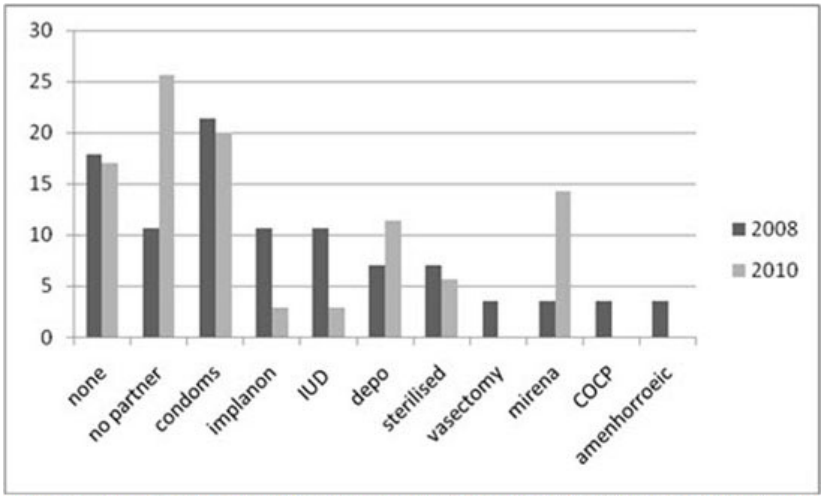

Figure 1 (abstract P112)

References

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P113

Assessing the risk of birth defects associated with atazanavir exposure in pregnancy

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Purpose of the study: The Antiretroviral Pregnancy Registry (APR) is an international collaborative operation which utilizes a prospective exposure-registration design to study antiretroviral (ARV) drug exposures during pregnancy. This study assessed the potential for human teratogenic risk of atazanavir (ATV), a protease inhibitor used to treat HIV infection in combination with other ARV agents. ATV exposures are increasingly reported to the APR in this population, reinforcing the need to better understand the risk of birth defects.
Methods: The analysis population includes all prospectively reported pregnancy exposures with complete exposure and birth outcome data for HIV-infected women enrolled in the APR from January 1, 1989 through January 31, 2010; the ATV subset includes those enrolled since June 2003, when ATV received FDA approval. The prevalence of birth defects after pregnancy ARV exposure is compared both externally, with rates from a population-based surveillance system, and internally between first-trimester and combined second/third-trimester exposures.
Summary of results: Through January 2010, 698 women with ATV-exposed pregnancies were enrolled. The mean age of these women was 29 years; 12.9% were White, 63.9% Black and 16.7% Hispanic; 87.9% were from the US. 82.5% had a baseline CD4 > 200 cells/mm^3. Of the ATV-exposed pregnancies, 588 were eligible for analysis including 567 live births. Among 368 first trimester exposures (167 since 2008), 8 had birth defects (2.2%). The birth defect rate in infants with second/third trimester exposures was 2.5%, and the rate in a non-HIV-infected population (CDC) was 2.72% (95% CI = 2.68-2.76). The risk of defects of first trimester exposures relative to second/third trimester exposures was 0.87 (95% CI = 0.29-2.61). No pattern of birth defects suggestive of a common etiology was observed.
Conclusions: Prevalence of birth defects among infants prenatally exposed to ATV is not significantly different from internal and external comparison groups. These findings may be useful in counseling patients who are exposed to ATV during pregnancy.

Table 1 (abstract P113)

	Exposure to any ARV (Jan 1989-Jan 2010)	Exposure to ATV (Jun 2003–Jan 2010)
Earliest exposure to ARVs		
First Trimester		
• # of defects/live births	127/4563	8/368
• Prevalence (95% CI)	2.8% (2.3%-3.3%)	2.2% (0.9%-4.2%)
Second/Third Trimester		
• # of defects/live births	158/6184	5/199
• Prevalence (95% CI)	2.6% (2.2%-3.0%)	2.5% (0.8%-5.8%)
Any Trimester		
• # of defects/live births	285/10747	13/567
• Prevalence (95% CI)	2.7% (2.3%-3.0%)	2.3% (1.2%-3.9%)

P114

Administration of darunavir tablets in patients with difficulties in swallowing – two case reports

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Background: For various reasons it can be necessary to administer antiretrovirals permanently or temporarily in a dissolved form: swallowing difficulties, stomach tube or patients in an ICU. However, not all drugs are available as oral solution. Crushing and dissolving may be an option, but data on plasma levels and efficacy are limited or not existing.
Methods: We report efficacy and plasma level data for two patients, one with dysphagia and Candida esophagitis and one with a stomach tube, who received darunavir (DRV) crushed and dissolved.
Results: Patient 1 is 57 year old HIV+ male (CDC C3), first diagnosed in 1990, who has been on various antiretroviral regimens since 1992. He presented with a VL of 72.551 copies/mL, 56 CD4 cells/mm^3 and candida esophagitis. HAART was initiated with DRV/RTV 600/100 mg in combination with etravirine (ETR) and raltegravir (RAL). DRV and RAL tablets were crushed, ETR was suspended and ritonavir (RTV) was given as oral solution. The medication was well accepted with exception of RTV oral solution. Trough levels (10 h post dose) for DRV were 6.950 ng/mL; measured one month post treatment initiation. At that time, VL had declined to 102 copies/mL; CD4 count had increased to 111 cells/mm^3. The patient was then switched to tablets, viral load has been <40 copies/mL since then.
Patient 2 is a 48 year old HIV+ paraplegic woman (CDC C3), first diagnosed in 2004 with a permanent stomach tube. HAART with DRV/RTV 600/100 mg bid, RAL and tenofovir/emtricitabine via tube was initiated in 2008. Since then, viral load has been permanently < 40 copies/mL; CD4 count is stable between 440 and 540 cells/mm^3. Plasma levels for DRV were within the therapeutic range: 4.430 ng/mL (5 hours post dose) in January and 5.210 ng/mL (3 hours post dose) in June.
Conclusions: Crushing DRV tablets and combining them with RTV oral solution reached adequate DRV plasma levels. In these two patients, HAART administered via artificial feeding was an effective option for short and long-term treatment.

ADHERENCE

P115

Evaluating pharmacist involvement in HIV outpatient clinics: can medication histories, drug interaction checks and adherence assessments add benefit?

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Purpose of study: HIV patients often take complicated regimens with high propensity for drug-drug interactions (DDIs). Physician awareness has been found to be low, and recognition relies on a comprehensive and current medication history. Patients may receive treatment from various sources such as other hospital departments, their GP, over the counter from a pharmacy or via the internet. Patients may also use herbal medicines, vitamins or supplements, some of which have potential to affect antiretroviral (ARV) therapy. Recreational drugs may also impact ARV treatment, either by affecting drug levels or adherence. This study aims to assess whether detailed medication history taking, screening for DDIs and adherence checks by a pharmacist are beneficial in HIV outpatient clinics.
Methods: Consecutive patients taking ARVs were seen by a pharmacist prior to outpatient medical review. Patients were asked for a detailed medication history including ARVs, hospital prescribed medication, medication prescribed in primary care, over the counter medication, herbal medicines, vitamins, supplements and recreational drugs. Adherence to

Table 1 (abstract P115) Summary of Physician Responses

	Told me something I did not know (%)	Changed management of the patient (%)
Medication History	10 (18)	2 (4)
DDI Check	18 (32)	6 (11)
Adherence Check	22 (39)	2 (4)

ARVs was assessed using a modified MASRI scale. The medication list was screened for DDIs, and a personalised interaction printout from www.hiv-druginteractions.org placed in the clinical notes. Physicians were asked to respond via a brief questionnaire whether the information told them something they did not know, and if they changed management of the patient as a result.

Summary of results: Of 90 patients, 20(22%) were taking a prescribed medication which was not previously recorded, 10(11%) had a discontinued medication recorded in their notes and 8(8.8%) were taking a different dose than that recorded. 43(48%) patients had one or more DDI, with a total of 70 DDIs identified. Estimated adherence ranged from 60-100%. 57 physician responses were obtained as shown in Table 1:

Conclusions: Detailed medication history taking by pharmacists has an application in HIV outpatient clinics. Routine screening of HIV patients' full medication lists for DDIs can facilitate recognition of interactions which may otherwise not be identified and managed. These data suggest that pharmacist led consultations incorporated into HIV outpatient clinics can add benefit.

P116

Adherence, quality of life and number of daily pills in a large cross-sectional study

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Purpose of the study: To assess if with current cART regimens the number of daily pills is still a determinant of adherence and quality of life (QOL).

Methods: Cross-sectional study of patients (pts) on cART followed at our centre. An adherence and QOL questionnaire was offered between March and May 2010 to all pts at drug supply; both parameters were evaluated by visual scale. Results are described as median (IQR) or frequency (%). Linear correlation was evaluated by the Spearman correlation coefficient. Generalized linear model (GLM) was applied considering adherence or QOL as alternative outcome variables.

Results: 2114 pts [aged 46.3 (41.9-51.1) years, 448 (21.3%) females, infected since 13.7 (8.0-19.2) years, treated with antiretrovirals since 11.5 (5.4-14.1) years, 260 (12.4%) of whom with a previous diagnosis of AIDS] were included in the analysis.

At the time of survey, 1793 (87%) had <50 HIV RNA copies/mL and CD4+ were 570 (403-746)/μL. Adherence and QOL were 100 (100-100)% and 83 (61-100)%, respectively; the number of daily pills in the ongoing regimen was 3 (3-5); 914 (43.2%) pts were receiving a BID and 1200 (56.8%) a QD regimen. At univariate analysis (figure 1), adherence was correlated to QOL but not to the number of daily pills, whereas QOL was weakly and inversely related to the number of daily pills; both adherence and QOL were not different between pts receiving a BID or QD regimen.

At GLM, after adjustment for age, gender, HIV risk factor, current CD4+, number of pills or dosing interval, adherence was associated with current HIV RNA [adjusted mean±SE: 94.3±0.48% for pts with <50 copies/mL vs 88.6±1.10% for those with ≥50 copies/mL, p<0.0001], gender [90.4±0.94% for females vs 92.5±0.60% for males, p=0.023] and current CD4+ (β=0.003 p<0.001).

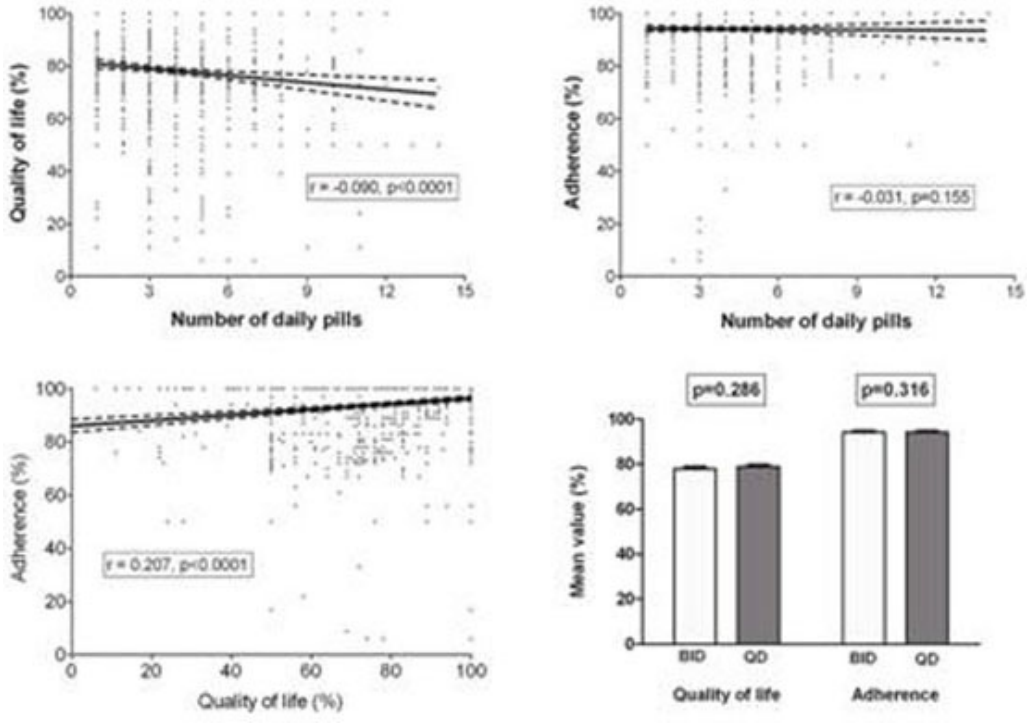

Figure 1 (abstract P116)

When adjusting for the same variables, QOL was higher in pts with undetectable viremia (78.7±0.7% vs 74.0±1.58%; p=0.004), in males (78.3±0.89% vs 74.5±1.39%; p=0.009), in MSMs vs heterosexuals vs others [78.5±1.37% (p<0.0001) vs 77.2±1.33% (p=0.008) vs 73.3±1.07% (reference group)], and also associated with age (β=-0.25, p<0.0001), current CD4+ (β=0.011, p<0.0001), and the number of pills (β=-0.77, p=0.019), but not with dosing interval.
Conclusions: In this highly adherent population, adherence was not associated with the number of daily pills or dosing interval. QOL was associated with the pill burden, but the pill burden explained <1% of QOL. Both adherence and QOL were strongly associated with virological response.

P117

Changing HIV guidelines: how to communicate treatment start

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Purpose of study: Recent treatment guidelines support the start of antiretroviral treatment (ART) in HIV-infected persons already at a CD4-cell count threshold 350 cells/µl. This includes to a large proportion asymptomatic individuals who do not necessarily see a good reason to start ART. In such cases, counselling can become a challenge. There is a lack of structured tools to optimally assess patients' readiness and to support them in this process. The purpose of this project was twofold: First to develop an algorithm for health care providers (HCP) to guide patients in the situation of treatment start. Second to develop a workshop during which HCP are instructed how to implement the algorithm and how to improve communication skills.
Methods: Based on an action research approach, consecutively literature review, own quantitative and qualitative studies and expert panel discussions were performed. We developed an algorithm and piloted an educational program for HCP. For this program critical incident reporting by experienced HIV providers was used and usability was evaluated in two workshops with HCP (self-reporting and group feedback).
Results: The readiness counselling algorithm has been integrated into updated European guidelines (http://www.europeanaidsclinicalsociety.org/guidelines.asp). It takes into account that patients are at different stages of readiness to start ART and that there are barriers (e.g. depression) before starting ART which have to be identified. An assessment of patients' actual stage of readiness and stage-based decision making support is recommended. The pilot workshop uses techniques of patient-oriented communication (waiting, echoing, mirroring, summarising) and a video-based interaction module, in which HCP present individual patients in whom the initiation of ART proved to be difficult. Re-playing these short case vignettes gives all participants a chance to apply newly acquired communication techniques. Participants rated these workshops very positive, emphasizing the high degree of practicality, closeness to their daily work, and usefulness of communication tools.
Conclusion: We developed an algorithm to assess and improve patients' readiness to start ART and a corresponding workshop on the use of the algorithm. Pilot workshops show that the algorithm is easy to implement into daily practice, shows excellent acceptance and provides a basis for the successful initiation of ART and long-term adherence to treatment.

P118

Relating protease inhibitor resistance at time of virological failure with drug exposure

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Background: The absence of detectable HIV resistance after treatment failure may result from non-adherence, especially for drugs such as ritonavir-boosted PIs (PI/r) for which minimum adherence may be sufficient to achieve suppression. This analysis aimed to investigate the association between adherence, indicated by a detectable PI plasma concentration, and development of PI resistance in patients presenting with virological failure of a PI/r regimen.
Methods: Patients were included if they had virologically failed a PI/r, defined as a viral load (VL) >1000 copies/mL after ≥4 months continuous exposure to a PI/r and with a plasma sample available within 1 month of the estimated VL failure date. Samples were analysed for PI levels by a validated reversed-phase HPLC method; an undetectable PI level was defined as below the PI-specific lower limit of detection. Genotypic sequencing was also carried out retrospectively on the identified sample for those with no previous PI failure and PI resistance was defined as the presence of ≥1 major PI mutation (IAS-USA). Logistic regression was used to assess risk factors for an undetectable PI level and for detection of PI resistance at VL failure using exact methods for small datasets.
Results: 85 patients were included. PI/r regimens were started in Sept 2002 (median) with VL failure occurring a median time of 17 months later. At time of starting the PI/r (baseline), 57% were ARV-naïve, median CD4 count was 217 cells/mm^3 and median VL was 4.8 $\log_{10}$copies/mL. 43 patients (51%) had an undetectable PI level at time of VL failure and were similar to those with detectable levels in terms of demographics, ARV history and previous VL failure. However, injecting drug use was associated with a greater risk of undetectable PI level (univariate odds ratio (OR) IDU vs. not: 3.7; 95% CI: 1.1-12.5; p=0.038).
44 (52%) of the 85 patients were successfully tested for resistance and had no previous PI failure. Those with undetectable PI levels were significantly less likely to have PI resistance (0% of 24 patients, 95% CI: 0-14%) than those with detectable levels (25% of 20, 95% CI: 9-49%), exact median unbiased estimate of OR: 0.1; p=0.029. Baseline VL, CD4 count, demographic and ARV-related variables were not associated with PI resistance due to limited power in this dataset.
Conclusions: Non-adherence to a PI/r regimen, as measured by an undetectable PI level is linked to a lower rate of detection of PI resistance at time of VL failure.

P119

Treatment adherence, quality of life and clinical variables in HIV/AIDS infection

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Purpose of the study: The purpose of the study was to analyze the relationship between treatment adherence, quality of life and clinical variables in HIV/AIDS infection.
Methods: Data was collected by voluntary fulfilment of three questionnaires: one for socio-demographic variables, one to Assess Adherence to Antiretroviral Treatment-HIV and the WHOQOL-Bref to measure the quality of life (QoL). Clinical records were inspected in order to collect clinical information from the patients. The relationship between these variables was accessed by ANOVA using Tukey and LSD as the post-hoc test. A 5% significance level was used.
Summary of results: The analysis was performed on a cohort of 295 HIV-1 infected to ART individuals followed at the two Portuguese Hospitals (Hospital de Joaquim Urbano and Curry Cabral). Median age was 40 years-old, 64.4% were men. Median (range) TCD4+ cell count and viral load were 402 (238-620) cells/mm3 and 50 (20-50) cps/ml. Regarding disease stage, the post-hoc analysis showed that asymptomatic patients have a better level of adherence (p<0.001) and QoL (p=0.000) when compared to those in more advanced stages of the disease. Undetectable viral load <20 copies/mL and T CD4+ cell count >500 cells/mm3 were also associated with higher QoL (p=0.04 and p<0.001, respectively) and higher adherence (p<0.001 and p<0.001, respectively). Patients on NRTI+NNTRI regimens

have higher adherence when compared to those on NRTI+PI regimens [72.4 (10.4) vs 69.1 (10.8); p=0.012] and higher QoL indexes [55.9 (20.1)] vs 49.6 (22.2); p<0.001]. When compared to twice daily regimens, patients on single dose per day regimens have higher adherence [73.5 (9.6) vs 68.9 (11.2); p<0.001] and higher QoL [55.9 (20.1) vs 49.6 (22.2); p=0.001]. The study also shows evidence of a positive and statistical association between the adherence behavior and quality of life overall, with the highest correlation found in the psychological domain (r=0.58, p<0.001) and the lowest in the social relations (r=0.35, p<0.001) domain.
Patients experiencing adverse events have lower QoL [47.6 (22.2) vs 56.5 (20.0); p<0.001] and lower adherence levels [66.9 (11.3) vs 74.0 (9.3); p<0.001] when compared to those not experiencing such events.
Conclusions: Both clinical variables and regimen characteristics were found to be associated with adherence and QoL. These should thus be considered when defining interventions to improve the adherence to the antiretroviral therapy.

P120

Does feedback of medication execution using MEMS caps aid adherence to HAART?: the MEMRI study (MEMS as Realistic Intervention)

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Purpose of the study: Medication adherence is crucial for successful Highly Active Antiretroviral Treatment (HAART). Adherence may be divided into execution (how dosing history corresponds to the prescribed drug dosing regimen) and persistence (the time from the first to last taken dose). Medical Electronic Monitoring System (MEMS) monitors record bottle opening events providing a graphical printout of adherence. This can be used to provide positive feedback and correct any perceptual inaccuracies as to adherence. MEMRI assesses the use of such feedback as an intervention to support adherence. The primary endpoint is based on execution.
Methods: 265 patients were recruited. 180 were suitable for randomisation. All subjects were attending for HIV outpatients at Birmingham Heartlands Hospital. MEMS cap data was available for analysis for 145 of these. 78 (Group A) were given regular feedback using graphical readouts by clinical staff predominantly pharmacists. 67 (Group B) were blinded to feedback and no graphical output was available. MEMS 6 monitors (LCD display) were used on the most frequently dosed component of the HAART regimen. MEMS were downloaded at each clinic visit. At time of this interim analysis 12 months of follow-up had been completed for all subjects.
Summary of results: 123 patients took qid regimens, 14 took bid regimens, and 8 took multiple regimens during monitoring each divided evenly between Group A and Group B. Medication execution was high in both groups (>90%) for those patients who continued using the MEMS cap. Feedback (Group A vs. B) was not associated with a significant difference in execution but execution improved over time. There was a larger drop-out rate in Group B vs. Group A (22 vs. 13 patients) although this was not statistically significant. Execution was significantly worse at weekends (p=0.0001).
Conclusions: A preliminary analysis of the MEMRI study primary endpoint is presented. On limited follow-up at 12 months MEMS feedback showed no effect on medication adherence but this was only on patients with high initial adherence execution. This large adherence study includes a wide range of patients and may be able to extrapolate to other groups. Data based further follow-up will be presented and when complete the study will include analysis of other factors such as perceived needs and concern, self-efficacy and conscientiousness.

P121

Antiretroviral regimen complexity as a predictor of adherence

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Purpose of study: Even with the introduction of once daily antiretroviral (ARV) regimens of low pill burden, long-term adherence remains a challenge, particularly in subgroups, such as patients with drug addiction. We aimed to determine levels of adherence and identify factors associated with suboptimal adherence in treated, HIV-infected patients attending a busy European inner-city HIV outpatient clinic.
Methods: In a prospective cohort study, adherence was assessed in HIV-infected patients on antiretroviral therapy by self-report (ACTG adherence questionnaire). Relationships between suboptimal adherence (defined as <95%) and 49 covariates, including demographics, treatment factors, Centre for Epidemiological Studies Depression (CES-D) score and comorbidities were assessed using simple regression. Variables significant ($P < 0.05$) in univariate analyses were evaluated using multivariate logistic regression.
Results: 130 subjects (median [IQR] age 38 [11]; 27% female; 33% African origin; 27% IDU, 30% heterosexual and 20% MSM) were recruited. 83% were on once daily ARV and 16%, 34%, 48% and 2% were on regimens comprising one, two, three and four ARV medications respectively. Median CD4+ was 389 [285] cells/μL. 91% had HIV RNA < 50 copies/ml. Median adherence was 92% [range 0-100%] and 28% had suboptimal adherence. In univariate analyses, recent illicit drug use, on methadone, higher CES-D score, taking a higher number of ARV medications, greater pill burden, missed clinic appointments and lower CD4+ were associated with suboptimal adherence. In multivariate analysis, missed clinic appointments [OR 1.45; 95% CI (1.16, 1.81)] a higher CES-D score [OR 1.14; CI (1.01-1.28)] and being on a higher number of antiretroviral medications [OR 3.45; CI (1.46, 8.54)] were all independent predictors of suboptimal adherence.
Conclusions: In a cohort where many patients are on once daily ARV, although attending clinic visits and psychological status remain important, the number of antiretroviral medications is the strongest independent predictor of adherence. Medication complexity (number of ARV) rather than the pill burden is more predictive of poor adherence in this cohort of patients from varied demographic backgrounds. Single pill, fixed dose combinations (FDC) may improve adherence and these data support further development of FDC especially for those with drug addiction and psychological issues in which current FDC medications may not be suitable.

P122

Naïve patients receiving TDF/FTC-EFV as 2 pills are more likely to modify regimen components than patients receiving a TDF/FTC/EFV single pill

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Purpose of the study: To estimate the short-term probability of treatment change in antiretroviral naïve patients receiving tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV) as a one (1p) or two pills (2p) regimen.
Methods: We evaluated, by logistic regression and Cox proportional model analysis, factors associated to treatment modification during the first year of HAART in antiretroviral naïve patients from a single HIV unit in Madrid who started treatment with TDF, FTC and EFV as 1 p or 2p. For this analysis we censored patients who switched from 2p to 1p.
Results: From Jan/06 to Dec/09, 136 patients started HAART with TDF, FTC & EFV as 1p (59, 42.8%) or 2p (79, 57.2%). Mean age: 38.5 (1p) and 38.6 (2p), 83.1% male (1p) and 75.3% (2p). Median CD4: 250 (1p) and 244 (2p), mean viral load (log): 4.53 (1p) and 4.48 (2p), HCV coinfected: 15.3% (1p) and 19.5% (2p). One-year probability of HAART modification was

14.7% (95%CI 9.7-21.6) globally, 20.78% (13.22-31.12) for 2p and 6.7% (2.67-16.18) for 1p. Proportions of patients with viral load <50 copies/mL after one year of follow up were 87.5% (1p) and 94.4% (2p). Reasons for HAART modification were toxicity (8.7%) and lack of efficacy (2.2%) or adherence (3.6%). HAART modification due to toxicity was more frequent (7.52%) with 2p (5 skin rashes, 2 SNC adverse events, 1 impairment of renal function and 1 osteopenia) than with 1p (2 skin rashes, 1.5%). Patients on 2p were changed to TDF/FTC + LPV/r (3), TDF/FTC + ATV/r (2), TDF/FTC + NVP (1), ABC/3TC + EFV (2), ABC/3TC + LPV/r (1), ABC/3TC + ATV/r (1), AZT/3TC/ABC + TDF (1) or stopped treatment (5). Patients on 1p switched to TDF/FTC + LPV/r (1), TDF/FTC + DRV/r (1) or stopped treatment (2). Multivariant logistic regression analysis showed that a 2p regimen [OR 5.0 (1.18-21.16)], prior AIDS-defining condition [4.09 (1.37-12.27)] and time (months) since HIV diagnosis [1.015 (1.006-1.025)] were significantly associated to HAART modification.
Conclusions: Our study suggests that patients receiving TDF, FTC and EFV as 1p are more likely to maintain the regimen after one year than patients receiving the same regimen as 2p. Reasons for this difference might be related to a higher threshold for both clinicians and patients to change therapy even in the context of adverse events when patients are receiving TDF, FTC and EFV as a single pill.

P123

High level of adherence to HAART among refugees and internally displaced persons on HAART in western equatorial region of Southern Sudan

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Background: Signature of the Comprehensive Peace Agreement (CPA) in 2005 marked the end of the 20 year war in Southern Sudan. However, the decades of war and lawlessness have completely disrupted the healthcare infrastructure in the whole of southern Sudan. HIV sero-prevalence in the western equatorial state of Southern Sudan (12.1%) is the highest in the country. the massive numbers and mobility of internally displaced persons as well as insecurity due to frequent rebel attacks make providing ART for HIV infected persons in this part of Africa very challenging.
Objectives: This study highlights the challenges and achievements of international medical corps, with support from the WHO, in providing HAART to returning refugees and internally displaced persons in western equatorial region of Southern Sudan.
Patients and methods: We analyzed clinic data of 159 (90 F, 69 M) adults were started on ART between July 2009 and march 2010. Most (69%) had been living in refugee camps while 12% were internally displaced persons at the time of ART commencement. 78% of patients presented with WHO stage 3 or 4 symptoms. All new patients went through a 3 day period of treatment preparation prior to ART commencement. Treatment education in the local language was done at group and individual levels during clinic visits. Songs addressing adherence were developed and used during Support group sessions to reinforce key adherence messages.
Results: 68% of patients had baseline CD4 testing prior to commencing ART. Mean baseline CD4 count was 97cells/uL. All patients are presently on first line HAART. 65% of patients were started on AZT/3TC/NVP, 20% on AZT/3TC/EFV, and 15% on D4T/3TC/NVP. The commonest side effect observed were anaemia (6%), skin rash (4%), and gastro-intestinal discomfort (3.5%).
Of the 102 patients who had taken HAART for at least 6 months, 88% reported adherence levels of >95% (had missed less than 3 doses within last month). Adherence was higher in females (92%) compared to males (80%). Of those who reported missing more than 3 doses, 71% gave rebel attacks as the reason they were unable to return to the clinic for their drug pick-ups.
Conclusions: Despite challenges related to insecurity in Southern Sudan, successful antiretroviral therapy can be provided. Good level adherence remains an important determinant of success of ART and efforts must be made to institute comprehensive treatment education as a key strategy especially in resource limited settings.

P124

Identifying causes of loss to follow up in newly diagnosed HIV-infected patients

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Purpose of the study: The aim of the study was to evaluate the cause of the lost to follow-up in the newly diagnosed HIV positive patients, after the first visit in the HIV clinic.
Methods: We retrospectively reviewed the clinical charts of the adult patients (P) who consulted for the first time in the Infectious Disease Clinic of the university associated hospital at Buenos Aires, Argentina, between June 1st 2005 and May 31st 2008. We identified between the P who were newly diagnosed with HIV infection, those who attended the clinic only once; we considered lose to follow up those P who never come back in a year time. We exclude those P who attended other clinic before coming to ours. We contacted via telephone those P who had only one visit and never came back, to know the reason why they never came back to the clinic; we compared the age, gender, and socioeconomic characteristics between the group of patient who continued medical care (those who are currently attending our clinic and were diagnosed in the same period) and those who lost to follow up. We considered the first visit, the one in which the P is informed about his HIV seropositive condition.
Summary of results: We included 227 adult P who consulted the clinic for the first time. We identified 123 P (54%) who never came back to consultation after the first visit. The main cause of lost to follow up was because the patient felt good enough and thought they do not need medical attention (31/123); 25/123 P gave us a wrong number so we could not contact them. Most of the P were under no medical attention at the time we called them (61/123). We compare those P with 104 P who continued attending our clinic; the group of P who continued under medical care were older (median age 40.4 vs 34.2), patient with 40 years or more were 50/104 in the first group and 24/123 in those lost to follow up (p=0.0000048 OR 3.82 CI 2.04-7.20), and were in most cases women (34/104 vs 30/123, p=0.16 OR1.51 (0.81-2.80). P who continue follow up were working in most cases (95/104 vs 45/123, p=0.0000 OR 18.3 CI 8.00-43.11), live with family/partner (94/104 vs. 77/123 p=0.01 OR 0.67) and got better scholarship degree (university studies 21/104 vs 7/123 p=0.000 OR 4.19 CI 1.60-11.43) than P that did not continue follow up.
Conclusions: We must reinforce the medical care need in recently diagnosed HIV patients during the first visit to avoid the loss to follow up, especially in those patients who are younger and socially excluded.

RESISTANCE

P125

Transmitted drug resistance associated with transmission clusters in newly diagnosed antiretroviral-naïve patients in Northern Greece

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Purpose of the study: To determine the contribution of transmission clusters on transmitted drug resistance (TDR) in newly diagnosed antiretroviral naive patients in Northern Greece, during 2000 -2007.
Methods: Viral reverse transcriptase and protease genes from 369 individuals with newly diagnosed HIV-1 infection were sequenced at baseline. A maximum-likelihood phylogenetic analysis method was employed to examine for linkage between viral isolates. Clinical data were retrieved from the database and cross-referenced with the patients'

medical files. Transmitted drug resistance was defined in accordance with the Surveillance Drug Resistance Mutation (SDRM) 2009 list.
Results: The study population characteristics were as follows: 82.8% male, 89.7% of Greek nationality, mean age 38, median CD4 cell count at diagnosis 295 cells/μl and mean HIV-1 RNA 4.94 log10 copies/ml. The most prevalent risk exposure category was men who have sex with men 59.1% (n=218) followed by heterosexual transmission 21.4% (n=79) and intravenous drug use 7.6% (n=28). Subtype B viruses were most prevalent (53.1%), followed by subtype A (32.5%). At least one drug resistance mutation was identified in 46/369 patients (12.4%). Twenty-eight patients (7.6%) harbored resistance mutations to nucleoside/nucleotide RT inhibitors, 20 patients (5.4%) to non-nucleoside RT inhibitors and 12 patients (3.3%) to protease inhibitors (PIs). Dual-class resistance mutations were identified in 14 patients (3.8%). The median CD4 cell count in patients with TDR was not significantly different compared to patients without (p=0.072). Phylogenetic analyses, supported by bootstrapping >90% and genetic distance <0.015, revealed three transmission clusters involving drug resistant strains, including one cluster of 11 patients infected with a strain carrying RT mutations Y181C and T215 variants conferring NRTI and NNRTI resistance.
Conclusions: The overall prevalence of TDR in our study population was 12.4%. Phylogenetic analyses of viral sequences from these new diagnoses demonstrated the impact of transmission clusters on the primary drug resistance. The outbreak of dual-class TDR, coupled with late HIV diagnosis in this population may require improved public health interventions.

Reference

1. Bennett DE, Camacho RJ, Otelea D, *et al*: Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance. *PLOS ON* 2009, 4: e4724, 2009 Update.

P126

Analysis of transmitted drug resistance, resistance mutations and future antiretroviral efficacy in HIV-1 subtype F infected-patients prior to therapy

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Background: Studies have shown that transmitted drug resistance mutations involving major antiretroviral classes appear to persist for months, even years, after infection. Efficacy of antiretroviral treatment in recently infected individuals imply resistance testing prior to initialize treatment. The prevalence of drug resistance mutations in patients newly infected with HIV-1 is high throughout the world and little is known about transmission of resistant virus in non B subtypes. In Romania from 1992 to 2009, analysis of the relative incidence of different HIV-1 circulating strains revealed a stable profile with high prevalence of subtype - F, in both long term survivors and recently infected adults.
Objectives: To study the prevalence of transmitted drug resistance and asses the type of mutations fond in F subtype recently diagnosed and naïve patients.
Materials and methods: Sequencing of the pol gene was carried out using Trugene genotyping kits, (Bayer diagnostics) in plasma samples from 10 recently diagnosed adults, average age 28.9±5.2 years, parenterally HIV infected. The nucleotide sequences were submitted to the Stanford database, and all strains were found to belong to the F subtype.
Results: All patients had clinical progression, median CD4 count was 143.6cells/mmc (range 8-490); median HIV ARN was 380278.5copies/ml plasma (range38000-1020000) and they need to initialize antiretroviral treatment. We found PI major resistance mutations in 2 patients: the mutations were V82S, V82 F, I84L; NRTI resistance mutations in 7 patients, the mutations were: M41L, A62P, D67G, F77L, Q151R, K219P, M41V, T215N, K219Q, D67A, T69N, K70R, T215I, K219N and NNRTI resistance mutations in 3 patients, the mutations were: L100S, K103N, F227L, V179D, Y181S . All patients presented other mutations in average number of 11.5 ±2 for protease and 26.7±19.8 for reverse transcriptase. From the type 2 TAMs recognized to confer NRTI drug resistance only K70R was found in 2 patients also K103N associated with primary NNRTI resistance was found in one patient. The L89M polymorphism, the most prevalent signature among treatment-naïve non-subtype B isolates, was found in 7 patients.
Conclusions: Due to transmitted drug resistance only 3 of the tested patients could have been treated with any kind of antiretroviral therapy, the rest, 70%, have limited therapy option. If genotyping is not performed prior choosing an antiretroviral combination the chances of therapy efficacy are low.

P127

Detection of HIV type 1 mutations on the pol region in untreated patients in Northern Vietnam: determination of drug resistance and subtypes

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Purpose of the study: The first antiretroviral therapy was introduced in Vietnam in 1990 and included two nucleoside reverse transcriptase inhibitors (NRTIs). More recently, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) were available, particularly through different programmes. In this context, it is interesting to survey the HIV drug resistance and also to determine the main subtypes circulating in this country.
Methods: Plasmas from 56 seropositive patients were collected before treatment. All patients originated from the area of Hanoi, North Vietnam. After RNA extraction using Nuclisens® easyMag® (Biomérieux), the sequencing of the pol region was conducted according to the ANRS recommendations. The DNA was sequenced on both strands with ABI Prism 3130xl and analyzed with SeqScape software to determine the differences compared to HXB2 strain: determination of resistance was done using the ANRS rules. ClustalX and Treeview software allowed determining the subtype of each strain.
Summary of results: Among the 56 patients, two revealed HIV resistance to the main NRTIs and NNRTIs (mutations Y181C and Q151M for one patient, and G190A, Q151M, Y115FY and K65R for the other). No resistance was observed for the PIs, except for tipranavir; almost all strains exhibited the association of M36I, H69K and L89M mutations. Concerning the integrase inhibitors, two patients (different from those exhibiting resistance for NRTIs and NNRTIs) revealed the mutation E157Q conferring a resistance to raltegravir. All the strains but one belonged to the subtype CRF15_01B; the last one exhibited a CRF08_BC subtype. Numerous polymorphic mutations were observed among these strains.
Conclusions: In this study, 2/56 (3, 6%) patients exhibited a resistance to the main NRTIs and NNRTIs before administration of treatment. The same percentage of patients had strains resistant to the raltegravir. The CRF15_01B is the subtype the most prevalent in the population studied.

P128

Population and ultra-deep sequencing for tropism determination are correlated with Trofile ES: genotypic re-analysis of the A4001078 maraviroc study

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Background: A4001078 is a study in therapy naive patients of Maraviroc (MVC) plus boosted atazanavir. The Trofile ES (ESTA) was used to determine tropism at Screening. Few re-analyses of genotypic tropism

Trofile ES Result	Population sequencing with a 5.75 FPR (g2p) UDS Median % X4 use (IQR%)			UDS result with 2% cut off (at g2p FPR of 3.5) Median % (IQR%)		
	R5	CXCR4 using	NR	R5	CXCR4 Using	NR
R5 = 123	114 0 (0)	5 47.5 (29)	4 0 (0)	111 0 (0)	7 47.5 (64.8)	5 NA
D/M = 39	19 0.11 (0.4)	18 43.3 (59.9)	2 0.54 (0)	14 0 (0.3)	22 39.4 (57.7)	3 NA
NR = 16	13 0 (0.04)	3 73.1 (97.7)	0	13 0 (0.1)	2 86.4 (26.7)	1 NA

Figure 1 (abstract P128) Correlation between methods and quantity of X4 use by UDS in concordant and discordant results and quantity of X4 using virus by UDS.

have examined all screened and non-reportable (NR) populations. We aimed to define correlations between methods at screening and evaluate the quantity of X4 using virus in discordant results using ultra-deep sequencing (UDS).
Methods: Population and UDS methods were employed on 178 of 220 screened subjects and 121 enrolled subjects. Correlation between methods was explored and the quantity of X4-using virus in both discordant and concordant samples was measured using UDS.
Results: ESTA defined 123 (69%) as R5, 39 (22%) as Dual or Mixed tropism (D/M) and 16 (9%) as NR. Population sequencing (single amplification) defined 146 (82%) as R5, 26 as X4, and 6 tests were non reportable [Either failure to get a PCR product (no result for both, population sequencing and UDS) or non-evaluable Sanger traces]. Correlation between population and UDS for R5 use was 95%. Of the patients screened as R5 by population sequencing, UDS showed a median of 0% X4 with only 3 of 114 results being over 2% X4 use, suggesting this method is suitable for selecting individuals for CCR5 antagonist therapy. All Trofile NR results were reportable by population sequencing and showed tropism results consistent with the overall population.
Conclusions: Population sequencing appropriately identified patients with <2% CXCR4 using virus and who would be suitable for CCR5 antagonist therapy.

P129

Clinical application of genotypic co-receptor tropism testing from viral RNA and proviral DNA: week 24 analysis of the Berlin maraviroc cohort

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Objectives: Before initiating an antiretroviral combination therapy which includes Maraviroc as one of its components, a coreceptor tropism test has to be performed. As Maraviroc is only effective against HIV strains that are using CCR5 as coreceptor a thoroughly validated and reliable assay should be performed. In case of treatment change due to toxicity, testing should also be possible using proviral DNA.
Material and methods: Included in the study cohort of this non-interventional observational study are 157 patients. Only inclusion criteria was a treatment with Maraviroc and a previous tropism test. Phenotypic tropism tests were performed by Monogram biosciences (TROFILE®). For Genotypic tropism determination from V3 loop sequence data geno2pheno$_{[coreceptor]*}$ was used. Data acquisition for week 12 and week 24 is already finished. It is planned to collect data for 96 weeks for all the patients. Data analysed are besides viral load and the other components of the HAART, genotypic resistance assay at baseline, immunologic parameters and treatment side effects.
Results: Genotypic tropism results were available for 88 patients from viral RNA sequences and for 53 patients from proviral DNA sequences. A TROFILE® result was available for 70 of the patients as 71 of the patients had a viral load below 1000 cop./ml and a testing with TROFILE® was not possible. In the intent to treat (ITT) analysis 70% of the patients were successfully treated at week 24, defined as a viral load decline of at least 3 logs or a viral load below detection limit of 50 copies/ml. The positive predictive value (PPV) of geno2pheno using a FPR cut-off of 10% was 77% (PPV TROFILE®: 66%). In the subgroup of patients where only a genotypic tropism test from proviral DNA was available 86% of the patients had a viral load below detection limit of 50 copies/ml (70% at baseline).
Conclusions: On this clinical dataset performance in terms of predictive power is slightly better when using geno2pheno compared to TROFILE®. Therefore genotypic tropism testing proves to be an easy and inexpensive alternative to phenotypic tropism testing.
Especially in the group of patients, where only a genotypic tropism test could be performed from proviral DNA, a high rate of successful treatments was observed, showing that this method makes it possible to perform tropism testing guided treatment change despite undetectable viral load.
*geno2pheno$_{[coreceptor]}$: http://www.geno2pheno.org

P130

Analysis of BENCHMRK 1 & 2 using PhenoSense® assay for darunavir (DRV/r) resistance and exploration of functional monotherapy with RAL vs DRV

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Purpose of the study: Previous analyses of the 2 BENCHMRK studies of raltegravir (RAL) vs placebo (Pbo) plus optimized background therapy (OBT) in treatment-experienced HIV-infected patients (pts) by PSS as contributed by OBT used assumptions of susceptibility to DRV/r based on prior use, since commercial phenotyping was not available. Re-analysis is now performed using newly available DRV/r phenotype data.
Methods: In BENCHMRK pts who used DRV/r in OBT, baseline PSS was recalculated using the DRV/r PhenoSense® result (Monogram Bioscience). A new analysis by PSS score of RNA <50c/mL for wk 48 and wk 156 was performed using the upper clinical cutoff (UC) of OBTs, including DRV/r. An exploratory analysis compared outcomes for pts whose only fully active ART was RAL or DRV/r.
Results: 184 pts in the RAL group and 99 in Pbo group used DRV/r in OBT at study entry; of these 166 and 90 pts, respectively, had no prior use of DRV/r and were previously considered DRV/r susceptible. 165 pts in the RAL group and 91 in Pbo group had baseline DRV/r Phenosense results: 7% and 7% of pts previously assumed susceptible to DRV/r

Table 1 (abstract P130)

	Efficacy at week 48, RNA<50 copies/mL %, (n/N)			
	Initial approach		New analysis	
	(DRV/r phenotype assumed)		(DRV/r phenotype data)	
PSS	RAL	Placebo	RAL	Placebo
0	51 (17/33)	8 (1/12)	52 (16/31)	8 (1/13)
1	48 (34/71)	13 (7/54)	45 (34/79)	15 (8/55)
2	67 (107/160)	30 (26/88)	69 (102/148)	29 (24/83)
≥3	73 (112/153)	60 (39/65)	72 (113/156)	59 (38/64)

showed phenotypic resistance; 17% and 44% assumed resistant to DRV/r were found to be susceptible.
Overall results at wk 48 were 64% vs 34% with RNA<50c/mL for RAL vs Pbo. Wk 48 virologic outcomes by PSS score are shown in table 1. Wk 156 outcomes by PSS were consistent (not shown). In the exploratory analysis comparing functional monotherapy with RAL (PSS=0) vs DRV/r (Pbo, PSS=1) at wk 48: 52% vs 30% of pts had vRNA <50 c/mL. Wk 156 results (not shown) were consistent with wk 48.
Conclusions: In BENCHMRK, prior use of DRV predicted DRV susceptibility similarly to the UC phenotypic criteria. Re-analysis of virologic responses by PSS score incorporating the UC Phenosense result for DRV/r demonstrated consistent treatment differences between RAL and Pbo groups for all PSS scores, generally similar to the earlier analyses. In an exploratory analysis approximating a direct comparison of RAL vs DRV/r as sole active agents, virologic responses using UC appeared higher for RAL than DRV at both time points, although numbers of pts receiving DRV monotherapy were small.

P131

Analysis of major and minor IAS-USA PI mutations in the MONET trial of darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs

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Background: For patients on treatment with HIV RNA <50 copies/mL, it is unknown whether the genetic barrier to evolution of resistance is different for DRV/r monotherapy, compared with standard triple combinations of antiretrovirals. Several minor IAS-USA mutations are detected frequently in samples from PI naïve patients.
Methods: In the MONET trial, 256 patients with no history of virological failure and HIV RNA <50 copies/mL on current HAART (NNRTI based (43%), or PI based (57%) switched to either DRV/r monotherapy (800/100 mg OD) versus DRV/r + 2NRTIs. HIV RNA levels were evaluated at Weeks 2, 12, 24, 36, 48, 60, 72, 84 and 96: all patient samples with HIV RNA above 50 copies/mL were sent for genotypic resistance analysis (VircoTYPE HIV-1, Beerse, Belgium). Virtual phenotype was also assessed when PI mutations were detected. The percentage of patients with major or minor IAS-USA PI mutations was analysed by treatment arm.
Results: Patients were 81% male and 91% Caucasian, with median age 43 years, and median CD4 count of 575 cells/uL. While patients were receiving randomised treatment, HIV RNA was above 50 copies/mL for 47/1051 (4.5%) patient-visits in the DRV/r + 2NRTI arm and 69/1009 (6.8%) patient-visits in the DRV/r monotherapy arm. Of 48 patients with at least one successful genotype (27 in the DRV/r monotherapy arm, 21 in the DRV/r + 2NRTI arm), two showed major IAS-USA PI mutations during short-term elevations in HIV RNA (one per treatment arm). Both patients remained phenotypically sensitive to darunavir, with sustained HIV RNA<50 copies/mL during the trial and no change in antiretroviral treatment. The five most common minor IAS-USA mutations detected in the DRV/r mono and DRV/r + 2NRTI arms were L63P (78%, 62% respectively), I93L (59%, 19%), V77I (33%, 43%), I62V (22%, 33%) and I64V (15%, 24%). These five mutations were also commonly observed in the Stanford HIV database of 7601 samples from PI naive patients. Fourteen patients in the DRV/r monotherapy arm had repeated genotypes during intermittent low-level viraemia — there was no evidence for evolution of minor IAS-USA PI mutations over time in these patients.
Conclusions: After 96 weeks of treatment in the MONET trial, there is no evidence for an increased risk of emergence of major or minor IAS-USA PI mutations with DRV/r monotherapy, compared to DRV/r + 2 NRTIs, and no evidence for evolution of PI mutations after repeated genotyping.

P132

Changing prevalence of darunavir resistance-associated mutations (DRV RAMs) in clinical samples received for routine resistance testing: 2003-2009

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Purpose of the study: Darunavir (DRV) is an HIV protease inhibitor (PI) first approved in 2006. This analysis evaluated the prevalence of DRV resistance associated mutations (RAMs) in clinical samples submitted for routine resistance testing to assess potential changes or evolution in the frequency of these mutations over time.
Methods: Annual prevalence of the IAS-USA 2009 DRV RAMs (V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V) was studied in approximately 232,000 routine clinical samples submitted to Virco for resistance testing between Jan 2003 and Dec 2009. Prevalence was assessed over time for individual DRV RAMs, DRV RAM combinations and presence of 0, 1, 2, or ≥3 DRV RAMs. Results for DRV RAMs were expressed as the proportion of (1) all clinical samples, (2) samples with evidence of PI resistance (defined by FDA mutation list, or a predicted fold change (FC) in IC50 for any PI greater than the respective virco®TYPE HIV-1 (VTY) lower clinical cut-off [CCO] (FC=10) and (3) samples with DRV resistance defined by predicted FC >10.
Summary of results: Overall prevalence of samples showing evidence of any PI resistance decreased gradually over time (from 2003 to 2009: 47.0% to 32.2% [VTY lower CCO]; 49.1% to 42.2% [US-FDA mutation list]. Mean prevalence of each of the 11 individual DRV RAMs also decreased over time (Figure 1)
Prevalence of samples harbouring ≥1 DRV RAMs also decreased over time. In 2009, 94.3% of all samples harboured zero DRV RAMs versus 85.3% in 2003. Among samples with evidence of PI resistance, 88% vs 72% (per FDA list) and 84% vs 70% (to any PI defined by predicted FC> low CCO) harboured zero DRV RAMs. The most common three DRV RAM combination was L33F,I54L,I84V which was detected with a prevalence of 0.15% in 2003 and 0.08% in 2009.
Conclusions: In 2009, most routine clinical HIV isolates (94.3%) harboured zero DRV RAMs. Despite widespread DRV use, the prevalence of DRV RAMs among all clinical isolates and among those with evidence of PI resistance has decreased since 2003. This could be due to pharmacologic suppression on the mutation rate and/or DRV's high genetic barrier to the development of resistance within the treatment regimen.

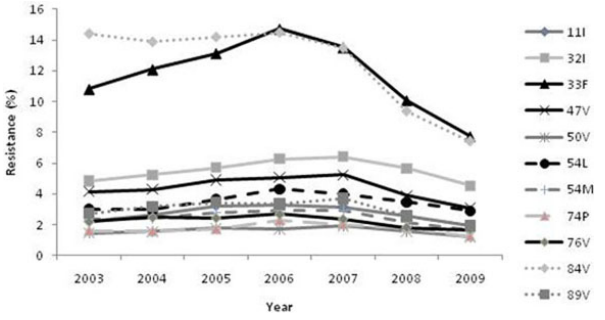

Figure 1 (abstract P132) 2009 IAS-USA DRV RAMs as a proportion of samples with evidence of PI resistance by VTY lower CCO.

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Darunavir resistance spectrum in darunavir-naive patients harboring virological failure to antiretroviral therapy

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Purpose of the study: Darunavir is one of the protease inhibitors that is recommended to treat protease inhibitor-naïve or -experienced patients. Recent studies have determined the spectrum of darunavir activity in patients failing to antiretroviral therapy. Darunavir resistance mutations in protease gene have been identified (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V) and allow to classify viruses as sensitive (<3 mutations), possibly resistant (3 mutations) or resistant (≥4 mutations) to darunavir.
Methods: 1583 genotypic resistance tests performed between 2008 and 2009 for darunavir-naïve patients experiencing virological failure (whatever the antireroviral combination used) were analyzed retrospectively. Protease gene was sequenced and aminoacid changes analyzed at time of virological failure. The number of darunavir resistance mutations were determined and the strains were classified regarding the spectrum of darunavir activity (ANRS algorithm V18).
Summary of results: Among these experienced patients failing antiretroviral therapy, 63% harbored no darunavir mutations in the protease gene and 12%, 16%, 4% and 5% harbored 1, 2, 3 and at least 4 darunavir mutations, respectively. Patients with viruses harboring darunavir mutations had lower HIV-1 viral load than patients with viruses without any darunavir mutations.
Conclusions: This study shows that the percentage of genotypic fully resistant strains to darunavir is rare in a population of darunavir-naïve patients experiencing virological failure. A large proportion of patients harbored viruses without any darunavir resistance mutations allowing the use of darunavir/r (800/100 mg) QD. Virological failures without selection of any mutations showed higher viral load level rebound probably related to lack of adherence.

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Resistance after viral failure on atazanavir-containing therapy: multinational clinical cohort (BMS AI424-128 — 'IMPACT') final analysis

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Purpose of the study: Real world data on the development of drug resistance after virologic failure (VF) on a protease inhibitor (PI)-based antiretroviral (ARV) regimen are limited. The I50L substitution in protease is the primary mutation associated with atazanavir drug resistance. The primary objective was to compare the prevalence of I50L from VF patients on an unboosted atazanavir (ATV)-based regimen vs. those on a ritonavir-boosted ATV (ATV/r)-based regimen regardless of prior treatment history.
Methods: IMPACT is a large cross-sectional study of patients with VF while on an atazanavir-containing regimen that was conducted at 220 sites in 8 countries. Demographic/medical information and blood for a genotype resistance test were collected at a single study visit. A substudy evaluated the efficacy of the regimen subsequent to the atazanavir-containing regimen based on when atazanavir was used in therapy.
Summary of results: IMPACT enrolled 703 patients, and genotype resistance tests were able to be performed for 678. 67 had been on both ATV and ATV/r, and 55 had incomplete ARV histories. Overall, 48/556 evaluable patients had virus with an I50L: 12/96 (12.5%) on ATV and 36/460 (7.83%) on ATV/r (p=0.116). Most patients had been on another PI prior to atazanavir.
88/678 patients were on atazanavir (either ATV or ATV/r) as a first PI, and 69 had a complete ARV history. 3/19 (15.8%) who started ATV and 5/50 (10%) who started ATV/r had an I50L at VF. Phenotype resistance tests were performed for these patients: 55 tests showed full susceptibility while 12 tests showed reduced susceptibility to atazanavir. The viral isolates from these 12 patients remained fully sensitive to both lopinavir and darunavir.
Enrollment for the substudy was below the target enrollment, and sample sizes in all of the comparison groups were too small for meaningful statistical inference.
Conclusions: In a large clinical cohort of subjects failing atazanavir-based therapy with resistance data, I50L is uncommon in subjects with VF on atazanavir. Most PI-naive subjects failing an atazanavir-based regimen failed with virus susceptible to atazanavir, and all viral isolates were sensitive to the other PIs commonly used to treat virus with PI drug resistance. These real world data provide further support of clinical trial data that have shown preservation of treatment options after VF when atazanavir is used as a first PI.

P135

High levels of polymorphisms related to raltegravir resistance among raltegravir-naïve individuals in Brazil

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Purpose of the study: Raltegravir (RAL) is an HIV-1 integrase strand-transfer inhibitor that has exhibited substantial efficacy and a favorable safety profile in HIV-1 infected patients. The goal of this study was to explore the presence of natural polymorphisms and primary mutations related to RAL resistance among HIV-1 patients failing to multiple antiretroviral agents.
Methods: 25 plasmas from HIV-1 infected patients with HAART failure were studied. Genetic analysis was performed amplifying and sequencing DNA encompassing 288 amino acids of HIV-1 integrase gene. Drug resistance mutations and polymorphisms were examined following Low et al, 2009. Genetic subtypes were analyzed using REGA HIV Subtyping Tool (http://www.bioafrica.net/subtypetool/html/subtypinghiv.html).
Results: Of the 25 patients, 15 were males and 10 females. All of them are more than 18 years old and 19 patients born in Sao Paulo city. 22 patients were infected by HIV-1 subtype B, 1 by subtype F and 2 by B/F recombinants. No Raltegravir resistance related mutations were observed, however we identified following polymorphisms: V72I (44%), T97A (4%), Q146K (4%), V151I (28%), V201I (52%), T206S (8%), I203M (12%), S230N (4%), M154L (4%), K156N (16%) e K156R (4%). Furthermore, we observed amino acid substitutions at codons 163 in two patients (G163E and G163V) and 138 in one patient (E138N).
Conclusions: Despite the absence of RAL primary resistance mutations, we found a high frequency of polymorphisms that were related to in vitro reduced susceptibility to RAL. Furthermore, substitutions at codons 163 (G163R) and 138 (E138K) are called secondary mutations, which are capable to restore viral fitness due to the presence of primary mutations. Further studies are needed to determine the importance of these

polymorphisms in reducing the genetic barrier to RAL resistance among treated individuals.

Reference

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P136

Prevalence of resistance and HIV-1 protease mutation patterns after failures with fosamprenavir-containing regimens

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Purpose of the study: Fos-Amprenavir is one of the protease inhibitor that is recommended to treat protease inhibitor naïve of experienced patients. Amprenavir and darunavir share at least in part chemical structures and thus a possible selection of close protease gene mutations. Little is known about the frequency and the type of resistance mutations selected after virological failure to Fos-Amprenavir containing regimen. The aim of this study was to determine the genetic patterns and the prevalence of resistance mutations associated to virological failure to Fos-Amprenavir containing regimens in a cohort of naïve and experienced protease inhibitor patients.

Methods: 172 PI experienced patients, treated by r/Fos-APV (100/700 mg BID) and 96 PI naïve patients treated by r/Fos-APV (100/700 mg BID n = 33 and 100/1400 mg OD n = 63) were analyzed. Reverse transcriptase (RT) and protease gene were sequenced and aminoacid changes analyzed before Fos-APV treatment and at time of virological failure. Mutations were analyzed with the ANRS algorithm V18.

Summary of results: In PI experienced patients, there is a direct link between the number of PI resistance that were present at baseline and the probability of selection of resistance mutation at failure (p=0.01). The most common mutations selected were: V32I, L33F, M46L, I50V, I54L/V, I84V and L90M. In all cases when the protease gene at baseline harbored at least one PI resistance mutation, at least one resistance mutation was added at time of virological failure. Taking into account of the ANRS algorithm, 15% of patient developed a resistance to DRV. In PI naïve patients, only 6% of patients harbored a PI resistance mutation selected at time of virological failure. The most frequent selected mutations were V32I, I47V, I50V and I84V. There is a link between the duration of virological failure under r/Fos-APV and the rate of selected mutation (1% of cases at month 1, 3% at month 3 and 6% at month 6. Taking into account of the ANRS algorithm, only one patient developed a resistance to DRV.

Conclusions: This study confirms that resistance mutations selected by Fos-APV occurs mainly in PI experienced patients. Except for patients with more than 6 months replication with Fos-APV, the risk to select cross resistance to DRV is very low.

P137

Abstract withdrawn

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P138

Is extended resistance to the historical antiretroviral drugs & drug classes still a risk factor for HIV progression?

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Background: Since recent observations demonstrated that extended resistance to all the three main antiretroviral classes (NRTI, NNRTI, PI) is a marker of disease progression and death, the aim of the present analysis is to evaluate if this situations persists in recent years when several new potent drugs entered in the current clinical use.

Methods: Patients undergoing genotypic resistance test after treatment failure between 1999-2008 were included. The risk of progression was calculated with survival analysis separately for patients who failed between 1999-2003 and 2004-2008. Class resistance for the three historical drug classes was assessed, using Rega interpretation system (v. 8.0.1), when no fully active drug in each class was detected. Tipranavir, darunavir and etravirine were not included in the historical drugs classes. The follow-up was carried out up to December 2009: new AIDS event/death were considered study endpoint.

Results: Overall, 1522 patients were included, of whom 782 in the 1999-2003 and 740 in the 2004-2008 group. During follow-up, 171 and 59 new AIDS/death events were observed in the two groups, respectively. At survival analysis, the proportion of patients who achieved the study endpoint after 5 year of observation was 24% in the 1999-2003 and 11% in the 2004-2008 group. In the 1999-2003 group, a higher risk of progression in patients with no active drug in all the three historical classes was found (41% vs. 19% in patients with ≥1 active class, p=0.03 at adjusted Cox model). In the 2003-2008 group, the risk of progression was lower in patients with 3-class resistance (25%) while less risk reduction was found in patients with ≥1 active class (14%). Indeed, in the 2003-2008 group, 67% of patients with 3-class resistance were treated with ≥1 drug among tipranavir, enfuvirtide, darunavir, raltegravir, maraviroc and etravirine, compared with 45% of patients with 2-class and 6% of ≤1-class resistance. The most widely used drug were darunavir (58% of 3-class resistant patients), tipranavir (55%) and enfuvirtide (45%).

Conclusions: The availability for current use of new drugs, in new classes and those belonging to old classes but with different resistance patterns, may explain the improved survival of the more virologically impaired HIV patients. However, the improvement in survival does not still appear so crucial, particularly in patients with active drugs where a 14% progression at 5 years is still observed.

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Prevalence of HIV drug-resistance mutations in HIV-infected Mexican patients heavily experienced to antiretroviral therapy

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Background: A significant number of HIV Mexican infected people are in virological failure, many of them are multiply experienced to antiretroviral therapy.

Objective: To assess the prevalence of resistance mutations in HIV Mexican infected patients heavily experienced to antiretroviral therapy (ART).

Materials and methods: A transversal observational study of resistance profiles in strains from HIV-1 infected patients multiple experienced to ART was analyzed by a national committee of HIV drugs resistance in Mexico (GERA-1 IMSS). Mutations were defined according Stanford Resistance Database.

Results: We assessed 178 subjects, mean age (SD ±) of our subjects was 41.9 ± 11.9; 91% where male, who failed 2 to 15 ART regimen (median 5). CDC status was A 20%, B 21% and C 59%; 4% were coinfected with HBV and 2% were infected with HCV. Month median drug exposure was 121 (range 12-219). Ninety nine (55.6%) had triple class drug mutations, 170 (95.5%) had NRTI mutations, 113 (63.5%) had NNRTI mutations and 173 (97.2%) had PIs mutations. The most frequent NRTI mutation belonged to TAM pathways, 74 (41.6%) to TAM1 and 40 (22.5%) to TAM2. These mutations were 215Y/F 139 (77.7%), M41L 111 (62%), D67N 97 (54.2%), L210W 85

(47.5%), K219E/Q 60 (33.5%) and K70R 53 (29.6%) and reflect the extensive use of ZDV and d4T. K65R was found in 8 (4.4%), Q151M was found in 2 (1.1%) and insertion 69 in 1 (.5 %). The most frequent NNRTI mutation was K103N in 57 (31.8%) followed by Y181C 40 (22.3%), G190A/S 40 (22.3%), V108I 18 (10%), K101E 16 (8.9%), L100I 13 (7.3%), Y188L 11(6.1%), A98G 10 (5.6%), V90I 9 (5%); 14 (8%) of them had resistance to ETV. Most common PI major mutation were L10V/F 144 (80%), I54L/M/V 126 (70.4%), M36I/L 102 (57%), L90M 101 (56%), 82A/T 92 (51.4%), M46I/L 91 (50.8%), L33F/I 69 (38.5%), I84V 64 (35%) and others. 15 (8.4%) of them had resistance to DRV and 33 (18.5%) to TPV.
Conclusions: Long term exposure to ART and fluctuating adherence has led to the selection of multiresistant strains in Mexican HIV infected patients, many of them have resistance mutation for ART of new generation.

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HIV drug resistance in children with treatment failure to first-line regimens in Ho Chi Minh City, Vietnam

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Background: ARV resistance in children with first-line ARV treatment failure in Vietnam is unknown because antiretroviral therapy (ART) has been available on a large scale only since Sept 2005 and resistance testing is not widely performed. We characterize patterns of mutations to identify common resistance patterns for choosing the second-line regimens in Ho Chi Minh City.
Methods: 54 HIV-infected children were identified as having suspected treatment failure from June to December 2008 in HCMC. Selection criteria were one of the clinical or immunological criteria defined by the Vietnam Ministry of Health (development or recurrence of a WHO stage III or IV condition, failure to thrive, slow growth, CD4 falling below pretreatment value or below 50% of peak treatment value). The genotypic test was done at Pasteur Institute (RT-PCR Promega, DTCS Beckman Coulter) and analyzed using Stanford University's HIV drug resistance database.
Results: Most of children were on first line regimens: 17 (31.4%) on D4T +3TC+NVP, 7 (13%) on D4T+3TC+EFV, 13 (24.1%) on AZT+3TC+NVP, and 8 (14.8%) on AZT+3TC+EFV. Six patients were on NRTI-only regimens and 3 patients were on PI-containing regimens due to allergy or intolerance to NNRTI. Mean duration of treatment was 15 months. Viral load was undetectable in 14 samples (26.9%). Genotype tests results were available on 36 patients. Overall, one mutation was detected in 34 (94.4%) patients. NRTI mutations were found in 33 (91.7%), NNRTI mutations in 25 (69.4%), and PI mutations in 3 (8.3%). Among the NRTI mutations, at least one Thymidine Analog Mutation (TAM) defined as M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E, was found in 24 patients (72.7%), of which 17 (70.8%) patients had >3 TAMs. M184V was detected in 22 (66.7%); K65R in 3 (9.1%). Combinations of TAMs+M184V and TAMs+K65R mutations were present in 15 (45.4%) and 2 (6.1%), respectively. For NNRTI mutations, Y181C was most frequent 14 (56%), followed by G190A/S 11 (44%), K101K 7 (28%), K103N 4 (16), V108I 3 (12%) and Y188L (8%). Only three patients with one single PI mutation (33.3%) including M46I, L10F and A71V were found.
Conclusions: TAMs and the M184V mutation were present in a majority of genotypic tests. K65R and Q151M mutations were less common. The second-line regimen TDF+3TC+LPV/r would be more effective than ABC +DDI+LPV/r for most children with virological failure on first-line ARV in HCMC. More options for second-line in developing countries are needed.

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Molecular epidemiology of antiretroviral resistance in therapy-experienced HIV-1 patients in Cuba (2009)

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Background: In 2001, Cuba launched a national ARV access program to provide ARV therapy free of cost. The first-line therapy combinations are composed of two nucleoside reverse transcriptase (RT) inhibitors (NRTIs) (AZT+3TC or d4T+3TC) associated with a non-nucleoside RT inhibitor (NNRTI) (NVP or EFV) or a protease inhibitor (PI) (IDV).
Purpose of the study: To identify resistance mutations in HIV-1 isolated obtained from Cuban treated patients presenting clinical and/or immunological failure.
Methods: Plasma samples from 84 HIV-1 infected patients were collected from June to November 2009 at the Tropical Medicine Institute from Havana City. Viral RNA fragments corresponding to the PR and RT region were amplified, sequenced and sub typed. Drug resistance was interpreted according to http://hivdb.stanford.edu.
Results: The most frequently found subtypes and recombinants were: B (40.4%), D (32.1%, presumably CRF19_cpx), C (9.5%) and CRF18_cpx (8.3%). The PI mutations, I54VML, M46IL and L90MVL were found in 61.7, 57.4 and 53.1% of cases, respectively. Whereas for RTI, primary mutations at positions M184V, T215Y, D67N, Y181C and K103N were present in 98.6, 67.1, 43.8, 47.5 and 40.9% of subjects, respectively. A high level resistance to antiretroviral drug was observed (NRTI=86.9%, NNRTI=72.6% and PI=55.9%). Full class resistance (NRTI/NRTI/PI) was found in 22 patients (26.1%), who presented history of several changes of treatment (media of 1.35 treatment changes per year, from 4 to 13 year under treatment).
Conclusions: The present study reveals a high rate of resistance compared with other international reports suggesting that alternative strategies for initial therapy and lab monitoring should be considered. These findings also warrant the study of antiviral resistance in therapy-naïve patients.

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Development of drug resistance among HIV-1 F1 sub-type patients with treatment failure

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Background: The HIV/AIDS epidemic in Romania presents a series of particularities linked to the high frequency of a particular HIV subtype, a subtype that hasn't been found in other European countries, clade F, and by the existence of an important number of long life survivors patients infected during 1988-1992 - today young adults who presents a long history of treatment.
Purpose of the study: In order to evaluate the development of drug resistant HIV strains, we sequenced the pol gene of HIV-1 isolates from heavily treated patients.
Methods: The study included 26 HIV-1 isolates from heavily treated adolescents, with frequent changes in the antiretroviral combinations. Drug resistance genotyping was performed using the TruGene HIV-1 Genotyping Assay (Bayer Diagnostics). HIV subtype was determined using the Stanford database algorithm.
Results: All the strains were found to belong to the F1 subtype. 65.4% of the patients presented resistance to at least one of the 3 antiretroviral classes of used drugs (NRTI, NNRTI and PIs), while 15.4% were resistant to 2 classes and only 7,7% were resistant to all 3 antiretroviral classes. The most frequent substitutions of amino acids in reverse transcriptase gene were from TAM2's ("thymidine analogue mutations"): D67N, K70R, T215F, K219Q/E-mutations that confer resistance to NRTI and K103N, Y181C/I associated with primary resistance to NNRTI. Only 23% from the patients presented substitutions associated with major resistance to PI , the most frequent: I47V, G48 G/V; I54V, V82A, that confer phenotypic resistance to regimens that include ritonavir as a booster. As a surprise a series of minor and accessories mutations were present in the protease gene (ordered in decreased frequency: L10V, M36I; L63T, K20M/R).
Conclusions: A follow up of the clinical progression rate of these patients will provide important data, as subtype specific resistance mutations have been reported and associated with different rate of CD4 cell count decline over time and with distinctive replicative fitness of the viral strain.

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Pro-viral DNA and antiretroviral treatment simplification

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The question of Highly Active Antiretroviral Treatment (HAART) simplification is important due to long term toxicity and cost of HAART.
Pro-viral HIV DNA associated with Peripheral Blood Mononuclear Cells (PBMC) is a marker of the HIV reservoir which is predictive of the evolution of HIV infection. It remains the only virological quantitative marker detectable during suppressive HAART. A pro-viral DNA > 2.7log before treatment interruption is predictive of a decline of CD4 T lymphocytes after interruption [1].
We measured PBMC's pro-viral DNA in patients treated with triple nucleoside analogue therapy containing zidovudine who had developed severe lipodystrophy and/or metabolic abnormalities. A switch to a nucleoside analogue bitherapy by stopping zidovudine was proposed for patients whose pro-viral DNA was < 2.7 log. We selected 11 patients (mean age 48 years, 5 women, mean duration of infection=10 years, mean CD4 nadir=288/mm^3, mean plasma HIV RNA zenith =4,44 log). Patients were on triple nucleoside analogue therapy for 7 years with plasma HIV RNA< 40 copies/ml ; mean CD4 cells = 600/mm^3. Mean pro-viral DNA was 2,43 log copies/million PBMC. Treatment was switched to abacavir+lamivudine in 5 patients and emtricitabine+tenofovir in 6.
After switch, with a mean follow up of 40 months, plasma HIV RNA remained< 40 copies/ml without blip and CD4 cells remained stable.
In conclusion, treatment simplification with an analogue nucleoside bitherapy is possible in a selected group of patients who were treated with a triple nucleoside analogue therapy in virological success and had a PBMC's associated pro-viral DNA < 2.7 log before treatment simplification.

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LABORATORY MONITORING OF DISEASE THERAPY

P144

Haemoglobin and anaemia in the SMART study

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Purpose of study: Data from randomized trials on the development of anaemia after interruption of therapy is not well described. We aimed to describe the development of anaemia after interruption of cART and the relationship between the development of anaemia and clinical events (AIDS, deaths or non-AIDS events) in the Strategic Management of Antiretroviral Therapy (SMART) randomised trial.
Methods: 2248 patients from the SMART study were included. We used Cox proportional hazards models to investigate development of new (<12 mg/dl for females, <14 mg/dl for males) or worsening (<8 mg/dl if anaemic at randomization) anaemia and poisson regression analyses to explore the relationship between anaemia and the development of AIDS, death or non-AIDS events.
Results: The change in haemoglobin and anaemia after randomisation to SMART is shown in Figure 1.
759 patients developed new or worsening anaemia; 420/1106 (38.0%) in the drug conservation (DC) arm and 339/1127 (30.1%) in the virological suppression (VS) arm; p<0.0001. In the first 4 months following randomization, there was no difference in the risk of new or worsening anaemia when comparing the DC arm to the VS arm (adjusted relative hazard [RH] 1.02, 95% CI 0.82-1.25, p=0.88). After the initial 4 months, patients in the DC arm had a significantly increased risk of new or worsening anaemia (adjusted RH 1.56, 95% CI 1.28-1.89, p<0.0001). 56 patients died during 5811 person-years of follow-up (PYFU), 56 developed

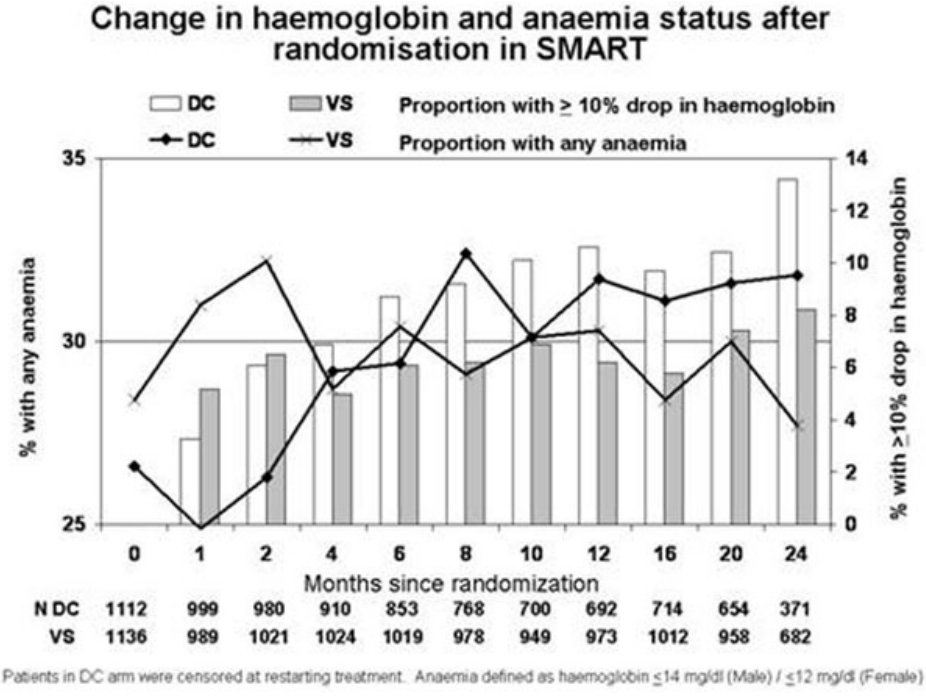

Figure 1 (abstract P144)

AIDS (5728 PYFU) and 100 developed a non-AIDS event (5664 PYFU). Currently anaemic patients had an increased incidence of AIDS (adjusted IRR 2.31; 95% CI 1.34-3.98), death (2.19; 95% CI 1.23-3.87) and non-AIDS events (2.98; 95% CI 2.014.40) compared to non-anaemic patients.
Conclusions: Patients in SMART who interrupted cART had a higher risk of new or worsening anaemia. Patients with anaemia had a higher incidence of AIDS, non-AIDS defining events or deaths; whether this relationship is causal or a consequence of the disease is not clear but suggests that anaemia, or drop in haemoglobin, might be of use as a pre-clinical marker of disease. Further research is warranted to further understand the occurrence of anaemia, its consequences and underlying pathological mechanisms.

P145

Genotype testing in HIV-infected pregnant women

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Background: Published guidelines recommend HIV genotype resistance testing for all pregnant women with detectable viraemia, regardless of antiretroviral therapy (ART) exposure, enabling to optimize ART.
Objectives:: To identify different HIV subtypes in pregnant women and correlate them with epidemiological factors.
Methods: HIV genotype resistance tests results were available on 50 HIV-infected pregnant women between 2003 and 2010.
Results: The results showed a majority of cases of non-B subtypes: subtype G 42%, subtype B 24%, subtype C 14%, CRF02_AG 12%, subtypes A, D, CRFO3_BG and CRF01_AE 2%. Comparative study of the different subtypes showed epidemiological differences:
•Subtype G: 81,6% of women of Portuguese origin, 14,4% of African origin, with 76% of infection acquired by sexual transmission and 23,8% by intravenous drug use, 28,6% of women were on ART, and the median time of HIV infection was three and a half years.
•Subtype B: all of the women of Portuguese origin, with 83,3% of infection acquired by sexual transmission and 16,78% by intravenous drug use, 50% of women were on ART, and the median time of HIV infection was eight years.
•Subtype C: all of the women of African origin, all acquired the infection by sexual transmission, none of the women were on ART, and the median time of HIV infection was three years.
•CRF02_AG: 63,2% of women of Portuguese origin, 28,6% of African origin, with 57,1% of infection acquired by sexual transmission, 28,6% by intravenous drug use, and 14,3% by vertical transmission, 14,3% of women were on ART, and the median time of HIV infection was 2 years.
Conclusions: The analysis of this data shows a bimodal distribution of the epidemic in Portugal: an initial epidemic with B strains, as in western Europe, and a second, latter one, with non-B subtypes, disseminated through patients from African origin and intravenous drug users. The presence on non-B strains, with intrinsic patterns of resistance, puts a burden on the management of these women.

P146

High prevalence of the UGT1A1*28 variant in HIV-infected individuals in Greece

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Background: Over the past few years there has been a remarkable increase in our knowledge of the variation in human genome. In parallel genotyping technologies have advanced significantly and allow sufficient throughput to accommodate genome-wide approaches. Hyperbilirubinemia is the most common adverse event in patients treated with atazanavir (ATV). Previous studies showed that polymorphisms in the uridine-glucuronosyl transferase (UGT1A1) enzyme and specifically the UGT1A1*28 variant may influence the risk of hyperbilirubinemia in patients treated with ATV/r.
Purpose of the study: Our objective was to estimate the prevalence of UGT1A1*28 polymorphism in HIV-infected individuals in Greece and to determine its potential association with hyperbilirubinemia in patients receiving boosted ATV (ATV/r).
Patients and methods: The prevalence of the UGTA1A1*28 variant was estimated in 80 HIV-infected patients retrospectively, (4/2009-5/2010) prior to the administration of the first-line treatment. Wilcoxon rank-sum test was used to determine whether the total bilirubin levels were different among carriers and non-carriers of the UGT1A1*28 polymorphism. The presence of the UGT1A1*28 allele was detected by PCR and DNA electrophoresis.
Results: The UGTA1A1*28 variant was detected in 45 out of 80 individuals (56.25%). Among 55 patients who received HAART, 20 received ATV/r as part of their first treatment. Of the ATV/r treated patients, 13 were found to be carriers of the UGT1A1*28 variant (65%). Total bilirubin levels were significantly higher in patients harbouring the UGT1A1*28 polymorphism (median value: 5.15 mg/dl) versus those harbouring the wild type UGT1A1 locus (median value mg/dl: 1.30) ($p<0.01$). The higher value of bilirubin was observed at week 4 of treatment whereas only 3 patients switched ATV/r to other Protease Inhibitor due to aesthetic problems. Hyperbilirubinemia (total bilirubin >1.3 mg/dl) was not detected in any patient with the UGT11A1*28 variant receiving any other therapy than ATV/r based first-line regimens.
Conclusions: Notably, 56% of the HIV-infected patients from a single HIV Unit in Greece carry at least one copy of the UGT1A1*28 allele. Carriers of the UGT1A1*28 variant treated with ATV/r based regimens had significantly higher levels of total bilirubin than those with UGT1A1 wild type locus, thus, suggesting the clinical utility of the UGT1A1 testing prior the administration of first-line treatment.

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Feasibility of testing antibodies to HIV from filter paper using HIV rapid test kits

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HIV rapid tests are widely used in resource limited settings. Dried blood spots on filter paper are an easy way to collect and transport blood samples from a remote area to a testing facility at ambient temperatures. Our objective was to evaluate the technical possibility of testing antibodies to HIV from filter paper using HIV rapid tests kits.
Dried blood spots on filter paper were obtained from 408 female sex workers (FSW), 136 Men Sex with Men (MSM) and 50 Intravenous Drug Users (IDU). Antibodies were eluted from DBS disks (punch 6 mm, approximately 5 µl serum) in 200 µl of sterile Phosphate Buffer Saline (PBS) (0.01 M, with 0.1% sodium azide) by agitating overnight at 2-8° C (refrigerator) for minimum 16 hours and tested for anti-HIV antibody using two ELISA (Microlisa, Enzaids). As per the guidelines of the National AIDS Control Organization Sentinel Surveillance of HIV, the reactive samples on the first ELISA are retested using a 2nd ELISA kit. We assessed all the HIV positive and HIV negative DBS samples using 3 HIV rapid tests kits (Combaids, Determine and EIAComb) procedures were followed according to the manufacturer's instructions.
Of the 594 DBS samples, 22 (3.69%) samples were positive for HIV antibodies using ELISA kits. Among HIV positive DBS samples, 3.67% (15/408) were FSW's, 2.95% (4/136) were MSM and 6% (3/50) were IDU's. All 22 DBS were positive in both ELISA kits (Microlisa, Enzaids) and the sensitivity and specificity of both kits were 100%, whereas Determine found 20 HIV positives, Combaids 21 samples Positive and EIAComb found all 22 HIV positive giving sensitivity was 90.91%, 95.45%, and 100% respectively and specificity was 100%.
This study demonstrates and confirms the usefulness and feasibility of the filter paper blood collection method for testing of HIV antibodies. DBS can be used with HIV rapid test devices. Using the latest and advanced techniques applied in rapid test technologies, DBS may provide a unique way to conduct sero epidemiological surveys in resource limited settings.

P148

Effect of lipemia and bilirubinemia on HIV-1 protease and reverse transcriptase genotyping and phenotyping success: a five-year analysis

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Background: Interference of clinical laboratory assays by endogenous & exogenous substances in the blood is well known. To date, there are no clear guidelines on the testing of lipemic or bilirubinemic (icteric) plasma in clinical laboratories. A conservative approach of alerting the physician with re-sampling and/or processing with caution is advised. This study focuses on the effect of processed (2005-2010) HIV-1 lipemic or icteric patient plasma (visual inspection) on genotyping (virco®TYPE HIV-1) and phenotyping (Antivirogram®) success at Virco.
Materials and methods: The viral RNA extraction kits (QiaAmp Virus MDx kit: 965652 or Easymag Nuclisens: 280130-280135) are highly sensitive in deriving intact, good quality RNA from lipemic or icteric plasma, leading to successful amplification of PR- RT genes. The validity of the obtained result was confirmed by comparing the results from previous or subsequent visits/services from the same patient, where available.
Results: Between 2005-2010, 569 lipemic (0.97% of total samples received) samples were processed. From the 510 genotype requests, 408 were successfully genotyped (positive & 265 had viral load (VL) >1000 cp/ml) and 102 failed (negative, 39 samples with VL <1000 cp/ml, 35 unknown VL & 28 with VL >1000 cp/ml). From the 335 phenotype requests, 267 were positive & 68 negative (36 with VL<1000 cp/ml, 16 unknown VL & 16 with VL >1000 cp/ml). From 2005-2010, 417 icteric (0.71% of total samples received) samples were processed. From the 394 genotype requests, 367 were positive (301 had VL >1000 cp/ml) & 27 negative (9 with VL<1000 cp/ml, 12 unknown VL & 6 with VL >1000 cp/ml). From the 166 phenotype requests, 153 were positive & 13 were negative (3 with VL<1000 cp/ml, 6 unknown VL & 4 with VL >1000 cp/ml).
Conclusions: No limitations were observed for the different Clades. The success rate for lipemic samples (265/293) & icteric samples (301/307) with VL >1000 cp/ml was 90% & 98% respectively, indicating that both lipemic and icteric samples can be processed for resistance testing using our genotyping and phenotyping assays, under circumstances where re-sampling is difficult. The sensitivity to phenotyping clearly demonstrates the integrity of the amplified product that can be used to generate viable recombinant virus stocks.

P149

Development of a single-tube, low-cost, analytical process to extract, separate and determine efavirenz and rifampicin plasma concentrations in HIV/TB co-infected patients

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Background: Tuberculosis (TB) complicating HIV-1 infection is a persistent significant clinical concern, particularly in resource limited settings. Treatment of HIV-infected patients with TB often comprises efavirenz-containing antiretroviral regimens particularly when on TB treatment containing rifampicin. Although rifampicin may reduce EFV concentrations, little is known of the effect of the HIV virus or efavirenz on the pharmacokinetics of rifampicin, particularly in resource limited settings where the burden of disease exists. We aimed to develop a low-cost, simple analytical method for the accurate determination of efavirenz and rifampicin plasma concentrations.
Methods: Using high-performance liquid chromatography (HPLC) employing UV detection (1050 series quaternary pump, 1100 series autosampler, a diode array detector (DAD) and a 1200 series degasser), we developed and validated a single tube column-based assay for the detection of rifampicin and efavirenz. Data was acquired and analysed using Agilent Chemstation for LC 3D software.
Results: Recovery for plasma samples spiked with the drugs were >90% for rifampicin and its metabolite deacetylrifampicin and >70% for efavirenz. Intra- and inter-assay precision relative standard deviation (RSD) values were <4% in all cases. The assay was validated on 300µl sample with a runtime of 10 minutes and both drugs measurable to concentrations of 100ng/mL.
Discussion: This relatively easy, UV-based assay can accurately detect efavirenz and rifampicin concentrations within a clinically relevant concentration range using standard chromatography equipment, making it potentially applicable to resource limited settings.

P150

Lack of utility of phosphate serum monitoring in HIV-infected patients on a tenofovir-based antiretroviral regimen

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Purpose of the study: Hypophosphatemia (HP) and renal dysfunction have been associated with antiretroviral therapy, especially with the use of tenofovir disopropil fumarate (TDF). Thus, recent guidelines recommend routine phosphate measurements in HIV-infected patients. We aimed to assess the utility of this monitoring.
Methods: Retrospective cohort study of 680 patients with renal monitoring on antiretroviral therapy from 2008 to 2010. The frequency of HP was compared in TDF recipients with that in non-TDF recipients, as well as assessed the reproducibility of HP, and identified the incidence of renal dysfunction in hypophosphatemic patients
Results: Phosphate measurements were obtained in 265 patients during follow-up. Mean age was 40.66 (±7.68) years, 76.2% were men, 47.9% were IDU, and 84.9 % received an antiretroviral regimen based on TDF. At baseline, before antiretroviral therapy, hypophosphatemia was observed in 4 of 67 patients (6%). Overall, during follow up, HP was observed in 56 of 265 (21.1%), but was confirmed only in 33 (12.5%). The median time to HP was 798(±13.95) days, usually with phosphate levels above 2 mg/dl (mild HP). A higher percent of patients prescribed TDF showed a phosphate measurement below normal limits (13.8%) in comparison with those patients receiving non-TDF based therapy (5%), although this comparison was not significant (p=0.103). There was no difference with regard to time to HP in patients receiving TDF or not (median time 798 vs 834 days, p=0.106 log-rank test), neither in the values of serum creatinine or MDRD in patients with or without hypophosphatemia.
Conclusions: HP is relatively frequent in HIV infected patients on antiretroviral therapy, although we did not find any clear association with any specific therapy or renal dysfunction as measured by serum creatinine or glomerular filtration. This fact questions the utility of routine phosphate testing, in isolation, in TDF recipients.

P151

CCR5 D32 modifies 15-year mortality risk associated with well-established clinical and immunological factors among HIV-infected patients

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Purpose of the study: In the era of long term follow up of HIV+ patients analysis of factors modifying risk of death is vital. The aim of the study was to evaluate predictive value of selected parameters in a cross-sectional analysis.
Methods: Epidemiological (age, gender, date of HIV diagnosis, route of transmission), clinical (date and reason of AIDS, date and reason of death, baseline viral load, history of cART) and immunological (baseline, nadir, zenith lymphocyte CD4 counts, time of CD4 count > 500 cells/ml) data from 506 patients followed-up from 1996 to 2010 in the Department of

Infectious Diseases and Hepatology, Szczecin, Poland were collected with CCR5 D32 genotyping performed for every subject. 15-year survival analysis was performed using Kaplan-Meier methodology with log rank test and univariate Cox regression for hazard ratio calculation. Selected data were implemented into a Cox multivariate model and p< 0.05 assumed of statistical significance.
Results: Cumulative 15-year mortality rate was 18,5% (95% CI 0,15-0,21), with 64 (68,8%) of AIDS associated and 30 (32,2%) non-AIDS deaths. At 15 year timepoint factors associated with higher probability of survival were CCR5 D32/wt genotype (78,3% vs 65,3%, p =0 ,033, univariate [univ.] HR=2,21, p=0,044), female gender (81,7% vs 62,5%, p=0,014; univ. HR=1,98, p=0,015), AIDS-free at HIV diagnosis (70,6%vs 59,3%, p <0,01; univ. HR=2,8, p<0,01) and no AIDS during observation (79,4% vs 50,8%, p<0,01, univ. HR=3,58, p<0,01), introduction of cART (74,4% vs 34,2%, p <0,01; univ. HR=3,68, p<0,01), baseline lymphocyte CD4 count >50 cells/ml (71,3% vs 56,5%, p <0,01, univ. HR=2,52, p<0,01), lymphocyte CD4 nadir >50 cells/ml (75,8% vs 55,9%, p =0 ,00007, univ. HR=2,31, p<0,01), CD4 zenith >500 cells/ml (85,1 % vs 52,8%, p <0,01, , univ. HR=5,22, p<0,01), stable lymphocyte CD4 count > 500 cells/ml for one year (88,2% vs 60,4%, p<0,01, univ. HR=7,59, p<0,01). In multivariate model with gender (HR=1,86 , p=0,04), cART initiation (HR=4,62 p<0,01), lymphocyte CD4 zenith >500 (HR=3,86, p<0,01), nadir > 50 (p=n.s) and history of AIDS (HR=2,2 p=0,03) positive effect of CCR5 D32/wt on survival was confirmed (HR=2,2, p=0,046).
Conclusions: CCR5 D32 mutation proves to improve survival of HIV+ patients acting in concert with clinical and immunological factors, however data suggest that interventions related to early testing and treatment would strongly influence survival in HIV+ patients.

P152

What drives a normal relation between T-CD4 and T-CD8?

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Introduction: Inversion of the CD4/CD8 ratio, in the context of HIV infection, is a frequent finding, even though, if the patient has been on prolonged antiretroviral therapy. Nonetheless, in a small proportion undergoing antiretroviral therapy, this relation normalizes.
Purpose of the study: With the aim to investigate frequency and the population characteristics of this occurrence we proposed a retrospective analysis in our outpatient HIV clinic in Lisbon.
Methods: Patients with a proven inversion of CD4/CD8 ratio before the beginning of antiretroviral treatment and who, in the last five years, re-inverted to a normalized ratio (above one) in at least two consecutive estimations were eligible. Variables analyzed included: gender, age, former opportunistic infections, CD4+ nadir, viral load, length of antiretroviral therapy and therapeutic regime. Obtained data was tested for correlation and statistical significance using student T-test.
Results: Of 1.750 patients on antiretroviral therapy, 119 patients reverted to a normal T-CD4/CD8 ratio in the last five years. Six of these where infected with HIV-2, five did not maintain reversion, which lead to a 108 patients with a true reversion, corresponding to 6% of the population. Not being able to access the files in 18 cases, the analysis is based on 90 patients. The mean-time of antiretroviral therapy before reversion of the CD4/CD8 ratio was 69 month. The distribution reveals two peaks: one around month 40th and another around month 130th, probably related to former therapeutic regimes. No significant correlation was found if time-of-antiretroviral-therapy-until-reversion was analysed with respect to impact by opportunistic infection, T-CD4 nadir, viral load, gender or the ability of the antiretroviral therapy to penetrate the CNS. Though, not a frequent finding, it seems to be constant and strongly correlated to time-of-antiretroviral-therapy with a correlation of Pearson of 0,501 (p=0.01).
Conclusions: These findings suggest that the CD4/CD8 might be a marker for the follow-up in patient undergoing antiretroviral therapy. Its real impact, though, needs further investigation especially with respect to T-CD8 specific cytotoxicity and activation.

P153

Comparative evaluation of ARV therapy efficiency among patients at the Kiev regional AIDS center

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Background: Ukraine takes one of the leading places in the growth of the epidemic of HIV infection/AIDS in Europe. Nowadays, more than 1.4% adult population is HIV infected. All people who need, receive ARV therapy. Today almost 12000 patients use it.
Purpose of the study: Specialists of the Kiev regional AIDS center made a comparative evaluation of ARV therapy efficiency among patients at the center during the first half of the 2008 and the same period of 2009. They analyzed a number of virological and immunological faults in the treatment of the patients, who use ARV therapy during 1 year.
Results: Number of tested patients:
- 924(2008)
- 952(2009)

Among them, number of patients who received ARV therapy during 1 year:
- 170(2008)
- 169(2009)

Number of faults (both virological and immunological) abs\% from all persons who received ARV therapy:
- 58\32%(2008)
- 53\31% (2009)

Structure and % of the faults to the whole number of tested patients:
1. Only virological faults:
- 3\1%(2008)
- 2\1%(2009)

2. Only immunological faults:
- 41\24%(2008)
- 31\18%(2009)

3. Both virological and immunological faults:
- 14\7%(2008)
- 20\12%(2009)

All patients, who had both virological and immunological faults of the therapy, were suggested to change the scheme of the therapy. The effectiveness of these changes was analyzed after 6 month by the same criteria:
• Detected viral load level
• CD4 cells level lower than 200 cells/ml.

Effective change of the scheme of the ARV therapy:
- 10\71% (2008)
- 12\60% (2009)

Faults of the changed scheme of the ARV therapy : - 3\21%(2008)
- 7\35%(2009)

Conclusions: We can make a conclusion that in 2009 there were more both virusological and immunological faults as a result of the ARV therapy. It can be an evidence of the increasing of the number of the resistant viruses which are circulated in the population of HIV infected persons in Ukraine. This conclusion can be confirmed by the low effectiveness of the changing of the schemes ARV therapy. It can be a probable evidence of the formation of the multi-resistance variants of the viruses.
So this study shows the necessity of introduction of the researches of virus's resistance in the practice of laboratory researches for HIV infected people, who receive ARV therapy in Ukraine.

TREATMENT OF CHILDREN

P154

Feasibility and effectiveness of combination antiretroviral therapy in HIV-infected infants in Pietermaritzburg, South Africa

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Background: In the absence of treatment, 50% of HIV-infected children will die before 2 years of age. In a recent randomized controlled trial, a 76% decrease in mortality was observed in infants receiving early combination antiretroviral therapy [1]. The World Health Organization now recommends starting all HIV-infected infants on combination antiretroviral therapy on diagnosis [2]. However, few data are available outside a well-controlled research setting.
Purpose of the study: To show the feasibility and effectiveness of treating HIV-infected infants in a state-funded clinic located in a poorly resourced South African township.
Methods: A retrospective chart review was performed of all HIV-1 infected infants initiated on combination antiretroviral therapy (cART) between 1st May 2005 and 31st May 2008 at the Edendale Family Clinic, Pietermaritzburg, South Africa. All HIV-1 infected infants who were less than 1 year of age when antiretroviral therapy was initiated, and who had completed at least 6 months of treatment, were included. Weight for age Z scores, CD4 %, viral loads (VL) and haemoglobin were collected on initiation of treatment and at 6-monthly intervals thereafter. Virological success was defined as VL<25 copies/ml, immune recovery as CD4>25%. Z scores were analyzed using Epi-Info.
Summary of results: Of 129 treated infants, 94 completed 6 months of cART; 60 completed 12 months and 39 completed 18 months of treatment. Mean age at initiation was 8 months (range 2.1-11.7). 77.2% had advanced disease (WHO Stage 3 or 4). The infants were severely malnourished, with a mean Z-score of -2.4 (range -6.1 - +0.8). Mean baseline VL was 4700 000 copies/ml. After 6 months of treatment, 52.3% of babies had an undetectable VL, with 75% having a VL of < 400 copies/ml. Viral suppression was achieved in 34 (56.9%) out of the 60 infants who completed 1 year of cART and 79.3% had a VL <400 copies/ml. Undetectable VL was found in 78.8% of the 39 children who received 18 months of treatment. Weight for age Z score increased from a mean of -2.4 (<3rd centile) at initiation of treatment to -0.3 (38th centile) for the children who received 18 months of cART. The CD4% increased from a mean of 16.5% at the start to 31.9% at 18 months.
Conclusions: This study from a township in Kwazulu-Natal shows a good clinical, immunological and virological response to cART in HIV-infected infants, despite high baseline viral loads and advanced disease.

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P155

Promoting presumptive diagnosis of severe HIV disease to increase uptake of antiretroviral therapy in HIV-infected infants

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Purpose of the study: Despite successful scale up of anti-retroviral therapy (ART) in Malawi, the number of children initiating ART early in their life is low and mortality of HIV infected infants not accessing ART is high. Availability of PCR remains limited and despite presumptive diagnosis (PD) is recommended in the national guidelines, it is rarely used as a reason to start HIV-exposed infants on ART. Reasons may include factors at health worker and clinic level. Knowledge of these barriers is important to increase access to ART for this high risk group.
Methods: A structured questionnaire with 11 closed questions was administered to one ART clinic staff member for each site (nurse or clinician) by team-members of the regular national ART supervision for Quarter 1/2009 in the central and southern region. Questions addressed specific reasons for low uptake of PD and tested providers' knowledge of the PD definition. Finally, the interviewer explained how to make a PD correctly using a job-aid.
Results: Over 2 weeks, respondents of 49 of 173 ART-sites completed the questionnaire. They were mainly clinical officers (22) and nurses (17) from a central hospital, 5 district hospitals, 3 rural hospitals, 13 health centers, and 27 other facilities such as mission hospitals, smaller clinics run by NGOs, armed forces or privately. Forty-one clinics provided HIV testing and counseling for pregnant women on-site and 35 clinics offered antiretrovirals for PMTCT. Most providers felt that children <18 month of age are under-represented in their ART-cohort, mentioned that generally few HIV exposed children are eligible for ART in their catchment area and that limited access to PCR are reasons for low uptake of PD (34/49 respondents each). Twenty-nine saw the presence of maternal HIV-antibodies as a barrier that makes the diagnosis difficult, and 20 noted that staff at the under 5 clinic or postnatal ward rarely identifies and refers HIV exposed infants to HIV-services. Twelve providers said they generally don't register children at that age. Of the 49 providers, 15 defined presumptive diagnosis correctly and 15 partly correct.
Conclusions: Providers seem to be aware of the need to start more HIV-infected infants on ART and of structural barriers to access this service. Improved knowledge and sensitization of providers on how to diagnose severely ill HIV-exposed infants presumptively may increase access to ART for children in this age-group.

P156

Audit of outcomes of early initiation of antiretroviral therapy in children admitted to the paediatric wards at Kilifi district hospital, Kenya

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Background: Studies in adults suggest that early initiation of anti-retroviral therapy (ART), during treatment of those presenting with opportunistic infections, results in better outcomes than deferred treatment. However, data on the effects of early treatment of children are sparse. Kilifi district hospital (KDH) serves a population of over 250,000. It provides HIV services and ART. All children admitted to the paediatric wards at KDH are routinely tested for HIV.
Purpose of the study: To ascertain the outcomes of early initiation of ART in children in a rural African setting around the time of an acute admission.
Methods: We retrospectively reviewed inpatient and clinic records of all HIV antibody positive children admitted to the paediatric wards at KDH between May 2007- December 2008. The demographic surveillance system was used to ascertain outcomes.
Summary of results: Over the 19-month period, there were 9,377 admissions to the paediatric wards. Of these 407 (5.6%) children had a positive HIV antibody test. 47 children met criteria for starting ART according to Kenyan national guidelines. 22 (47%) of these children started ART in the acute phase, and a further 13 (28%) started subsequently in clinic, but 12 (25%) were lost to follow-up before ART initiation. The median age was 2.9 years (IQR 1-3.9 years). The median CD4 percentage was 11% (IQR 7.6%-15.5%). There was a high rate of default from follow-up even after initiation of ART (40%). Most of the children who remained in care were still alive 19 (90.5%) and had attained nutritional recovery (87%) with a minority having adverse events (13%) 6 months after initiation of ART. Comparing acute versus deferred initiation groups, those started early were younger and had lower baseline CD4 percentages. There was no difference between the 2 groups in terms of incidence of adverse events or survival to 6 months after starting treatment.
Conclusions: Our data suggests that commencing ART in children around the time of an acute admission even in children who are severely malnourished may be safe and result in nutritional recovery with good survival. However, due to the high number of defaulters, we were unable to draw definitive conclusions comparing early and deferred initiation. We recommend that defaulter tracing should be an integral part of all ART programmes, and randomised studies to compare timing of initiation in larger cohorts.

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Salvage therapy with raltegravir in a 3-month-old infant

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Background: The integrase inhibitor raltegravir (RAL) is widely used in adults. Only limited data are available for children and no data for infants. We describe the case of a three-month-old infant treated with RAL in combination with lopinavir/r (LPV/r) and lamivudine (3TC).
Methods: The mother emigrated from Ghana several years before and was insufficiently treated in a local hospital with AZT, 3TC and nevirapine (NVP) with constantly high plasma viral load (VL). At admission to the external birth clinic her VL was 160,000 copies/ml, the CD4 count 146/ml. The infant had a gestational age of 35 weeks with a birth weight of 1940g. A high-risk chemoprophylaxis with AZT, 3CT and NVP was given until the confirmation of a HIV1 infection three weeks later. The infant was then referred to our university hospital in an underweight state. His VL was 2.5Mio copies/ml, the CD4 count was 37% (2110c/ml). The genotypic resistance profile showed full resistance for all NRTIs and NNRTIs. We started an off-label therapy including RAL at 6mg/kg BID. The dosage was extrapolated from smaller trials in children ≥6 years of age. RAL is only available in 400mg tablets, so we pestled the tablet, attenuated the powder and distributed the required amount of mixture into a capsule. The content was then solved in water and administered by the mother. We combined RAL with LPV/r and 3CT BID which were dosed according to paediatric recommendations and adjusted monthly due to weight gain in closed cooperation with the pharmacologist.
Results: The therapy was well tolerated, no clinical or laboratory adverse events have occurred yet. The boy showed a catch-up growth and weight gain from <3rd percentile to >25th percentile at week 16 of therapy. In the same period his VL decreased from 1.8Mio copies/ml to 164 copies/ml and his CD4 count increased to 39% (3357c/ml). We performed a PK-profile and measured sufficient drug levels of RAL and LPV/r, comparable to the limited data of PK-studies conducted in older children. RAL Cmin: 146ng/ml, Cmax: 1960ng/ml, Tmax: 2h.
Conclusions: Due to the widely use of NNRTIs in developing countries an increasing number of mother-to-child transmissions of HIV with multi resistances can be expected in the near future. We describe a successful salvage therapy including RAL in a three-month-old infant. Further studies and investigation into the paediatric pharmacokinetics and application forms are warranted to confirm our results.

MOTHER-TO-CHILD TRANSMISSION

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High preterm delivery rates associated with initiation of HAART during pregnancy

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Purpose of the study: To understand the relationship between HAART and preterm delivery (PTD).
Methods: Analysis of prospectively collected data from all patients attending HIV antenatal services at a single UK centre 1995–2010. Fisher's exact test two tailed for categorical variables. T-test for continuous variables.
Results: Data are presented on all 324 deliveries up to 26/07/2010. 78% of the women were Black African, 10.3% Caucasian. Risk for HIV infection was heterosexual intercourse in 94%, injecting drug use in 1.2%. Median gestational age at first ante-natal clinic appointment was 13 weeks. 7 women took no therapy prior to delivery and 7 took dual NRTI treatment. Data on the remainder are summarised in Table 1

Table 1 (abstract P158)

Treatment	Number	Median CD4 /μL (Baseline ANC)	Median HIV viral load/ml	PTD Number (%)
Zidovudine monotherapy	61	445	2513	4 (6.6%)
START	64	360	8930	16 (25%)
new continuous HAART	58	150	23430	10 (17.2%)
pre-conception HAART	127	385	49	16 (12.6%)

Delivery before 37 weeks (PTD) occurred in 14.4% pregnancies of which 62% (8.8% of all pregnancies) before 34 weeks. Difference not significant comparing PTD in patients starting new continuous HAART (17.2%) with pre-conception HAART (12.6%). PTD occurred in 17/142 (12.%) women treated with nevirapine-based HAART compared with 24/102 (23.5%) treated with protease inhibitor (PI)-based HAART (p 0.02). Of the 64 patients treated with a short-course of HAART (START) during pregnancy to prevent mother-to-child HIV transmission 33 were eligible, if willing to delivery by pre-labour caesarean section (PLCS) to receive zidovudine monotherapy (ZDVm) according to the 2008 BHIVA guidelines [1]. Of these 10 had a preterm delivery (30.3%).
Conclusions: The role of HAART and PI-based HAART in PTD has been controversial. Even in this single-centre study, where all women were managed by one team in accordance with national guidelines, confounders abound. CD4 counts and viral loads differed significantly between patients starting HAART in pregnancy and those taking ZDVm or already on HAART at conception. We therefore compared PTD rates in women who were eligible for, and chose between, START (and the potential of a normal vaginal delivery) and ZDVm with PLCS. The rates of PTD were significantly higher (p 0.005)with START (30.3%) than with ZDVm (6.6%) in these ZDVm eligible mothers. These data suggest that PI-based HAART initiated during pregnancy is associated with a significantly increased rate of PTD and that this is influenced by maternal immune status. Further investigation to determine whether other regimens may have less impact on PTD are urgently required particularly with the increasing use of HAART in prevention of mother-to-child transmission.

Reference

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Minority M184V variants in women exposed to 3TC/FTC-containing lopinavir-ritonavir (LPVr) regimens in pregnancy

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Purpose of the study: Short-term antiretroviral therapy (START) consisting of 2 NRTIs and a ritonavir boosted PI is widely used in pregnancy. Resistance is rarely detected using population based sequencing. The aim of this study was to determine whether minority M184V variants emerge with 3TC/FTC containing START regimens in pregnancy and if so whether this impacted upon future treatment outcomes.
Methods: Multi-centre study. An allele-specific real time PCR (ASPCR), optimized for subtypes B, C and AG, was used to detect minority M184V variants. Participants took START for the prevention of HIV mother-to-child transmission (PMTCT). All received standard dose LPVr. Plasma

Table 1 (abstract P159)

	M184V mutants N=7	WT N=11
Median Age, yrs (range)	30 (26.5-37)	34 (21-38)
African origin	7 (100%)	7 (64%)
European origin	0	2 (18%)
Caribbean origin	0	1 (9%)
South American origin	0	1 (9%)
Median gestation at START initiation, completed weeks (range)	22 (19-26)	21 (15-29)
Median duration START, days (range)	115 (87-132)	121 (68-151)
Virological suppression at delivery	6 (86%) (other VL 57c/ml)	11 (100%)
Subtype B	1 (14%)	4 (36%)
Subtype C	5 (72%)	1 (9%)
Subtype AG	1 (14%)	6 (55%)
Previous ART	2/7 (29%)	3/11 (27%)
Previous ART regimens	ZDVm, CBV/LPVr	ZDVm, CBV/nelfinavir, CBV/nelfinavir
Population based sequencing performed	7/7 (100%)	10/11 (91%) (1 failed)
WT on population based sequencing	7/7	10/10
Number of Lopinavir TDM performed	6/7 (86%)	5/11 (45%)
Median Lopinavir concentration (μg/L) (range)	4446 (2791-7551)	2991 (2023-7782)
Subsequent ART	4/7 (57%)	3/11 (27%)
Virological suppression with subsequent ART	4/4 (100%)	2/3 (67%) (1 stopped after a few weeks)

samples were tested pre and post treatment. Routine population based sequencing was also performed.
Summary of results: ASPCR failed in 13/31 (42%) women. Among the remaining 18, 11(61%) were wild type (WT) and 7(22.5%) had minority M184V sequences (range of detection 0.5 to 14%). All samples were WT with population based sequencing. ASPCR failed to amplify from pre-treatment samples in 4/7 women with minority M184V and was WT in 3. Table 1 compares women with and without M184V mutants detected by ASPCR. Therapeutic drug monitoring (TDM) was performed in a subset.
Conclusions: M184V mutants were detected after LPVr based START for PMTCT in 22.5% women. No difference in prior ART, START duration, drug concentration or virological suppression was observed. The presence of minority M184V variants post-partum did not affect future treatment success. The possible association with HIV-1 subtype C requires further evaluation but clade effect on the development of resistance has been reported following intra-partum nevirapine.

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Antiretroviral strategies for the treatment of pregnant HIV+ women and prevention of perinatal HIV transmission in Dodoma, Tanzania: AMANI Study

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Background: The use of HAART during lactation has also been discussed as an approach to reduce postnatal HIV-1 transmission. The benefits and safety of HAART used solely for prevention of postnatal transmission in healthy HIV infected women have not yet been demonstrated in clinical trials. The extension of maternal HAART through the period of breast feeding can be proposed as pivotal strategy to reduce breast milk HIV transmission.
Objectives: To assess the safety of breastfeeding during antiretroviral treatment in terms of virological and clinical outcomes in pregnant HIV-infected women in the Dodoma area of the United Republic of Tanzania. Secondary objective is the study of viral dynamic and therapeutic drug monitoring of antiretroviral drugs into breast milk of HIV-infected women treated with HAART during breastfeeding.
Results: The enrolment phase of the AMANI Study started on May 2010 at Makole Health Centre (Makole UHC). After the first two months 68 HIV positive pregnant women (HPW) out of 68(100%) HCWs attending the site were counseled. 50 HPW (73.5%) were enroled in the study and are being followed up at Makole UHC. Of the remaining 16(23.5%) were not eligible and only 2(2.9%) refused to participate. Among the 50 HPW enroled only 6 (12%) have opted not to breastfeed after delivery, 12 HPW have started HAART prophylaxis from the 28 weeks of gestation, 3 HPW were found eligible and started HAART. 1 HPW has given birth on 16th July 2010 with no fetal and maternal complication. No patient reported any side effects to the ARV drugs.
Conclusions: At the moment the study is progressing over the expectation. The procedures of the study where well accepted by the local Health Personnel with the totality of the HPWs counseled and by the HPW with only the 2.9% of refusal. Data from the study show that this kind of implementation research is well accepted by the Health personnel in terms of capacity building and by the HPW in terms of compliance and acceptance of the treatment. The benefits of the expanded treatment are well understood and overtake the discomfort of a higher pill burden and the risk of more adverse events.

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Use of antiretroviral therapy during pregnancy among HIV-infected women attending an urban care centre

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Background: With the large international mobilization of resources against HIV/AIDS and the great improvement of ARV drug access within the last 7 years in resource-limited countries, more HIV-infected people are expected to access antiretroviral therapy (ART) including pregnant women. However, coverage of PMTCT services in many Sub-Saharan countries is still low. The aim of the study was to characterize and estimate the number of pregnant women who were receiving ART at adult Infectious Diseases Institute clinic (AIDC).
Methods: We retrospectively analyzed routinely collected data in HIV/AIDS clinic within a period of Jan-2008 to Oct 2009 among HIV positive

pregnant women attending care at (AIDC). Descriptive data analyses were conducted to characterize and estimate the number of pregnant women on ART at AIDC.
Summary of results: A total of 649 pregnant women were recorded with median age 30(IQR: 26, 33) years and (196/427) 45% had unintended pregnancy. Ninety-five percent had formal education while 84% were married. Their health status in regard to current median CD4 was 376 (IQR: 282, 550) cells/mm^3 while 315 women were on ART (85% NVP-based & 14% PI-based). Among 208 women who had reported to have delivered, only (83/208) 40% knew the sero-status of their babies (79/83) 95% HIV-ve and (4/83) 5% HIV+ve).
Conclusions: Our results indicate inadequate follow-up of PMTCT service utilization and low documentation of pregnancy outcomes among HIV positive pregnant women attending care. There is a need to strengthen PMTCT and ART integration in already existing HIV/AIDS care program. Establishing linkages with paediatric HIV/AIDS care programs in order to enhance effectiveness of PMTCT services is essential.

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A complex of measures effectiveness in reducing mother-to-child HIV transmission

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Background: At the early stage of the HIV epidemic in Russia pregnant women who planned having a baby underwent a single HIV testing. Following the sharp increase of the HIV+ number in 2001-2002 (including women) with the aim of reducing mother-to-child HIV transmission risk the Ministry of Health and Social Development recommended providing 2-fold HIV testing for pregnant women during the early stage of pregnancy and before the delivery.
Purpose of the study: To evaluate the influence of 2-fold HIV testing in pregnant women on HIV- detection, prophylactic interventions (including 3-step prevention), and the risk of HIV transmission to a newborn.
Methods: We studied HIV incidence and HIV detection in pregnant women and HIV perinatal transmission preventive interventions data, new cases of HIV+ children born in the region in the period of 2004-2009. The years of 2000, 2004 and 2009 have been taken as the key points. Standard statistical methods were used.
Results: HIV was detected in 5.1 per 100,000 tested pregnant women in 2000, and after the Health Ministry Recommendation was approved HIV was detected in 77.1 per 100,000 tested pregnant women in 2004 and in 61.6 per 100,000 tested pregnant women in 2009. Maximum early detection of HIV infection in pregnant women enabled not only provide mother-to-child HIV transmission prevention but increase the rate of mother-child pairs who received the 3-step prevention (HAART during pregnancy, during delivery, to newborns): in 75% of pregnant women (including 50% 3-stage scheme) in 2000, in 91% (82.1%) in 2004 and in 97.6% (85.8) in 2009. The rate of children perinatally infected reduced and comprised 12.5% in 2000, 10.4% in 2004 and 6.3% in 2009. These measures have led to a great reducing the rate of children infected perinatally: 12,5% in 2000, 10,4% in 2004, and 6,3% in 2009.
Conclusions: Introducing of the 2-fold HIV testing in pregnant women enabled to 15.1 times increase in HIV detection in pregnant women while there was a 2 time increase in HIV incidence among the whole population as well as the rate of women among all infected ($p<0.05$). Maximum early preventive interventions extended the 3-step mother-to-child HIV transmission prevention and reduced the risk of newborns infecting.

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Amniocentesis is a low-risk procedure in HIV-treated pregnant women

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Background: The iatrogenic risk of HIV vertical transmission, calculated in initial epidemiologic studies of this infection seemed to contra-indicate the performance of invasive prenatal diagnosis (PND) techniques. The implementation of highly active antiretroviral therapy (HAART) represented a turning point in PND management, owing to a rapid and effective reduction of the maternal viral load.
Purpose of the study: To evaluate the risk of vertical transmission in pregnant women infected with HIV, submitted to amniocentesis during the second trimester of pregnancy.
Methods: Analysis of the amniocentesis performed in our institution, in pregnant HIV positive (N=23). The sample was obtained from the database which included all HIV-infected pregnant woman who gave birth between 1996 and 2009 (n= 731), in our institution. Data were collected in order to obtain: demographic characteristics of the sample, HIV subtype and its transmission category, antiretroviral therapy, gestational age, indication of amniocentesis, viral load and T CD4+ lymphocyte count determined close to performing amniocentesis and close to labour, result of the chromosomal analysis, obstetrical complications, type of labour and data referring to the newborn. Our sample was divided in two subgroups: one comprising women with adequate pregnancy surveillance in our immunodepression unit (Group A, n=17) and other comprising women with the diagnosis of HIV infection after performing amniocentesis, with no surveillance or therapy until the amniocentesis (Group B, n=6).
Summary of results: Among the 23 newborns, only one case of HIV 1 infection was diagnosed, in group B. It occurred in a patient with a diagnosis of HIV infection at 30 weeks gestation, after being submitted to amniocentesis at 16 weeks gestation for primary CMV maternal infection, and she had a vaginal delivery at 38 weeks. Antiretroviral therapy was not accomplished as well as adequate pregnancy surveillance.
Conclusions: When there is an indication to perform an amniocentesis in a pregnant woman infected with HIV, it is legitimate to perform it if the woman is following a HAART, and is ideally under viral suppression. Although the number of our sample is limited, there was no case of vertical transmission among pregnant women with adequate pregnancy surveillance, who were submitted to amniocentesis under HAART. It would be extremely important to analyse wider results, in a multicentric study.

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Pregnancy decisions and contraceptive use among HIV-positive women: a study in a large urban clinic in sub-Saharan Africa

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Background: The IDI is an HIV treatment and research centre in Kampala, Uganda with over 24000 patients of whom 9000 are on antiretroviral therapy.
Purpose of the study: We conducted a study in March 2007 to determine the accessibility and utilization of Sexual Reproductive Health (SRH) services among female clients.
Methods: Using a structured questionnaire, a cross-sectional survey of female clients aged 18-49 years attending the IDI clinic was conducted. SPSS version 12.0 was used to fit a logistic regression model to determine the following outcomes; pregnancy decisions, desire for children and pregnancy risk behaviour among sexually active female clients.
Results: Of 493 respondents, 322 (65%) were sexually active at the time of the survey. Over 30% of the respondents had become pregnant after knowing their sero-status, 66% of the pregnancies were unintended of which 39% ended in abortions. Over 52% of the pregnancies were due to the influence of the husband, 33% was a result of mutual agreement between the clients and their partners while 15% of them were because of the client's decision. Of the women who made their own decision about pregnancy, 57% had a secondary level of education. Among married 40% of the pregnancies were a result of mutual agreement while relatives influenced 45% of the pregnancies among the singles. Of the participants 96% reported awareness of family planning methods; however, the level of utilization was at 40%. Overall 31% of the women stated a desire for children. 41% engaged in pregnancy risk behaviour

and of these 63% did not desire children. Women aged 24-34 years had the highest desire to have children. The husbands made pregnancy decisions for 62% of the women who did not want more children.
Conclusions: Family planning utilization is low even among those females who have no desire for more children resulting in unwanted pregnancies. Despite their HIV status women remain sexually active and have a desire for more children. A level of education had no bearing on contraceptive use but was important for decision making about pregnancy.

EVALUATION OF ARV DELIVERY AND COVERAGE

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A method to estimate the number of people in a country or region with HIV who are undiagnosed and in need of ART

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Purpose of the study: It is important to estimate the number of people in a country who have undiagnosed HIV and low CD4 count as they are in need of ART. New methods are required to derive such estimates.
Methods: The HIV surveillance data needed are the number of previously undiagnosed people presenting with AIDS (simultaneous HIV/AIDS) in a year, with their CD4 count. The number of people with a simultaneous HIV/AIDS diagnosis in a given CD4 count stratum represents a proportion of the total undiagnosed population with CD4 count in that stratum. This proportion is equivalent to the annual incidence of AIDS in persons in that CD4 count stratum, estimable from cohort studies. For each CD4 count stratum, the number of people with undiagnosed HIV can be estimated by dividing the number of people with simultaneous HIV/AIDS diagnoses (with CD4 count in the stratum) by the CD4-specific AIDS rate. The uncertainty associated with this estimate was evaluated by allowing the AIDS incidence to vary according to a Normal distribution, based on the 95% confidence interval for the incidence rate. The number of simultaneous HIV/AIDS diagnoses was allowed to vary according to a Poisson distribution. These two sources of uncertainty were simultaneously accounted for over 10000 runs.
Summary of results: The method is illustrated for estimation of the number of people with CD4 count below 200 cells/mm^3. The incidence rate of AIDS in this CD4 count range has been estimated to be 0.322 (95% CI: 0.268-0.376), using data from CASCADE. Suppose that in the region of interest, in the past year there have been 50 simultaneous HIV/AIDS diagnoses with CD4 count below 200 cells/mm^3. Then the estimated number of people with undiagnosed HIV with CD4 count below 200 cells/mm^3 is 156 (as 50/0.322 = 155.3), with a 95% uncertainty range of (109, 213).
Conclusions: This method allows estimation of the number of people with undiagnosed HIV in any given low CD4 count range, for example below 50 cells/mm^3 or below 350 cells/mm^3 (the consensus cut-off used to define a late presenter). These estimates are important for prompting increased efforts to identify people with undiagnosed HIV and low CD4 count, and for planning future delivery of ART.

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BEST: Better Equipped to Start Treatment

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Introduction: BEST was developed by a board of key stakeholders of European community group representatives, People Living with HIV (PLWHIV), researchers, clinicians, nurses and medical organisations, representing 6 European countries, (UK, Germany, France, Italy, Portugal and Spain). BEST focuses on empowering PLWHIV to make decisions about starting Antiretroviral Therapy (ART) as per current EACS Guidelines. It aims to educate tested, but not treated PLWHIV on the benefits of starting ART according to current guidelines to improve their long-term health and quality of life.
Rationale: In Europe many people start ART with a CD4 count lower than current guidelines recommend, with associated increased morbidity and mortality [1]. Lack of understanding of guidelines, and ineffective communication between PLWHIV and their healthcare professionals (HCPs) may delay the commencement of ART in PLWHIV.
Programme development: The programme was developed by an Advisory Board, and Review Committee of HCPs and community members, with material content at the Boards' discretion. It is organised and funded by Bristol-Myers Squibb and Gilead Sciences.
Materials: The toolkit contains 5 presentation sections to facilitate discussion around; Preparing and Readiness to Start ART: When to Start Treatment: The Rationale; Reasons to start at a CD4 of 350 or above; Building the Best Relationship with Your HIV Clinic and HIV and ART: Questions and Answers. A 6th section, 'Running Workshops' provides information on running workshops, facilitating audience participation and evaluation. It is intended for use by advocacy workers and/or healthcare workers.
Progress to date: BEST was launched at EACS 2009 to a group of mainly community advocacy workers from 6 European countries. Evaluation showed that the materials and workshop format were well received and addressed an unmet need in the countries represented. BEST was rolled out locally in the 1st half of 2010 in 6 pilot countries, where it has had considerable success. Feedback and evaluation from the national rollout will be provided in detail in this poster presentation.
Future plans: We hope BEST will result in more PLWHIV starting ART at the recommended optimum time, possibly determined by prospective surveillance or audit at a local level. Evaluation systems will enable the BEST Advisory Board to respond to the changing needs of users; and to develop appropriate new materials. Regular updates to BEST are planned every 6 months.
Reference

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Older HIV-infected individuals present late and have a higher mortality: a UK clinic cohort study

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Introduction: Current UK guidelines recommend initiation of HAART in all patients with a CD4 count of <350 cells/mm^3. The success of this policy depends on early HIV diagnosis. One-third of individuals in the UK have a CD4 cell count <200 cells/mm^3 at diagnosis.
According to the European consensus, late presentation for care refers to persons presenting with CD4 cell count <350 cells/mm^3 or presenting with an AIDS-defining event, regardless of the CD4 count.
Purpose of the study: Applying only the current CD4 definition for late presentation, we examined the influence of age and calendar period on stage of HIV presentation and the impact of late presentation on mortality.
Methods: Data were collected on patients diagnosed with HIV infection from 1st January 1996 to May 2010. Age was studied as a binary exposure variable (< 50 versus > 50 years). Patients were further stratified by time of diagnosis into 1996-2001, 2002-2005 and 2006-2010 periods. Logistic regression modelling was used to estimate the likelihood of late presentation. Poisson regression modelling was used to estimate mortality in the cohort.
Results: 1531 patients had documented CD4 cell counts within 3 months of diagnosis. The median age at HIV diagnosis for those under 50 and over 50 years was 33.3 (IQR 28.0-38.7) and 54.7 (IQR 51.9-60.6) respectively. 49% of the cohort had a CD4 cell count < 350 cells/mm^3 at HIV diagnosis. The median CD4 cell count for late presenters was 211 cells/mm^3 (IQR 83-289). The majority of the cohort were white males and homosexual. After adjustments, individuals aged over 50 were more likely to present late (OR 2.17; 95% CI: 1.51-3.11). Late presentation was less likely in calendar periods 2006-2010 and 2002-2005 compared to 1996-2001 (OR 0.62; 95% CI: 0.47-0.81 and OR 0.72; 95% CI: 0.55-0.94). Mortality rate in the cohort after 6719.80 person years (pyrs) of follow up was 15.33 per 1000 pyrs (95% CI: 12.64-18.59). After adjustments, age greater than 50 (OR 2.62; 95% CI: 1.64-4.20) and CD4 cell count <350 at diagnosis (OR 1.93; 95% CI: 1.20-3.11) remained independently associated with increased mortality.

Conclusions: In our cohort, late presentation and mortality are decreasing; however, individuals older than 50 were more likely to present late and had a higher mortality. Initiatives to expand HIV testing in clinical and community setting should not neglect individuals aged over 50 whom are often erroneously perceived not to be at risk of HIV infection.

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Offering HIV testing in an emergency admission unit in Newcastle upon Tyne, UK — a pilot audit study

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Background: The UK National Guidelines for HIV Testing 2008 recommends that HIV testing should be offered to all general medical admissions where the reported prevalence of HIV is >2/1000 [1]. We have previously reported that in Newcastle, 72% of new diagnoses in 2007 were late presenters [2] compared to 55% nationally.
Purpose of the study: A prospective audit was undertaken offering HIV testing to all general medical admissions attending the Emergency Assessment Unit (EAU) in Newcastle to assess feasibility, acceptability and point prevalence.
Methods: All patients attending EAU with capacity to verbal consent were offered HIV testing during two block periods of 6 and 11 weeks in 2009/10. The first period was physician led, the second physician-assistant led. Training was undertaken and led by the Infectious Diseases Team. Information regarding HIV testing and the reasons for this audit was given to patients on admission. A standardised proforma documenting data including patients' demographic, reasons for non-consent and its acceptability was completed. A fourth generation blood test (Enzygnost HIV Integral II) was used with the aim of providing results within 36 hours.
Summary of results: 586 patients were considered for testing (16% of total admissions during audit period). 396(67.5%) consented (mean age 59.3 with 42% >age 65). Tests were not performed on 190 (mean age 72.6 with 75% >age 65). 108(57%) of these lacked capacity to consent. 82 (43%) refused testing with 59% believing they were not at risk and only 5% believing EAU was an inappropriate place to test. Patients that were approached but not tested were on the average 13.3 years older than those who consented ($p<0.001$). There were two new HIV diagnoses. Both had PCP (one from Zambia, one MSM). Point prevalence of HIV in EAU was ~5 per 1000. 100% of results were available within 36 hours.
Conclusions: This pilot study demonstrates that HIV testing in an EAU setting is acceptable to the majority of patients and providing results within 36 hours of admission is feasible. Factors limiting testing include stigma (patients/staff), restrictions on time and misperceptions about what an HIV test entails. It is likely to be more cost effective to offer testing in an EAU setting to those in high risk groups or presenting with indicator diseases. An 'HIV test indicated?' prompt on an admissions proforma may be a useful reminder for staff to consider offering testing and normalise HIV testing in a general medical setting.

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A high occurrence of late presenters and missed HIV diagnosis in clinical care in Sweden

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Purpose of the study: To identify and predict factors for late HIV diagnosis in Sweden
Methods: In a prospective study involving 12 Swedish HIV clinics, all newly diagnosed patients, >18 years, are invited to participate to explore what characterize a late presenters (LP), defined by CD4 <350 and/or AIDS diagnosis, from those diagnosed earlier. Demographic and biomedical data are collected as well as HIV-related symptoms and AIDS diagnosis. Four questionnaires are completed; medical history, psychosocial history, general knowledge of HIV and barriers to testing. Enrolment is Oct 2009–Sept 2011. The abstract is a survey of the first 100 patients.
Summary of results: 69% were LPs; 45% had CD4 counts < 200 and/or AIDS; 15% > 500. 70% were immigrants from non-European countries. 57% of these had lived > 1 year in Sweden. This group also had the highest overall risk of being diagnosed late (37/45, 82%) followed by IDU's (3/5, 60%), heterosexuals from the EU (7/12, 58%) and MSM (14/28, 50%). Median age at diagnosis was 35 years for non-Europeans among both LPs and non-LPs. For Europeans it was 49 and 40 years respectively. 29% (18/63, 6 missing data) of late LPs had been investigated or treated for HIV-associated symptoms (STI, hepatitis B or C, seborrheic eczema, penia of the blood, SR elevation or fever of unknown origin > 1 week) including 4 patients with AIDS diagnosis (candidiasis of the oesophagus or wasting) three years previous to HIV diagnosis without having been offered an HIV test. 32% (9/28, 3 missing data) of the non LPs had a history of previous health care contacts for HIV associated symptoms without HIV test performed. 56/100 patients answered the question if they ever had thought of the possibility of being HIV infected. 18% (10/56) responded yes, independent of being a LP or not.
Conclusions: LPs are even more common in Sweden today than previously known. 2/3 is diagnosed at a stage when treatment already should have started. Of the 70% represented by immigrant population as many as 57% had lived > 1 year in Sweden and earlier testing should have been possible. The group with the lowest risk of late diagnosis was the MSM indicating their higher awareness, although as many as 50% were diagnosed late. As many as 1/3 of all newly diagnosed HIV patients had been in contact with the health care system for HIV associated symptoms without being HIV tested. The awareness of HIV needs to increase both on a population level and among healthcare professionals.

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Audit of telephone HIV clinics: effective and acceptable

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Purpose of the study: A Telephone HIV clinic was set up and offered to patients with chronic, stable HIV-infection to replace face-to-face appointments for three out of their four HIV reviews in a 12 month period. We initiated these telephone clinics in 2007. We audited the effectiveness and acceptability of these Clinics.
Methods: A total of 72 patients were included in the audit: 88% were male, 68% were men who have sex with men, 22% were heterosexuals of non-UK origin. This population reflects the wider patient cohort of this busy, city centre Genitourinary Medicine clinic. A retrospective case note analysis was conducted of patients seen in the telephone clinic over an 8 month period from December 2008 until July 2009. Clinic eligibility, consent documentation, compliance with recommended frequency of appointments and default rates were assessed. A patient satisfaction survey was conducted during this period.
Summary of results: Eligibility for the telephone clinic was met in 77% of cases. In the rest (23%), failure to meet inclusion criteria related to the limit set for CD4 count (N=7), viral load (N=1), previous poor

appointment attendance (N=5) and outstanding contact tracing issues (N=1). Consent was documented in 82% of cases. 94% of telephone appointments were conducted within the designated time frame and the correct ratio of telephone to face-to-face appointments was achieved in 63% of instances. Overall attendance was better for the telephone clinics with only 15% of appointments failing to make contact as compared to 23% DNA rates for the equivalent face-to-face clinics. There were no cases where an urgent clinical review was needed after a telephone consultation; however, four patients were assessed in person for reasons including pregnancy, abnormal blood results and genital herpes. Overall 90% of patients scored their satisfaction as "very high".
Conclusions: According to standards set at inception the clinics can be considered a success with less than 1% patient dissatisfaction, greater than 90% successfully conducted telephone appointments and only one respondent indicating a preference to return to face-to-face clinics. Documentation of consent and compliance with inclusion criteria needs to be improved. However, overall telephone clinics have proven to be a convenient and effective alternative to face-to-face appointments for patients with stable HIV infection.

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Newly diagnosed HIV patients in Lima, Peru: a comparison of individuals diagnosed through an intervention program versus self-referred individuals

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Background: An extensive intervention program to promote awareness, HIV testing, diagnosis and access to medical care in at-risk populations was developed by Via Libre between Nov 2007 and Oct 2009 in Lima, Peru (Proyecto Somos).
Purpose of the study: We evaluate the impact of this type of intervention on the presenting clinical conditions of newly diagnosed persons.
Methods: Review of medical records of self-referred individuals (Group 1) and patients diagnosed through the intervention program (Group 2), and presenting for the first time to Via Libre HIV Clinic. We compared the initial condition of both groups. Cases included in the analysis completed a baseline clinical and laboratory evaluation, and had a decision made by the treating physician regarding whether HAART was required or not.
Results: During the study period, 523 HIV-positive persons presented for initial care at our clinic. We reviewed 303 records, out of which 216 were eligible for analysis. One hundred and thirty-two corresponded to the self-referred group (Group 1) and 84 to the intervention group (Group 2). Both groups had similar mean age (35.5 yrs., Group 1; 28.8 yrs., Group 2; p:0.44), and time between diagnosis and presentation to clinical evaluation (1.8 mos., Group 1, 1.0 mos., Group 2). Mean baseline CD4+ cell count was significantly lower in Group 1 (287.6 +/- 217.6 vs. 392.56 +/- 249.8, p< 0.5). A higher number of patients in Group 1 presented with AIDS-related clinical symptoms (Group 1: 47.7%, n=63; Group 2: 28.6%, n=24), and had indication of immediate initiation of antiretroviral therapy (Group 1: 62.8%, n=83, Group 2: 48.8%, n=41).
Conclusions: Patients diagnosed through the intervention program presented with less advanced HIV infection and had chance to earlier initiation of HAART. Intervention programs to actively diagnose HIV give a significant opportunity to provide timely medical care to HIV-infected individuals in resource-limited settings. These initiatives should be integrated to national HIV care programs.

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Adherence to HIV treatment guidelines for initiation of antiretroviral therapy in Australia

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Background: In Australia, the DHHS guidelines for treatment of adults and adolescents have been adopted with an Australian Commentary.
Purpose of the study: An audit was conducted to determine adherence to these guidelines.
Methods: Case records were examined of 500 sequential adults initiating ART in primary care and hospital sites (125 per site) in Sydney and Melbourne from 2004 to 2008 inclusive. Data on ART initiation and regimen prescribed, as well as adherence to all specific guidelines on patient management and monitoring, were recorded.
Results: Of 500 subjects initiating ART (by 54 physicians with mean 14 years HIV experience), 95% were male (mean age 40 years, CD4 count 287 cells/μL, HIV RNA 89,000 copies/mL). ART initiation was mean 3.1 years after diagnosis, via clinical trial in 20.4% and as hospital in-patient in 7.7%. For "When to start", adherence to Dec 1 2009 guidelines was 91%, 82% for Nov 3 2008 guidelines, and 88% for guidelines current at ART initiation. Preferred or alternative regimens were prescribed (after exclusion of patients receiving experimental clinical trial regimens) in 79%, 90%, and 89%, according to 2009, 2008 and guidelines current at ART initiation, respectively. Preferred regimen was prescribed according to guidelines in 50%, 55% and 65%, respectively. Contraindicated ART was prescribed in 4%. Strong recommendations (level A) in 2008 guidelines were adhered to variably: for hepatitis serology (74%), oral/dental check (63%), fasting lipids (52%), fasting glucose (47%), CMV serology (50%), resistance testing (48%), vaccination history 39%, Chlamydia screening (38%), gonorrhea screening (36%), chest X ray (35%), pap smear (32%), urinalysis (26%), and TB testing (9%). Sydney patients were more likely than Melbourne patients to have co-morbidity history assessed (96% vs 62%, p<0.0001), and to commence ART via a clinical trial (36% vs 5%, p<0.0001), but less likely to have treatment adherence ability assessed (62 vs 84%, p<0.0001) with no significant difference in STI testing. Hospital sites were more likely than GP sites to perform investigations - resistance testing (71 vs 46%, p<0.0001), but less likely to discuss lifestyle health promotion (36% vs 63%, p<0.001).
Conclusions: HIV treatment guidelines in primary care and hospital sites in Australia have been largely adhered to for when to start and what to start with, but less closely followed for co-morbidity related parameters.

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Five-year outcomes of HAART at a non-governmental treatment center in Lima, Peru

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Background: Ministry of Health in Peru launched an HIV treatment program with the initial support of the Global Fund in 2004. A few months later, our institution, an NGO working in HIV prevention, entered the treatment program in order to contribute to the national efforts to improve access to HIV care. There are no other available reports on long-term results of HAART in our country.
Methods: Retrospective medical records review of 149 consecutive patients that initiated HIV treatment through the national program at our outpatient Clinic between February and July 2005. Main clinical and laboratory outcomes were recorded and reported.
Results: After an observation period of five years, 127 (85.2%) persons continue their care at our Clinic. Mean baseline age was 34.6 yrs. The group included 34 women (22.8%). Eight patients died (5.3%), 7 (4.7%) patients were referred to other centers at their request, and 7 (4.7%) were lost to follow up. Eighty-five patients (57.0%) were treatment naive at the moment of joining our treatment program. One hundred sixteen patients show current virological success (HIV VL<400 c/ml), with an ITT success rate of 77.8%, and an "on treatment" success rate of 89.7%. Ninety-five persons have shown sustained virological success over the 5 years (89 on NNRTI-based regimens). Mean baseline CD4 cell count at the moment of treatment initiation was 86/μL. Mean CD4 cell count at five years follow up is 254/μL. Forty-five patients have required change of a drug due to an adverse event (most commonly during the initial months of therapy). Causes of mortality were opportunistic infections related to IRIS or previously active (TB, PCP, disseminated histoplasmosis) and 2 cases of NHL. All deaths occurred within then initial year of treatment. Significant morbidities such as cancer or TB after the first year of

treatment occurred in 8 patients (5.3%). No cardiovascular event has been observed in this cohort so far.
Conclusions: Outcomes observed at 5 years of HAART are comparable to the ones observed in other treatment programs developed in limited resource settings. The model of care supported by our NGO is highly successful with no additional support from public funding other than medications and monitoring laboratories.

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The impact of late presentation: analysis of a cohort of 313 Portuguese patients

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Background: In Europe, 15–38% of HIV infections are diagnosed at advanced stages. Late presentation is associated with increased morbidity and mortality, greater burden for the healthcare system and higher risk of transmission.
Purpose of the study: To describe the epidemiological and clinical characteristics of a Portuguese cohort of patients diagnosed with HIV infection between 2000 and 2008; to characterize late presenters (LP); to analyse their clinical, immunological and virological evolution and to compare them with non-late presenters (NLP).
Methods: Retrospective, observational study of patients assisted in an infectious diseases clinic, who were diagnosed with HIV between 01/01/00 and 31/12/08. LP were defined by TCD4+<200/µl or an AIDS defining illness at presentation. SPSS 15.0 was used for statistical analysis.
Summary of results: Three hundred thirteen patients were included. Most were males (60%) with ages 20-40 years old. About 1/3 (30%) was non-Portuguese. Diagnosis was made by routine serology in 36% of individuals and, in 36%, after development of symptomatic infection. At the time of diagnosis, 42% (n=132) of patients were considered LP. The only risk factor associated with late diagnosis was male gender (p=0,020). Average TDC4 count at baseline was 132/µl for LP and 497/µl for NLP (p=0,0006). Combined antiretroviral therapy (cART) was started in 100% LP vs 74% NLP (p<0,0001), with NNTRI being the most frequent regimen (non significant). Both groups showed an increase in TCD4 counts over time (average increase of 366/µl LP vs 121/µl NLP; p<0,0001). At present time, 87% LP have undetectable plasma HIV RNA vs 79% NLP (non significant) and average TCD4 counts are 495/ µl for LP vs 610/ µl for NLP (p=0,0006). LP had more hospital admissions (51% vs 22% in NLP; p<0,0001), most of which AIDS related (LP 52% vs 15% for NLP; p<0,0001. Most patients in both groups remained adherent to regular medical follow-up and there was no significant difference in the mortality rate.
Conclusions: LP represented a significant proportion of HIV diagnosed patients and were associated with more AIDS related events and hospital admissions, but not higher mortality rate. Prompt institution of cART allowed a significant immune recovery, although not enough to match NLP CD4 counts. These data support the need for effective screening strategies in order to allow an earlier diagnosis of HIV infection and a better long term prognosis.

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T-CD4+ cell count at the date of the HIV diagnosis

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Background: Some studies state that HIV patients' immunological stage at the date of diagnosis has not been significantly altered in the last few years despite a better access to health care, and the innumerable campaigns for the detection of infection due to HIV. Others come to the conclusion that the mean T CD4+ cells count has been reducing since 1985 but no explanation for this fact has yet been found.
Purpose of the study: Evaluation of the influence of epidemiological parameters and year of diagnosis on the immunological stage of the HIV infected patients at the time of diagnosis.
Methods: Retrospective analysis of a random survey of the clinical files of HIV positive patients followed at Hospital de Joaquim Urbano, from 1995 to 2008.
Summary of results: 730 files have been analysed. 80.1% of these patients were male and 19.9% female. The average age at HIV diagnosis was 36 years (minimum 14, maximum), 1.9% where under 20 years old and 4.2% over 60 years old. 59.3% were intravenous drug users, 26.6% heterosexuals, 6.2% homosexuals and in 7.3% of the patients the risk factor for acquisition of infection was unknown. Of the total, 38.2% were HIV mono-infected, 48.2% where HIV/HCV; 9.2% HIV/HCV/HBV and 4.4% HIV/HBV co-infected. The global mean T CD4+ cell count at the time of diagnosis was 293/mm^3. There were no significant statistical differences (p>0.05) between gender: male 289.5/mm^3 and female 305.8/mm^3, nor age at the time of diagnosis. The mean TCD4+ cell count was higher in the homosexual patients (391.9/mm^3) when compared with heterosexuals (273.9/mm^3) and iv drug users (300.7/mm^3) (p<0,05). The mean TCD4+ cell count at diagnosis was: 306/mm^3 in HIV mono-infected patients, 288.2/mm^3 in HIV/HBV, 285.4/mm^3 in HIV/HCV and 278.2/mm^3 in HIV/HCV/HBV co-infected patients, although these differences are not statistically significant among them. At diagnosis a more severe immunosuppression (CD4<200/mm^3) was registered in 48.7% of the male population, 53.8% of patients over 60 years old, 54.1% of the heterosexuals, and 62% of VIH/VHB co-infected. When comparing the mean T CD4+ cell count between 1995-1997 (432/mm^3), and 2005-2008 (246/mm^3) significant statistical differences were found (p<0.05).
Conclusions: The homosexual group of patients presented a better immunological stage at the date of diagnosis. In the remaining groups there were no significant statistical differences in the immunological stage when the HIV infection.

CLINICAL PHARMACOLOGY

P176

Pharmacokinetics of lamivudine, abacavir and zidovudine administered twice daily as syrups versus scored tablets in HIV-1-infected Ugandan children

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Purpose of the study: Currently there is an effort to develop simple, more convenient antiretroviral regimens for children to reduce costs and promote adherence. We report the plasma pharmacokinetics (PK) of lamivudine (3TC), abacavir (ABC) and zidovudine (ZDV) taken twice daily as syrups versus scored tablets in HIV-1 infected Ugandan children.
Methods: Eligible children from 2 Ugandan centres in the ARROW trial, weighing 12-15kg, had taken ZDV, 3TC and ABC syrups twice daily for at least 24 weeks, and were ready to switch from syrups to scored tablets. Children were expected to remain in the 12-15kg weight band (i.e. same dosing band) for the next 4 weeks. Those with illnesses affecting PK (e.g., severe diarrhea, vomiting) were ineligible; children who missed any dose in the 3 days before sampling were excluded. Blood samples were collected at 0, 1, 2, 4, 6, 8 and 12 hours after the child's last morning dose on syrups prior to switching to scored tablets of Combivir (ZDV +3TC) and ABC, and then repeated 4 weeks later. Adjusted Geometric Mean Ratios (aGMR) were calculated to compare plasma area under the curve (AUC0-12) and peak concentrations (Cmax) between tablets versus syrup.

Results: 19 eligible children (6 boys) were enrolled with median age of 3 (range 1.8-4) years. Following WHO tables, actual doses increased by 25% as children switched from syrups to scored tablets within the 12-15kg weight-band, and so PK parameters were normalised to the tablet dose. For ZDV and ABC, dose-normalised tablet AUC0-12 and Cmax were equivalent to syrup, but dose-normalised 3TC exposure was ~55% higher on tablets.
Actual 3TC exposure on 75mg tablet dose (AUC0-12 (%CV) 8.2 (20%) h. mg/L) was higher than expected compared to previous paediatric studies, and lower than expected for 60mg syrup dose (4.2 (36%) h.mg/L). There was no evidence of dosing or bioanalytical errors, or problems with administration (vomiting), or with integrity of the product batches, such as degradation.
Conclusions: Although ZDV and ABC syrups and tablets gave equivalent exposures, we found higher plasma exposure from twice daily 3TC scored tablets compared to syrups. Further studies to understand the underlying mechanism for differing 3TC exposures from solution and tablets in the target population of HIV-infected children are needed.

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Therapeutic drug monitoring (TDM) of atazanavir in pregnancy

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Background: Pregnant women experience physiological changes during pregnancy resulting in clinically significant alterations in antiretroviral pharmacokinetics (PK). Therefore, achieving and maintaining optimal plasma concentrations of antiretroviral drugs is essential for maternal health and minimising the risk of mother-to-child transmission of HIV.
Purpose of the study: To describe atazanavir/ritonavir (ATV/r) PK during pregnancy.
Methods: In this prospective, open labelled study, pregnant HIV-positive women received ATV/r as part of their routine pre-natal care. Demographic and clinical data were collected, and ATV plasma concentrations [ATV] were determined in the first (T1) and/or second (T2) and/or third (T3) trimester using HPLC-MS/MS (LLQ = 0.05 μg/mL). Postpartum (PP) sampling was performed where applicable. Antepartum (AP) and PP PK parameters were compared using a One-way ANOVA (for independent data sets) and a paired t-test (for paired data).
Summary of results: From January 2007 31 women (25 black African) were enrolled in the study. All received ATV/r at standard dose of 1 tablet once daily (300/100 mg od). 10/31 women initiated ATV/r treatment during pregnancy. Median (range) gestation at initiation in these patients was 24 weeks (7-35). Median (range) baseline CD4 count was 393 cells/μL (153-869) and 17 patients had a baseline plasma viral load of < 50 copies/mL. [ATV] were determined in 10/31 (T1); 17/31 (T2); 27/31 (T3) and 21/31 (PP) patients. Time of TDM sampling and [ATV] (geometric mean; 95%CI) are given in the Table. 2/17 patients at T2, 2/27 (T3) and 2/21 at PP had concentrations <LLQ (suggesting non-adherence). [ATV] were lower AP relative to that observed at PP (Table 1). Equally, in a paired analysis of 17 patients (T3 vs. PP), [ATV] were significantly reduced at T3 (P=0.0005).
Conclusions: Although ATV concentrations were reduced in the third trimester, standard ATV/r dosing did achieve therapeutic levels (>150 ng/mL) both antepartum and postpartum, suggesting the current regimen is appropriate in pregnancy.

Table 1 (abstract P177)

	T1 (n=10)	T2 (n=17)	T3 (n=27)	PP (n=21)	P value
[ATV], μg/mL	1.03 (0.49-2.53)	0.75 (0.59-1.45)	0.66 (0.63-1.03)	1.17 (1.09-1.81)	0.06
CV, %	108	84	59	55	-
Time of sampling, h	14.6 (12.5-17.5)	18.0 (16-21.8)	19.0 (17.6-21.9)	19.1 (17.4-22.3)	0.102

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SLCO3A1 expression is a major determinant of atazanavir PBMC penetration in HIV-infected patients

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Background: Atazanavir (ATV) is administered at a dose of 300 mg boosted with 100 mg of ritonavir once daily (boosted). However, in the clinical setting use of unboosted ATV can be warranted. Although plasma concentrations are used clinically as a marker of drug exposure, ATV predominantly acts within HIV infected cells and therefore intracellular concentrations may better correlate with therapeutic efficacy. To date, the factors that define ATV flux into peripheral blood mononuclear cells (PBMC) are not fully characterized and several efflux and influx transporters may influence intracellular pharmacokinetics.
Purpose of the study: To evaluate gene expression of efflux (ABCB1, ABCC1, ABCC2) and influx (SLCO3A1) transporters and relate to the cellular accumulation of unboosted ATV.
Methods: Patients administered with unboosted ATV were recruited in Torino. Written informed consent was obtained. Main inclusion criteria were: no concomitant interacting drugs (except for TDF), no hepatic or renal impairment and self-reported adherence > 95%. Blood samples were collected 22-26 h after dosing and PBMC and plasma separated. Plasma samples were analysed by a validated HPLC-PDA method and PBMC extracts (intracellular) analysed using a validated LC-MS method. The cell count and mean cellular volume (MCV) was used for determining intracellular concentrations. Gene expression was evaluated by relative quantification using real time PCR.
Results: 13 Caucasian patients met the inclusion criteria and were included in the study. Median plasma ATV Ctrough was 134 ng/ml (IQR, 113-153), intracellular concentrations were 322 ng/ml (IQR, 210-448), and the median accumulation ratio (intracellular/plasma concentration) was 1.84 (IQR, 1.21–3.58). Intracellular concentrations were not correlated with plasma concentrations (rho= -0.22 p=0.41). SLCO3A1 expression was significantly correlated with cellular accumulation ratio. (rho=0.626, p=0.022). In multivariate linear regression analyses, SLCO3A1 expression was the only independent predictor of ATV cellular accumulation (â=0.726, p=0.007).
Conclusions: Intracellular ATV concentrations were higher than plasma concentrations, indicating an accumulation of ATV in PBMC and potentially a role for influx transporters. The correlation between SLCO3A1 expression and ATV accumulation supports this hypothesis and suggests that the SLCO3A1 uptake transporter may be a determinant of intracellular ATV concentrations.

P179

A filter-based cross-sectional analysis of an HIV-positive, HAART-treated cohort in rural Burundi: pharmacokinetics, pharmacogenetics and viral load

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Background: In Burundi Triomune® is the first-line HIV treatment and it is estimated to reach 30% of those in need, but efficacy monitoring does

not rely on viral load (VL) quantification, due to cost and technical limitations. Furthermore nevirapine (NVP) is known to have a highly variable pharmacokinetics (PK) and pharmacogenetics (PG), but no data are currently available in this population.
Purpose of the study: To study virological outcome, PK and PG of nevirapine-based HAART in Burundi, by relying on previously validated alternative tools for samples collection.
Materials and methods: A cross-sectional analysis was performed at the rural hospital of Kiremba, northern Burundi. All patients on HAART (>6 months) presenting for care and willing to participate were enrolled. After sample collection, whole blood (50 μL) was spotted on Whatman 903 Cards (Dried Blood Spot, DBS); afterwards plasma (100 μL, after centrifugation) was spotted on glass paper filter (dried plasma spots, DPS). DBS were used for VL testing (NucliSENS EasyQ HIV-1 v2.0) and PG analysis (516G>T and 983C>T SNPs in CYP2B6, 3435C>T and 1236 C>T in MDR1). A validated HPLC method was used to measure NNRTIs concentrations on DPS.
Results: 239 patients (68.2% female) were enrolled; mean (±SD) age and BMI were respectively 37.9 years (±10) and 20.7 Kg/m^2 (±2.8). The majority of them (90.8%) were in WHO stage 3 and last CD4+ cell count was 543 cell/mm^3 (±345). 237 were on first line treatment (220 on NVP and 17 on EFV) and 2 (0.8%) on second line (LPV/r). Mean time on treatment was 25.7 months (±13.7) and it correlated to the last CD4+ count (Pearson 0.23, p=0.001). 43 (18%) had a detectable viral load with 14 patients (5.8%) having more than 800 copies/ml. Nevirapine and efavirenz Ctrough were 7727 ng/ml (± 3796) and 4027 ng/ml (± 3041). CYP2B6 mutated SNPs were common (48,5% in 516G>T, 13,6% in 983C>T) and associated to increasing exposure (p=0.01 and p=0.02). A higher proportion of patients (95.6% vs. 88.5%, p>0.05) had viral loads below 800 copies/ml in the higher range of NVP concentration (Ctrough >4300 ng/ml).
Conclusions: DPS and DBS showed to be useful tools to collect and transport samples from a rural area of Burundi. Even with the limit of a cross-sectional analysis a high effectiveness was noted, showing 82% of patients with undetectable VL at a mean of 2 years since start of treatment. High NVP plasma concentrations along with favorable genetic profile could partially explain these results.

P180

Pharmacokinetics of plasma lopinavir/ritonavir following the administration of 400/100, 200/150, and 200/50 mg twice daily in HIV-negative volunteers

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Purpose of the study: Development and post-marketing data suggest that some licensed ARV doses could be reduced. We assessed the pharmacokinetics (PK) of lopinavir/ritonavir (LPV/r) following the administration of 3 different doses to HIV negative volunteers as a preliminary to the design of clinical trials to examine the safety and efficacy of novel dose regimens in HIV positive subjects.
Methods: Following written consent, male and female volunteers were administered LPV/r 400/100 (2 LPV/r Meltrex 200/50 tablets; regimen 1), 200/150 (1 Meltrex tablet, 1 100mg ritonavir capsule; regimen 2), and 200/50 (1 Meltrex tablet; regimen 3) mg twice daily (BID) for 7 days sequentially. Each 7-day phase was separated by a 7-day wash-out period and LPV/r steady-state PK was assessed over 12 hours on the last day of each dosing phase (days 7, 21 and 35). PK parameters were compared using Phase 1 as reference by determining geometric mean ratios (GMR) and 90% confidence intervals (CI). Safety and tolerability were assessed throughout the study period.
Summary of results: Twenty-two subjects (8 female) were enrolled and completed the study. GM PK parameters (90% CI) of the 3 doses are shown in Table 1.
LPV PK parameters in regimens 2 and 3 were lower: GMR (90%CI) AUC 0.74 (0.65-0.84) and 0.45 (0.40-0.51); Cmax 0.75 (0.66-0.85) and 0.54 (0.40-0.60); C12h 0.74 (0.62-0.89) and 0.30 (0.25-0.36). All subjects in regimens 1 and 2 had LPV concentrations above the suggested minimum effective concentration (MEC) of 1000ng/mL, 3 subjects receiving regimen 3 had lower concentrations. No serious adverse events were observed and as expected mild/moderate diarrhoea was the most common adverse effect.
Conclusions: These PK data indicate that therapeutically relevant plasma concentrations of LPV can be achieved with lower administered doses and support further exploration of these lower LPV doses in properly designed randomised clinical trials. Preservation of therapeutically relevant LPV doses requires administration of higher doses of ritonavir. A new dose of LPV/r could lower cost and improve access in developing countries.

P181

Population pharmacokinetic and pharmacogenetic analysis of nevirapine in hypersensitive and tolerant HIV-infected patients from Malawi

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Purpose of the study: Despite risk of hypersensitivity (HS), nevirapine (NVP) underpins first-line HIV therapy in Africa. The relationship between NVP exposure and HS is unknown but could be influenced by polymorphisms in CYP2B6 and CYP3A4 affecting drug metabolism.
Methods: 180 HIV patients (101 female) from Malawi receiving NVP-based therapy (200mg twice daily) between March 2007-September 2008 for a median (range) 6weeks (1-26) were included in the population pharmacokinetic (PK) model (n=383 NVP serum concentrations). Rich and sparse (n=40 and 140 patients, respectively) sampling was performed. Median (range) age, weight, BMI and CD4 cell count were 34yr (21-62),

Table 1 (abstract P180)

PK parameter	400/100 BID	200/150 BID	200/50 BID
	regimen 1	regimen 2	regimen 3
Lopinavir			
AUC0-12 (ng.h/mL)	99599 (87180-113787)	73603 (65121-83191)	45146 (39251-51927)
Cmax (ng/mL)	11965 (10400-13766)	8939 (8047-9930)	6404 (5648-7262)
C12h (ng/mL)	5776 (4884-6831)	4293 (3603-5115)	1749 (1419-2156)
Ritonavir			
AUC0-12 (ng.h/mL)	4664 (3808-5664)	10462 (8972-12200)	1625 (1390-1899)

54kg (35-94), 20kg/m^2 (15-38) and 156cells/mm^3 (1-812). In total 25 individuals were HS and 23 hepatitis B/C co-infected. Pharmacogenetic data were available for single nucleoside polymorphisms (SNPs) CYP3A5*6, CYP3A5*3, CYP2B6 983T>C, CYP2B6 516G>T, CYP2B6 785A>G in 89/180 patients obtained by Sequenom iPLEX. NONMEM (VI 2.0) was applied to determine NVP PK parameters, interindividual, interoccasion variability (IIV, IOV), residual error and influence of patient demographics, HS and genetics on NVP apparent oral clearance (CL/F). A visual predictive check was used to validate the model.

Summary of results: A one compartment model with first order absorption best described NVP concentrations. For the final model (n=89) NVP CL/F (relative standard error; RSE%) was 2.67 (5%) with IIV and IOV of 30% (29%) and 32% (26%), respectively. Apparent volume of distribution and absorption rate constant were 141L (22%) and 0.77h^{-1} (31%), respectively. None of the patient demographics were significantly related to NVP CL/F. No association between NVP CL/F and HS or hepatitis infection was observed. Of the SNPs analysed CYP2B6 983T>C and CYP3A5*3 had a significant impact on NVP CL/F; reducing it by 25% in 983C heterozygotes (allelic frequency 18%) and 40% in CYP3A5*3 homozygotes (allelic frequency 5%).

Conclusions: Available patient demographics and development of HS were not associated with NVP CL/F in this population of HIV-infected patients from Malawi. Genes associated with loss of function in CYP2B6 and CYP3A5 reduced NVP CL/F. However, NVP exposure was not associated with the development of HS, which is more likely to be an immunological phenomenon.

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PK/PD modeling supports the dose-escalation decision in VIKING

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In the VIKING study a 50 mg once daily regimen of the next generation HIV integrase inhibitor (INI) S/GSK1349572 (572) exhibited promising antiviral activity in an initial cohort (Cohort I) of treatment-experienced subjects with documented raltegravir (RAL) resistance. The purpose of this work was to evaluate via simulation techniques whether improved virologic responses could be achieved with higher doses in a second cohort (Cohort II) by utilizing pharmacokinetic (PK) and pharmacodynamic (PD) models derived using Cohort I data.

Interim PK data from VIKING Cohort I were combined with data from Phase 1 and 2a studies in healthy and HIV+, INI-naïve subjects, respectively; data were analyzed using a linear two-compartment PK model. The population PK/PD analysis incorporated $\log_{10}$ HIV-1 RNA viral load (VL) sampled throughout 10 days of dosing during the Phase 2a and VIKING studies. The VL was modelled using an indirect response model in which the 572 plasma concentrations inhibited HIV-1 RNA production. Final PK and PK/PD models were validated using the visual predictive check (VPC) technique. Two sets of simulations were used to predict responder percentage for dose regimens proposed for Cohort II of VIKING. First, change from baseline in $\log_{10}$ VL (ΔVL) at Day 11 was simulated for cohorts of 1000 subjects for each dose regimen according to different fixed levels of baseline fold change (FC) in 572 IC50 from wild type virus. The second set of simulations predicted responder percentages for clinical RAL-resistant HIV populations with diverse 572 susceptibilities. The data were well-described by the respective models. Model parameters were generally well-determined and VPC plots verified predictive performance.

Simulations predicted increasing the dose regimen from 50 mg once daily to 50 mg twice daily would increase the percentage of patients with FC=8 that achieved ≥ 1.5 $\log_{10}$ ΔVL at Day 11 by ~28%. Similarly, improvements in response of ~20% and ~18% were predicted for patient populations with HIV resistance profiles observed in RAL PhIIb and BENCHMRK virologic failure and VIKING screening populations, respectively. Our models predict 572 50mg twice daily will appreciably increase Day11 virologic responses in RAL-resistant subjects, supporting the dosing strategy for the ongoing Cohort II. 572 shows promise to demonstrate further the activity in this difficult to treat patient population.

P183

Impact of CYP2B6 and CYP2A6 polymorphisms on efavirenz plasma concentrations in Ghanaian HIV-infected patients

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Purpose of the study: Genetic variations in the enzymes responsible for the metabolism of efavirenz partially explain inter-individual variability in serum efavirenz concentrations. In this cross-sectional study we determined the frequency and impact on efavirenz plasma concentrations of the CYP2B6 516G>T and CYP2A6*9 polymorphisms.

Methods: Following informed consent, blood samples were obtained from 521 adults on efavirenz based ART. Drug concentrations approximately 12-14h post-dose were measured using a validated HPLC with UV detection. Total genomic DNA was extracted by standard methodology and patients were genotyped using real-time PCR with allelic discrimination.

Results: The frequency of CYP2B6 516G>T and CYP2A6*9 genotypes were GG 29.8%, GT 44.3%, TT 25.9% and CC 91.6%, AC 8.7%, and AA 0.39%, respectively. Both polymorphisms were statistically associated with efavirenz plasma concentrations. Median plasma concentrations according to CYP2B6 516G>T were 1297, 1833 ($P < 0.05$) and 2248 ($P < 0.001$) μg/ml for GG, GT and TT individuals, respectively. Median plasma concentrations according to CYP2A6*9 were 1713, 3225 ($P < 0.0001$), and 1231 μg/ml for CC, CA and AA individuals, respectively. Median efavirenz concentrations in 268 males were 1759 μg/ml and in 253 females were 1826μg/ml ($P > 0.05$).

Conclusions: Our results show that polymorphisms in CYP2B6 and CYP2A6 genes are significantly associated with plasma concentrations of efavirenz in Ghanaian HIV infected patients. Further studies are now warranted to explore the potential for pharmacogenetics-directed dose individualisation of efavirenz. A prospective phase of the study is in progress to evaluate the influence of genetic polymorphisms on efavirenz concentrations and CNS toxicity.

P184

Population pharmacokinetic modelling of once-daily ritonavir-boosted darunavir in HIV-infected patients

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Purpose of the study: Once daily ritonavir-boosted darunavir (DRV/RTV) is a preferred antiretroviral regimen for treatment-naïve patients. The pharmacokinetics (PK) of DRV/RTV may be influenced by patient demographics and co-medications. Also with an increased aging HIV population, investigations into the impact of older age on PK are important.

Methods: Data were pooled from 3 DRV/RTV PK studies. In total 51 HIV-infected patients (7 female) stable on DRV/RTV (800/100mg or 900/100mg once daily; n=32 and 19, respectively) were included. Median age, weight, BMI, RTV area under the curve over 24h (AUC_{0-24}) and baseline CD4 cell count were 39yr (21-63), 74kg (57-105), 24kg/m^2 (18-31), 4.35mg.h/L (2.27-10.99) and 500cells/mm^3 (227-1129), respectively; 49 patients had undetectable viral load at time of study. PK sampling was performed at steady-state and between 1-3 PK curves were available per patient. Nonlinear mixed effects modelling (NONMEM v. VI 2.0) was applied to determine DRV PK parameters, interindividual and interoccasion variability and residual error. The following covariates were evaluated: age, weight, BMI, sex, ethnicity, RTV AUC_{0-24} and raltegravir co-medication (400mg twice daily). The model was validated by means of simulation and visual predictive check.

Summary of results: A 2-compartment model with first-order absorption (k_a 0.914h^{-1}) and lag-time (0.358h) best described the data. Inclusion of a different apparent oral clearance (CL/F) and volume of distribution (V2/F)

for one of the studies improved the fit (Study 1,2 *vs.* Study 3 CL/F: 12.5 *vs.* 15.6L/h; V2/F 125 *vs.* 192L). RTV AUC_{0-24} and age were significantly associated with DRV CL/F. An increase in age of 1yr produced a fractional decrease in DRV CL/F of 0.014, equivalent to a 14% reduction in CL/F with every 10yr increase in age. Based on the visual predictive check 94% of observed DRV concentrations were within the 95% prediction interval, indicative of an adequate model.
Conclusions: A population model describing the PK of once daily RTV-boosted DRV has been developed and validated. RTV AUC_{0-24} and age were significantly related to DRV CL/F. The impact of age requires further investigation and clarification over a wide age range, particularly in an elderly population.

P185

Pharmacokinetic (PK) and pharmacodynamic analyses of once- and twice-daily darunavir/ritonavir (DRV/r) in the ODIN trial

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Background: In the Phase III, randomised, open-label ODIN trial, treatment-experienced HIV-1-infected adults with no screening DRV resistance-associated mutations received DRV/r 800/100mg qd or DRV/r 600/100mg bid (both arms + ≥2 NRTIs). At Week 48, 72.1% qd vs 70.9% bid patients achieved HIV-1 RNA <50 copies/mL (95% CI = -6.1 to 8.5%, p<0.001; ITT-TLOVR), confirming non-inferiority of DRV/r qd. The relationship between DRV PK and efficacy and safety following treatment with DRV/r is explored.
Methods: Sparse blood sampling for PK evaluations was taken at Weeks 4, 8, 24 and 48 to determine DRV trough concentrations (C_{0h}) and exposure (AUC_{24h}, calculated as AUC_{12h} x 2 for bid) using a population pharmacokinetic model. Relationships between PK parameters and efficacy (change in log_{10} HIV-1 RNA and virological response [HIV-1 RNA <50 copies/mL]) were assessed using ANCOVAs. Relationships between PK parameters and occurrence of adverse events of interest and laboratory lipid abnormalities were evaluated using descriptive statistics.
Results: PK data were available for 280 DRV/r qd patients and 278 bid patients. Median (range) C_{0h} was 1896 (184-7881) ng/mL for DRV/r qd and 3197 (250-11,865) ng/mL for DRV/r bid. Median (range) AUC_{24h} for DRV/r qd was 87,788 (45,456-236,920) ng.h/mL and 109,401 (48,934–323,820) ng.h/mL for bid. No relevant relationships were observed between DRV PK and efficacy: changes from baseline in HIV-1 RNA log_{10} copies/mL at Week 48 for pooled data by DRV AUC_{24h} quartile ranges (≤79,576; 79,577-100,376; 100,377-119,356; >119,356 ng.h/mL) were -2.06, -2.22, -2.19, and -2.08 log_{10} copies/mL, respectively. The % patients achieving HIV-1 RNA <50 copies/mL by these quartile ranges were 82.0%, 88.5%, 82.6% and 76.5% (observed data), respectively. In a logistic regression analysis adjusting for baseline viral load, AAG levels and number of sensitive NRTIs in the optimised background regimen, there were no relevant relationships between PK and virological response. No apparent relationships were observed between DRV PK and occurrence of rash-, cardiac-, GI-, liver-, lipid- and glucose-related AEs or laboratory lipid abnormalities.
Conclusions: Dosing with DRV/r 800/100mg qd resulted in lower C_{0h} and AUC_{24h} compared to DRV/r 600/100mg bid; however, comparable efficacy between DRV/r qd and bid confirmed adequate DRV concentrations were achieved following qd dosing. No relevant relationships were observed between DRV PK and efficacy or safety at Week 48.

P186

Effect of intrinsic and extrinsic factors on the pharmacokinetics of TMC278 in antiretroviral-naïve, HIV-1-infected patients in ECHO and THRIVE

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Purpose of the study: The current analysis examined the pharmacokinetics of the next-generation investigational NNRTI, TMC278, in the pooled double-blind Phase III trials ECHO (NCT00540449) and THRIVE (NCT00543725) in ARV-naïve, HIV-1-infected adults [1] and explored the influence of intrinsic and extrinsic factors on the pharmacokinetic parameters.
Methods: A total of 1368 patients (24% female) were randomised (1:1) to either TMC278 25 mg q.d. or EFV 600 mg q.d., in combination with TDF/FTC (ECHO) or a choice of either TDF/FTC or AZT/3TC or ABC/3TC (THRIVE). The pharmacokinetics of TMC278 were best described by a two-compartment disposition model in which absorption was characterised by a lag time followed by a sequential zero- and first-order process. Individual values for TMC278 trough plasma concentrations (C_{trough}) and area under the plasma concentration-time profile over the dosing interval (AUC_{24h}) were estimated from sparse pharmacokinetic sampling in 679 patients in the TMC278 treatment group (8 samples/48 weeks/patient) using the population pharmacokinetic model. In addition, the potential relationship between selected covariates and the TMC278 apparent oral clearance was evaluated.
Results: There were no differences in the pharmacokinetics of TMC278 between the two trials. The mean (SD) TMC278 C_{trough} and AUC_{24h} for the pooled trials were 80.0 (36.5) ng/mL and 2397 (1032) ng*h/mL, respectively. The apparent oral clearance of TMC278 was estimated to be 11.8 L/h (inter-individual variability 39%) and the apparent volume of the central compartment was estimated to be 152 L (inter-individual variability 117%). The exposure to TMC278 was not influenced by N(t)RTI background medication, age, bodyweight, BMI, estimated glomerular filtration rate and hepatitis B and/or C co-infection status. Gender and race had a statistically significant effect on the TMC278 apparent oral clearance, resulting in a slightly lower apparent oral clearance (and thus higher AUC_{24h}) in females (13.6% lower clearance), and in Asian patients (17.2% lower clearance). These small effects had little impact on the overall inter-individual variability in apparent oral clearance and are considered not to be of clinical relevance.
Conclusions: A population pharmacokinetic model was developed, describing the pharmacokinetics of TMC278 in ARV-naïve, HIV-1-infected adults receiving TMC278 25 mg q.d. No covariates with a clinically relevant effect on exposure to TMC278 were identified.

Reference

1. Cohen C, Molina JM, Cahn P, *et al*: Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised, Phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected patients. *18th International AIDS Conference, Vienna, Austria* 2010, Abstract THLBB206.

P187

Herb-drug interaction between Echinacea purpurea and darunavir/ritonavir in HIV-infected patients

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Purpose of the study: To investigate the potential of a commonly used botanical supplement, Echinacea purpurea, to interact with the boosted protease inhibitor darunavir/ritonavir.
Methods: Open-label, fixed-sequence study in 15 HIV-infected patients receiving antiretroviral therapy including darunavir/ritonavir (600/100 mg twice daily) for at least 4 weeks. Echinacea purpurea root extract-containing capsules were added to the antiretroviral treatment (500 mg every 6 hours) from days 1 to 14. Darunavir concentrations in plasma were determined by using HPLC immediately before and 1, 2, 4, 6, 8, 10 and 12 hours after a morning dose of darunavir/ritonavir on days 0 (darunavir/ritonavir) and 14 (darunavir/ritonavir + echinacea). Individual darunavir pharmacokinetic parameters were calculated by using non-compartmental analysis, and were compared between days 0 and 14 by using the geometric mean ratio (GMR) and its 95% confidence interval (95% CI).

Table 1 (abstract P187)

	DRV/r	DRV/r + Echinacea	GMR (95% CI)	p
Cτ (ng/mL)	2.1 (1.6-2.7)	1.7 (1.4-2.2)	0.84 (0.59-1.19)	0.311
AUCτ (ng.h/mL)	46.2 (39.0-54.7)	41.6 (35.1-49.2)	0.90 (0.71-1.14)	0.374
Cmax (ng/mL)	6.4 (5.5-7.4)	6.2 (5.3-7.25)	0.98 (0.79-1.21)	0.810

Results: Median (range) age was 49 (43-67) years, and body mass index was 24.2 (18.7-27.5) kg/m^2. Echinacea was well tolerated and all participants completed the study. Relative to administration of darunavir/ritonavir alone, its coadministration with Echinacea purpurea resulted in little change in darunavir pharmacokinetic parameters. Table 1
Conclusions: Coadministration of Echinacea purpurea with darunavir/ritonavir was safe and well tolerated in HIV-infected patients; data suggest that no dose adjustment for darunavir/ritonavir is necessary.

P188

Moringa oleifera supplementation by patients on antiretroviral therapy

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Purpose of the study: This survey determined the extent to which the herb Moringa oleifera commonly used for medicinal and nutritional purposes is being consumed among HIV positive patients.
Methods: The study was a cross-sectional survey carried out at Parirenyatwa Hospital Opportunistic Infections Clinic. A convenience sample of 263 HIV-infected adults was taken from the Zimbabwe National Antiretroviral Roll-out Program. Using a previously piloted researcher administered questionnaire; patients who reported to the clinic over six months were interviewed about their use of herbal medicines. The focus was on Moringa oleifera use, and included plant part, dosage, prescribers and the associated medical conditions.
Summary of results: Sixty-eight percent (68%) of the study participants consumed Moringa oleifera. Of these, 81% had already commenced antiretroviral drugs. Friends or relatives were the most common source of a recommendation for use of the herb (69%). Most (80%) consumed Moringa oleifera to boost the immune system. The leaf powder was mainly used, either alone (41%) or in combination with the root and/or bark (37%).
Conclusions: Moringa oleifera supplementation is common among HIV positive people. Because it is frequently prescribed by non-professionals and taken concomitantly with conventional medicine, it poses a potential risk for herb-drug interactions. Patient medication history taking should probe for herbal supplementation and appropriate counselling done. Further experimental investigations into its effect on drug metabolism and transport would be useful in improving the clinical outcome of HIV positive patients on HAART.

P189

The use of a darunavir/ritonavir once-daily regimen in two pregnant women

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Purpose of the study: Darunavir (DRV) is a second generation protease inhibitor (PI), first licensed for use in 2006. It is indicated for use in a treatment experienced population and is effective in vitro against both wild type and PI-resistant HIV. As a relatively new drug there is little published information on the pharmacokinetics of darunavir in pregnancy. Here we examine the pharmacokinetics of darunavir/ritonavir [DRV/r 800/100mg once daily (OD)] in two women, over the course of pregnancy and postpartum.
Methods: A prospective open labelled study was established to enrol HIV positive pregnant women on DRV/r as part of their routine maternity care. DRV plasma trough concentrations were determined in the first (T1) and/or second (T2) and/or third (T3) trimester using a validated HPLC-MS/MS methodology with a limit quantification of 16 ng/ml. Postpartum (PP) sampling was also performed.
Summary of results: To date two women have been recruited. Both were black African and initiated treatment prior to pregnancy. Each woman was virally suppressed (HIV RNA <50 cpm) throughout pregnancy and had CD4 cell counts >300 cells/mm^3 (range 341-470). Patient 1 had a TDM sample drawn in each trimester and at PP. DRV concentrations in T1 [3790ng/ml], T2 [1285ng/ml] and T3 [1773ng/ml] were considerably (27-75%) lower relative to concentrations at PP [5227ng/ml]. Patient 2 had TDM samples taken in T2 and PP only. Again a considerably lower (~72%) DRV concentration was noted at T2 compared with PP. In both cases, DRV concentrations in pregnancy and postpartum were above the accepted minimum effective concentration for wt virus (MEC; 550 ng/ml, based on in vitro studies).
Conclusions: In the two cases examined, DRV/r (800/100mg, OD) was effective at achieving adequate therapeutic drug levels (>550ng/ml) during pregnancy. However, reduced DRV plasma concentrations in the second/third trimesters, highlights the need for TDM in this population, and warrants further study of pregnancy-associated changes in DRV pharmacokinetics.

HIV-RELATED INFECTIONS, CO-INFECTIONS AND CANCER, ETC

P190

Treatment of chronic invasive fungal sinusitis with voriconazole in an HIV patient

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Purpose of the study: Chronic invasive fungal sinusitis is a rare condition, and the conventional treatment surgical debridement and systemic antifungal therapy such as amphotericin B. Recently, voriconazole has demonstrated superior efficacy in the treatment of invasive aspergillosis, compared to amphotericin B. However, its use in invasive fungal sinusitis in an HIV patient has not been reported.
Methods: We describe a case of chronic invasive fungal sinusitis in a patient with HIV infection successfully treated with surgical clearance and a prolonged course of oral voriconazole.
Summary of results: A 39 year old Malawian lady presented to the Ear, Nose and Throat (ENT) surgeons with recurrent nasal polyps and was noted to have proptosis in April 2009. She had had a previous polypectomy in 2007, which grew *Streptococcal pyogenes* and *Aspergillus flavus*. MRI sinuses in May 2009 demonstrated extensive soft tissue mass involving right maxillary, bilateral ethmoid and frontal sinuses, causing right axial proptosis. Dural enhancement suggested intracranial extension, and there was erosion into pituitary fossa posteriorly. Her only complaint was epiphora, with no visual disturbance. An HIV test was positive. Baseline CD4 count was 395 cells/cm^3, and viral load 103,469 copies/ml. She underwent endoscopic sinus surgery to debulk tissue from her sinuses. Grocott staining of biopsy specimen demonstrated presence of fungal hyphae, and tissue culture grew *Aspergillus flavus*. She was commenced on oral voriconazole 300mg b.d. Due to potential drug interactions with non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI), she was treated with tenofovir, emtricitabine and raltegravir. Follow-up MRI after 4 months of therapy showed marked

improvement with resolution of proptosis. She has been on voriconazole for 12 months with no progression.
Conclusions: Invasive fungal sinusitis has been rarely reported in HIV patients, but recent case reports in non-HIV immunocompromised patients have shown a favourable response to new triazoles. It has previously been associated with high mortality even with amphotericin therapy. There are important potential interactions with antiretroviral (ARV) drugs. The optimal duration of treatment for immunocompromised patients is unclear.

P191

Opportunistic infections (OIs) present in HIV-seropositive patients: a study

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Background: HIV doesn't kill directly but it weakens the body's ability to fight disease. Infections, which are rarely seen in those with normal immune systems, are deadly to those with HIV. People with HIV can get many infections (opportunistic infections or OIs). Many of these illnesses are very serious, and they need to be treated. Some can be prevented.
Purpose of the study: To study the spectrum of OIs occurring during HIV infection among seropositive patients.
Methods: BOSS & CIPCA, a charitable non-Govt. voluntary community based organization, having 475 doctors and 8900 blood donors as members working on HIV/AIDS since 1987 has conducted 3 years (from January 2006 to December 2009) retrospective controlled study on the spectrum of OIs occurring during HIV infection among 10,500 seropositive patients attending VCTC and 50 bedded community care center run by BOSS & CIPCA. Their medical records were retrieved and scrutinized and the following data were extracted:
(1) Age, sex, race, occupation and marital status.
(2) Clinical manifestations with bacterial, viral, fungal, protozoal and other relevant neoplasms.
(3) Laboratory surrogate markers — routine haemogram, routine biochemical analysis, bacteriological, fungal examinations and serology.
(4) Radiological studies including ultrasound and CT scan where applicable.
Summary of results: Out of the 10,500 seropositive patients only 3,703 have opportunistic infections. The most common bacterial infections were TB 38% (1407) (pulmonary and extra-pulmonary) and atypical pneumonia 12% (445) (streptococcal, staphylococcal, pneumoccocal and H. influenzae). In the protozoal group, malaria, helminthiasis and leishmaniasis 23% (852) were common. The common fungal infections were candidiasis, cryptococcosis and dermatophytosis 10% (370). Amongst the viral infections, Herpes zoster 8% (296) was most dominant followed by 9% (333) Hepatitis B and Herpes simplex infections
Conclusions: TB was confirmed the most prevalent OI in the country. Differential diagnosis of these opportunistic infections may be useful in the early diagnosis of HIV infections in the various health facilities in the country. The study also highlights the regular availability of effective drugs for the treatment of the OIs and its preventive measures.

P192

Immunological diagnosis of CMV infection in HIV-infected patients

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Background: The Quantiferon-CMV assay is a test for Cell Mediated Immune (CMI) responses to peptide antigens that simulate CMV proteins. Individuals infected with CMV usually have CD8+ lymphocytes in their blood that recognize these antigens. This recognition process involves the generation and secretion of the cytokine and interferon (IFN). The detection and subsequent quantification of IFN forms the basis of this test.
Purpose of the study: To evaluate the accuracy of Quantiferon-CMV assay in diagnosis of CMV infection in HIV positive patients and compare it with older ELISA method.
Methods: This is a prospective study on a group of 48 HIV infected patients that are in a constant supervision of the Regional HIV Centre Constanta, Romania. The patients were tested by Quantiferon-CMV assay and by CMV ELISA. In the study were included adults patients with known HIV infection and CD4 < 200 cells/mm^3, asymptomatic or with suggestive clinical manifestations: neurological (central or peripheral), ocular, gastrointestinal, pancreatic or hepatic symptoms. The patients with other associated opportunistic infections were excluded from the study.
Results: Sixteen women and 32 men were included in the study, with a mean age of 32.8 years (range between 20-62 years), of whom three were antiretroviral naive patients and 45 were multiple experienced. Of these, seven patients were asymptomatic, 41 had different clinical manifestations: pancreatitis (12), esophagitis (3), gastritis (2) colitis (6), liver involvement (9), cholecystitis (7), central and peripheral nervous system involvement (8) retinitis (4). IgM ELISA was negative in all cases, IgG ELISA was positive in 45 patients (95.5%) and Quantiferon-CMV assay was reactive in 38 cases (79.1%). All patients with CD4 < 50 cells/mm^3 with clinical manifestations showed both positive reactions (14 patients). The patients who were treated with gancyclovir for CMV retinitis showed positive ELISA IgG, but negative Quantiferon-CMV assay. The sensitivity of Quantiferon-CMV assay was 92.7%.
Conclusions: Quantiferon-CMV assay has increased sensitivity in the detection of CMV reactivation induced by severe immunodepression (92.7%). There is a strong correlation ($p < 0.01$) between severe immunodepression (CD4 < 50 cells/mm^3) and CMV reactivation detected by Quantiferon. This test is easy accessible and an efficient method of monitoring therapy with gancyclovir.

P193

Epidemiology of HIV-associated tuberculosis (TB) co-infection in Krasnoyarsk region, Russian Federation

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Background: Incidence of HIV-associated tuberculosis (TB) co-infection is increasing in Krasnoyarsk region as well as in RF. Total number of registered TB/HIV new cases has increased from 7 in 2000 to 170 in 2009. Mortality rate of patients with HIV/TB co-infection has increased: 2004-7 cases, 2008-40, 2009-48. On January 1st, 2010 we have 407 TB/HIV co-infected patients, which makes 6% from the HIV+ patients under supervision (n=6801) in our region.
Methods: A retrospective chart review was conducted on HIV-positive patients diagnosed with TB in 2009. All patients were HIV-positive and had confirmed diagnosis of mycobacterial tuberculosis, or clinically presumptive diagnosis of TB with response to anti-tuberculosis therapy.
Summary of results: A total of 170 HIV/TB co-infection patients were identified. The general characteristics of the patients are: male (75%), median age 28 years old [1;55] when HIV has been diagnosed and 33 years old [5;56] at the time of TB diagnosis. HIV was acquired vertically - 0,6%, sexually in 22% of the cases, and through intravenous drug injections - 74%. At the time of TB diagnosis, 70 (40%) had a CD4 count of less than 200. 23% had a baseline HIV viral load greater than 100,000 copies/ml, median VL were 338787 copies/ml. 9,4% of cases had a history of TB prior to HIV diagnosis. 14% had TB as the primary AIDS-defining event; 82 patients (48%) had pulmonary disease, 47 patients (28%) presented with extra-pulmonary disease and of these, 22 (13%) had disseminated disease. 28% cases had extra-pulmonary TB involvement and are related to lower CD4 count (median 189/uL vs. 388/μL, $p<0.001$), and mortality rate. 28 patients (16,5%) had multi-drug resistant TB. 16,5% patients received antiretroviral treatment (ARV) at the time of TB diagnosis. Anti-TB treatment was associated with ARV on 39% (6% PI and 33% NNRTI). Out of 170 HIV/TB patients 35 (21%) were died. Risk of death is related to severity of immunosuppression and TB diagnostic time (median CD4 count 353 in survivors vs 79 in dead, $p<0.001$). The chronic hepatitis C was found in 69% of patients with HIV/TB infections.

Conclusions: 1. HIV/TB co-infection has a high incidence rate due to delayed verification of TB infection, as a result the prognosis is poor; 2. Risk factors for such patients are low CD4 cell count and extra-pulmonary involvement; 3. The high prevalence of the chronic hepatitis C causes the hepatotoxicity increasing during ART and antitubercular therapy for patients with HIV/TB infections.

P194

A minority of tuberculosis cases occurring during HIV care is possibly preventable

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Background: It is often recommended to test patients presenting for HIV care for tuberculin skin test reactivity at the initial visit if they have a prior stay in tuberculosis-endemic areas.
Purpose of the Study: To assess whether incident cases of tuberculosis (tb) in our cohort could have been prevented by such testing and subsequent preventive treatment of patients with a positive skin test.
Setting: HIV clinic in northern Europe caring for about 1000 patients. During the observation time preventive treatment was only rarely prescribed.
Methods: File review of all tb cases occurring more than two months after presenting for HIV care during the ten years 2000-2009. Cases were classified as possibly preventable, probably non-preventable or non-preventable based on residence and travel history, strain typing by restriction fragment length polymorphism technique and/or skin test reactivity.
Results: 24 cases in 23 patients were identified. 9 (38%) were classified as possibly preventable, 3 (13%) as probably non-preventable and 12 (50%) as non-preventable.
Conclusion: A minority of tb cases occurring during HIV care is preventable by a policy of testing new patients from endemic areas and treating patients with positive skin tests.

P195

Generalized tuberculosis in HIV-infected patients with AIDS

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Purpose of the study: To estimate peculiarities of diagnosis and clinical course of generalized TB in HIV patients with AIDS who received treatment in TB Hospital #7, Moscow in 2006-2009.
Methods: 94 cases (47,9%) of generalized TB have been analyzed. Most of them are men (82,9%), the mean age of the patients being 31,2±7,02. The average period from HIV detection to TB diagnosis is 5,7±2,96 years.
Results: In 62 cases (66%) the clinical TB symptomatology developed quite fast, in 2,2±1,9 months on average. An acute beginning was seen in 32 cases (34%). 44 patients (46,8%) had both TB and other secondary diseases. The CD4 lymphocyte mean level was 91 cells/mm^3. M. tuberculosis was found in 52 cases (55,3%): in the sputum analyses of 26 patients (27,7%) and in 26 more analyses of other biological materials (such as exudates, urine, feces, liquor, bioptic and surgical material). Among 29 patients tested for TB drug resistance 13 (44,8%) proved to be multidrug-resistant TB cases. The chest X-ray examination showed intrathoracic lymphoadenopathy in 68,1% cases, interstitial dissemination in 29,7% cases and only 7,5% cases revealed disintegration of tissue. 77 patients (81,9%) underwent different surgical interventions for the purpose of diagnosis or treatment, namely: diagnostic laparoscopy (16 cases), curative laparotomy (22), mediastinoscopy with intrathoracic lymph node biopsy (4), pleura biopsy (9), debridement of a peripheral lymph node (17), pericardial microdrainage (6), pleural cavity drainage (2), orchectomy (1). While examining the received diagnostic material morphological markers of TB inflammation were found in 56 cases (59,6%). Among most often discovered extrapulmonary localizations are abdominal involvement (53,3%), nodal involvement (27,7%), meningoencephalitis (15,9%), pericarditis (15,9%). Involvement of more than 3 systems was diagnosed in 25 patients (26,6%). Specific TB treatment included 4 to 6 drugs, the follow-up period for complete treatment was 6 months. Treatment results: cured - 36 cases (38,3%), defaulters - 34 cases (36,1%), died - 24 cases (25,5%).
Conclusions: Thus, providing treatment and diagnosis to patients with multiple-localization TB is complicated and requires an interdisciplinary approach including different surgical methods of diagnosis and treatment. The CD4 lymphocyte level lower than 100 cells/mm^3 before treatment increases significantly the probability of an unfavorable outcome of generalized TB.

P196

Therapy of the patients with HIV/TB infection and dynamics of level 'naïve' CD4-lymphocytes

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Background: Increase of number of patients with HIV/TB and prevalence of the given pathology in structure of the reasons of death rate of HIV-infected patients.
Objective: Study of indicators of cellular immunity and their change in the course of therapy at patients with HIV/TB.
Methods: 106 patients were studied in 4 groups: 39 HIV/TB co-infected individuals (HIV+/TB+), 25 patients with HIV infection, 17 HIV-negative patients with active pulmonary TB (HIV-/TB+) and 25 healthy controls. Measures of T-cells and viral load were at baseline and after initiation of HAART and/or antitubercular therapy (4 and 12 weeks) for potential immune correlates of disease progression and prognosis. Definition immune indicators were spent by flow cytometry (BD Biosciences, USA).
Results: Before treatment: percent of CD4+CD45RA+ differs in investigated groups. The lowest values registered at patients of 1 and 2 groups (fig.1). For patients in the group 3, the deviation of the given indicator from control group was small. If HAART and antitubercular therapy were effective we registered increase level % CD4+CD45RA+ in all groups. Δ % CD4+CD45RA+ increased more slowly in patients of group 1. The same results turn out at research of absolute number CD4 +CD45RA+ in all groups.
Conclusions: Low-level % CD4+CD45RA+ in patients with HIV/TB and HIV infection is connected with the general decrease ÑD4-lymphocytes. After first months of efficient therapy of patients with HIV/TB, infringements in immune system still remained, which, probably, are caused by joining of opportunistic infections.

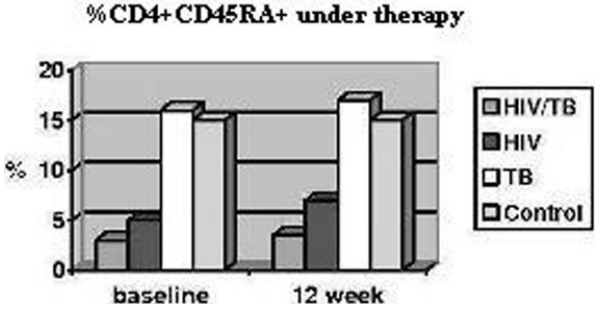

Figure 1 (abstract P196)

P197

Enfuvirtide in therapy at patients with HIV-infection and tuberculosis

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Background: The certain difficulties in a choice of HAART regime arise at presence at the patient with HIV-infection and tuberculosis. Enfuvirtide (ENF) not metabolized by enzymes of system cytochrome Ð450. It does not cooperate with NNRTI, PI and rifamycins and can be added to HAART regime if the patient to accept antimycobacterial drugs.
Purpose of the study: Comparison of efficiency and safety of HAART regimes with and without ENF in patients with HIV-infection and tuberculosis.
Methods: This research was not randomized and was lead in conditions of real clinical practice. 81 pts with HIV-infection and tuberculosis were divided on 2 groups: 1 gr. - 26 pt. with the standard regimes of HAART (2 NRTI + PI/r or NNRTI) and ENF; 2 gr. - 55 pts with the standard regimes of HAART. We determined clinical symptoms, CD4+ lymphocyte's count, viral load, haematological and biochemical parameters before, 4, 12 and 24 weeks therapy.
Summary of results: Within 24 weeks HAART the survival rate of patients of 1 gr. has made 96,2%, and 2nd - 89,1%. After 24 weeks HAART the share of pts with VL <500 copies/ml at pts 1 gr. was 81,8% and 2 gr. - 65% (OT- analysis, p <0,05) and 76% - 50% (ITT-analysis, p <0,05). After 24 weeks HAART the median of a gain of quantity CD4+ lymphocytes at pts of 1 gr. has made +110 cells, and 2 gr. - 69 cells (p <0,05). Safety of both regimes of HAART was quite good. Only 1 pt after 12 weeks of treatment has refused therapy with ENF because of local reactions.
Conclusions: Inclusion in regimes of HAART of ENF promoted increase in a share of pts with not determined HIV RNA level and to more essential growth of CD4+lymphocyte's count. Addition to standard regime of HAART of ENF essentially did not influence on the frequency of the clinical or laboratory adverse events caused by treatment.

P198

Sudden unexplained death in a patient with HIV and MDR-TB

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Purpose of the study: We report the case of a patient who presented with HIV and MDR-TB who died unexpectedly of presumed cardiac arrhythmia.
Methods: A 25 year old Lithuanian man was admitted with symptoms consistent with TB. He had cavitation on CXR consistent with TB. He was HIV+ve with a CD4 count of 16. His CMV titre was low positive. Standard TB treatment was commenced on day 4. He started efavirenz and Truvada on day 12. On Day 18, his TB proved to be multi-drug resistant; his anti-tuberculous therapy was changed to IV amikacin, moxifloxacin, prothionamide, ethambutol, and pyrazinamide. Cycloserine and linezolid were added on day 21. Efavirenz was changed to darunavir/boosted ritonavir due to psychiatric side effects at day 28, and clofazamine and valganciclovir were added on day 35. Fluconazole was added due to oral candidiasis at day 45. Clinically, he improved over the subsequent few days, and his CD 4 was 121 by day 41.
He was found dead unexpectedly on the ward on day 52, and the presumed cause of death was cardiac arrhythmia. He was on low molecular weight heparin and had been well during the week prior to his death. There was no clinical suspicion of cardiac disease. Observations were stable the day of his death and on day 50 he had Hb 80g/dl WCC 1.51(neuts 0.78) CRP 78 and K+3.2 which were improved or similar to baseline. No post mortem was performed.
Results: HIV is associated with cardiovascular complications, including ischaemic heart disease, cardiomyopathy and sudden death due to arrhythmia. It is also associated with high early mortality in MDR-TB. He was on moxifloxacin, ondansetron, ritonavir and fluconazole which are all known to prolong the QT interval. We suspect he had a fatal arrhythmia due to his medication, plus or minus HIV infection in combination with MDR-TB. Immune reconstitution is postulated to cause sudden death, but there was no evidence of cytokine storm in this case.
Conclusion: We now plan to perform regular ECGs on patients on long-term moxifoxacin and exercise caution in using multiple agents which prolong the QT interval.

P199

Hepatitis C virus (HCV) infection and re-infection among HCV- and HIV/HCV-infected injection drug users

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Background: The possibility of re-infection is often cited as a reason for not initiating treatment in injection drug users (IDUs). Recent observational data suggest that the rate of re-infection may be reduced following spontaneous or treatment-induced virologic clearance, although such data are often retrospective and incomplete.
Purpose of the study: With this in mind, we have undertaken a systematic, prospective study to evaluate the incidence of HCV viremia in IDUs at risk of new infection.
Methods: We identified a cohort of IDUs receiving care at the Pender Community Health Centre on Vancouver's Downtown East Side. Potential subjects were identified as either never having been infected with HCV (non-infected arm), having spontaneously cleared the virus (spontaneous arm), or having achieved a sustained virologic response on antiviral treatment (SVR arm). A questionnaire to identify demographics, health status, risk behavior and drug use was administered at baseline and every 6 months, along with blood tests to identify their HCV status.
Results: A total of 73 subjects met criteria for inclusion in the study: 20 in the non-infected, 30 in the spontaneous and 23 in the SVR arms respectively. Their mean age was 44.7, 17 were female, 9 were HIV-positive. There were no significant differences among the 3 groups with respect to age, ethnicity, source of income, unstable housing and being on opiate maintenance program. Over a mean follow-up period of 10.3 months, 20% of the non-infected group became viremic, as compared to 0% of the other two groups (p=0.04). Injecting drugs in past 30 days (p=0.05), heroin (p=0.015), amphetamines (p=0.05), and combined drugs use (p=0.001) were significantly higher in the non-infected arm compared to SVR arm. There were no significant differences in drug use and risk behavior between non-infected and spontaneous arms.
Conclusions: Our study shows that viremic HCV infection is more likely to occur in those who have never been previously infected, and that this susceptibility to infection cannot be completely explained by an increase in risk behavior, at least as compared to individuals who have cleared their viremia spontaneously. In addition, HIV co-infection is not a significant factor associated with recurrent HCV viremia. Whether a decreased rate of viremia following SVR relates to some host-related protective factors or is due to a change in IDU-related risk as a result of engagement in the health care system is currently under study.

P200

Increasing numbers of acute hepatitis C infections in HIV-infected MSM and high reinfection rates following SVR

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Objective: To analyze the characteristics and outcome of acute Hepatitis C and the risk of reinfection following SVR in HIV+ MSM.
Methods: Database analysis of the ICH cohort (n=4851), analysis restricted to MSM seen between 1/2002 and 6/2010. Acute HCV infection

was defined as a sudden rise in liver enzymes with a positive HCV PCR and/or a newly positive HCV serology (if negative before). The probability of reinfection was analyzed from primary diagnosis or end of HCV treatment until reinfection or last f/u (last blood sample).
Results: 99 episodes of acute Hepatitis C (aHCV) were identified in 88 MSM since 2002. Case numbers increased since 2006, with no association with ART treatment status, HIV viral load or CD4 count. 42% had GT1a/b, 1% GT 2, 17% GT3, and 26% GT4. SVR was achieved in 45 (74%) of those 61 patients observed for more than 6 months after diagnosis or the end of HCV therapy either spontaneously (n=13) or after treatment with pegIFN/RBV (n=32). Reinfections occurred in 10 of these cases (11%), 3x with the same GT, 7x with a different GT (1x 1->3, 4x 3->1, 1x 4->1, 1x 1->4); reinfection was observed after spontaneous clearance in 4 and after treatment-induced clearance in 6 cases. 1 patient exhibited spontaneous clearance of two GT1a reinfections and an initial GT3 infection. In those achieving SVR, the cumulative probability of becoming reinfected after primary diagnosis or the end of HCV therapy, respectively, was 45% within six years (Kaplan-Meier). Within the time-frame of the analysis, only three cases of aHCV were observed in our STD clinic population in HIV-negative MSM (all GT4).
Conclusions: Acute hepatitis C is an increasing problem in HIV+ MSM. The distribution of genotypes indicates an epidemic separate from the general population. Despite a high overall rate of spontaneous or treatment-induced SVR, patients are at high risk of reinfection with the same GT or others. These observations strongly support the EACS guidelines with regard to routine HCV testing and evaluation of LFT abnormalities. All HIV+ MSM, but especially subjects with previous aHCV should receive intensive and repeated counseling in order to reduce transmission risks.

P201

High prevalence of genotype G in HIV co-infected patients compared with HBV monoinfected patients in México

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Background: It has been reported in Mexico that genotypes H and G are the most common, although genotypes prevalence in HIV co-infected patients is unknown.
Purpose of the study: We estimated the prevalence and identified the resistance pattern of HBV/H and G genotypes in HIV co-infected patients and compared them in mono-infected HBV patients.
Methods: A cross-sectional prevalence and analytic study were realized. Risk factors, HIV or HCV co-infections, antiretroviral therapy (ART) experience, HBsAg, HBeAg, HBV viral load and mutations genetic analysis were collected; CD4+ cells count from HIV co-infected patients and HIV viral load were measured. We calculated the prevalence and exact 95% binomial confidence interval as well the Odds ratios (OR) and 95% confidence intervals to assess the relationship between risks factors and the risk of having HBV/H or G genotype.
Results: We enrolled 84 patients, 72 men and 12 women with 41 HIV co-infected patients. The distribution of HBV genotypes was: HBV/H 56 (66%), HBV/G 22 (26.1% [95% CI 17% to 36%]), HBV/F 4 (4.7%) and HBV/A 2 (2.3%). The most frequent mutations presented in 9 HIV co-infected patients and one mono-infected patient with ART experience were rtM204V and seven of them showed genotype G (7/9). Mono-infected HBV patients exposed more probability to HBV/H genotype than co-infected HIV patients OR 13.0 (CI 95% 3.40-49.79), P=0.0001 In contrast co-infected patients presented less possibility to have genotype H, 0.56 (CI 95% 0.42-0.75).
Conclusions: Our results suggest that HBV/G genotype predominates in co-infected patients. As well, rtM204V and rtL180M mutations are common in HBV/HIV co-infected patients with genotype G and ART experience.

P202

Acute hepatitis C in persons infected with the human immunodeficiency virus (HIV): the 'real-life setting' proves the concept

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Purpose of the study: The aim of this retrospective analysis was to review treatment decisions and outcomes in HIV positive patients with acute hepatitis C in a routine clinical setting. Outbreaks of acute HCV infection have been described in several cities recently. The epidemic affects mainly MSM who are coinfected with HIV and is supposedly linked to certain sexual risk practices. Here, we compared our findings with current knowledge and recommendations.
Methods: HIV-positive patients with the diagnosis of acute HCV infection were included in the retrospective analysis. The patients came from outpatient infectious disease centers in northern German cities. We looked at markers of HIV and HCV infection and compared patients who received treatment and those who did not. Treated patients were followed up to 72 weeks.
Summary of results: Three hundred nineteen HIV-positive patients with acute hepatitis C between 2001 and 2008 and were included in the analysis. All patients were male, 315 (99%) patients were of Caucasian origin, 296 (93%) declared homosexual contacts as a risk factor for HCV infection, intravenous drug use was declared in 3 (1%) cases. Median age at HCV diagnosis was 40 years (range 20-69 years). Median HCV viral load was 1.2 x 106 IU/mL. The HCV genotype distribution was as follows: 222 patients (70%) had genotype 1, 7 (2%) genotype 2, 26 (8%) genotype 3, 59 (18%) genotype 4. The median time of HIV infection was 5.5 years (range 0 to 22.4 years). Median HIV viral load was 110 copies/mL (range 25 to $10x10^6$ copies/mL). The median CD 4 count was 461 cells/mm^3 (range 55-1331 cells/mm^3). Two hundred and forty-six patients (77%) received anti-HCV treatment, and 175 (55%) had completed therapy by the time of the analysis. Median treatment duration was 33 weeks (IQR 24.1-49.9). 93 of the 175 treated patients (53%) reached a sustained virological response (SVR). Treatment duration was significantly higher in the SVR group (40.6 weeks vs 26.6 weeks, p<0.0001). Seventy-three patients (23%) did not receive anti-HCV treatment. In 19 of the untreated patients (26%) the hepatitis C virus was cleared spontaneously.
Conclusions: Our findings indicate that acute hepatitis C in HIV infected patients affects mainly MSM who acquire HCV sexually. Patients had a short duration of HIV infection and a stable immunological situation. In this real-life setting from urban regions in northern Germany, treatment rates appear to be high and effective.

P203

Correlates of hepatic stiffness by FibroScan© in a multicentric Italian cohort of HIV-infected patients

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Purpose of the study: The availability of FIBROSCAN© for non-invasive assessment of liver stiffness may be a valuable tool for investigating rates and correlates of liver fibrosis in HIV infected patients.
Methods: Consecutive HIV patients followed at 3 Italian Institutions, with or without coinfection with hepatitis viruses, were enrolled Jan to Jun, 2010. Transient Elastography (FibroScan©) was performed by 1 physician per site, blinded to patients' data. Only procedures with ≥10 successful

acquisitions and a success rate of ≥60% were evaluated. Elastographic results were expressed in KiloPascal (KPa, detection range 2.5 to 75).
Summary of results: We included 214 patients, 146 (68.2%) males, mean age 44.5±9.1y (r. 22-79). As to risk factors, 154 (72.0%) were infected through heterosexual (61.0%) or homosexual (10.0%) exposure, the remaining due to drug abuse (26.6%) or blood transfusion (1.4%). Patients coinfected with Hepatitis C (69) or HCV/HBV (3) were overall 72 (33.8%), alcohol abusers 53 (24.8%), patients with a BMI ≥30 13 (6.0%). CD4 T-cell counts at the time of FIBROSCAN© were 509±275 (r. 23-1648), 185 (86.4%) patients being on HAART. ALT were ≥2UNL in 103 (48.1%) patients, normal or near-normal in the remaining patients. Mean platelet counts were 216±73 x10^3 (r. 56-429). Mean KPa values were 8.2±9.6 (r. 2.7-73). Univariate analyses revealed that higher liver stiffness scores were significantly associated with male gender (p=0.01), age (p=0.0004), coinfection with Hepatitis C/B (p<0.0001), parenteral transmission of HIV (p=0.0009), lower platelet counts (p<0.0001). They were near significantly associated with alcohol abuse (p=0.06) and higher BMI (p=0.13), not with being on HAART (p=0.5) and normal ALT values (p=0.6). Multivariate linear regression analyses revealed that only coinfection with Hepatitis C and/or B Viruses was independently associated with higher stiffness scores, whereas all other variables were not confirmed.
Conclusions: Many variables have been reported as associated with increased liver stiffness in the HIV infected population. Our investigation reinforces that coinfection with hepatitis viruses plays an outstanding role in fostering liver fibrosis. Although considering other factors in HIV infected patients may be of value, curing hepatitis coinfections remains one major task to prevent end stage liver disease, even in a HIV population with a high prevalence of sexual transmission as ours.

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Role of HCV infection in the development of carotid atherosclerosis in a cohort of HIV-infected patients

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Background: HIV-infected patients have an increased risk of cardiovascular disease. Measurement of carotid artery intima-media-thickness (c-IMT) with colour-doppler-ultrasonography is a well-accepted, non-invasive method to assess carotid atherosclerosis.
Purpose of the study: To investigate whether HCV infection could be involved in the development of carotid atherosclerosis beside the well-known risk factors.
Patients and methods: In this cohort study, 322 consecutive HIV+ subjects were identified and enrolled between May 2009 and May 2010. A total of 153 patients were HIV/HCV co-infected, whereas 169 were HIV+ mono-infected; 237 patients were treated with highly active antiretroviral therapy (HAART), and 85 subjects were HAART-naïve. All patients underwent at least one c-IMT measurement by the same examiner; an IMT of >0.9 mm was considered pathological.
Results: Overall, 112/322 (35%) patients showed c-IMT >0.9. Table 1 shows the correlation between c-IMT and the following risk factors: age, cigarette smoking, intravenous drug use, CD4 cell count <200/mmc, CDC stage C of HIV infection, PI-based regimens and HCV co-infection. A significant statistical association between all considered factors and increased c-IMT was found. In particular, HCV co-infection showed a greater association in addition to older age, dyslipidemia, stage C of HIV infection.
Conclusions: In this cohort, several risk factors seem contribute to inflammatory damage and c-IMT development. Among them, HCV co-infection has been identified as a major determinant of carotid atherosclerosis. If the role of HCV infection will be confirmed in further studies, HIV-HCV co-infected patients should be strictly monitored for the vascular status.

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Do interleukin-28B single nucleotide polymorphisms influence the natural history of chronic hepatitis B?

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Background: Single nucleotide polymorphisms (SNPs) nearby the IL28B gene have been associated with spontaneous hepatitis C virus (HCV) clearance and response to interferon-based therapies in both HCV-monoinfected and HIV-HCV co-infected patients. However, little is known about the impact of IL28B SNPs on HBV natural history.
Methods: A case control study was performed in which cases were HIV+ patients with chronic hepatitis B (HBsAg+ for >6 months). All were genotyped for the rs12979860 SNP (protective CC genotype). One control for each case was chosen among HIV patients with anti-HBs and anti-HBc. Controls were matched for gender and coinfection with HCV.
Results: A total of 49 cases fit the inclusion criteria. Most were male (90%), with a median (IQR) age of 42.6 (39-46.7) years-old. Eighteen (36.7%) were or had been chronic infected by HCV. Among HBsAg+ patients, 19 (41.3%) were HBeAg+ and 13 (26.5%) were superinfected by the hepatitis delta virus (HDV). No differences were found in the distribution of CC genotypes when comparing patients with chronic hepatitis B and those who spontaneously cleared HBsAg (59.2% vs 44.9%, respectively; p=0.3).
Conclusions: There is no evidence for a beneficial role of the IL-28B CC genotype on the development of chronic hepatitis B in HIV-coinfected patients.

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No impact of IL28B polymorphisms on liver enzymes in patients coinfected with HIV and HCV

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Background: IL-28B single nucleotide polymorphisms (SNPs) strongly influence both spontaneous HCV clearance and response to peginterferon-

Table 1 (abstract P204)

	c-IMT<0.9		c-IMT> 0.9		
	n. 210	%	n. 112	%	p
age >40 years	121	57.6%	105	93.8%	<0.0001
cigarette smoking	42	20%	70	63%	0.03
IVDU	79	37.6%	56	50%	0.03
Cholesterolemia >200 mg/dL	50	23.8%	51	45.5%	0.0006
Triglyceridemia >170 mg/dL	58	27.6%	52	46.4%	0.0006
CDC Stage C	69	38.9%	68	60.7%	<0.0001
HAART - PI exposure	56	40.9%	81	59.1%	0.001
CD4 cell count <200/mmc	36	17.1%	36	32.1%	0.002
HCV co-infection	85	40.5%	68	60.7%	0.0005

ribavirin therapy. There is no information about the impact of IL28B SNPs on the natural history of HCV liver disease and/or the rate of elevated liver enzymes.
Methods: A cohort of HIV/HCV coinfected individuals with normal (<41 IU/L) or elevated (41 IU/L) ALT levels for >12 months were screened for the rs12979860 SNP at the IL-28B gene. The proportion of patients with the favorable (CC) or unfavorable (CT/TT) genotypes were compared in both groups.
Results: A total of 124 patients (44% normal ALT levels, median age 42 years, 68% males, 93% IDUs, 33% alcohol abuse, 5% HBsAg+, median CD4 count 511 cells/μL, median serum HCV-RNA 6.05 $\log_{10}$ copies/mL, 62% HCV genotype 1) were analyzed. Overall 34% of the whole population displayed the IL-28B CC genotype. When comparing ALT groups, 18 (32.7%) with normal ALT showed CC vs 25 (36.2%) with elevated ALT (p=0.71). Using elastometry (FibroScan), liver fibrosis estimates were significantly lower at baseline in patients with normal vs elevated ALT (6.3±2 vs 14.4±12 kPa, respectively, p<0.001). Other differences amongst groups were not significant, as follows: baseline serum HCV-RNA (5.95 vs 6.05 $\log_{10}$ IU/mL, p=0.62), CD4 counts (499 vs 543 cells/μl, p=0.34), and prothrombin activity (91% in both groups, p=0.99). Patients with normal vs elevated ALT were found to be coinfected more frequently with HCV genotypes 1 or 4 (45% vs 26%, p=0.02).
Conclusions: IL28B genotypes do not influence ALT levels in HIV-HCV coinfected patients. Higher ALT levels are associated with a greater extent of liver fibrosis.

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Effectiveness of pegylated interferon alfa plus HAART in HIV/HBV treatment-naïve coinfected patients

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Background: To our knowledge, the antiviral activity of pegylated interferon alfa plus HAART has not been studied in patients with human immunodeficiency virus type 1 (HIV-1) coinfected with chronic hepatitis B virus (HBV).
Objective: To evaluate the effectiveness of pegylated interferon alfa plus HAART in HIV/HBV treatment-naïve coinfected patients.
Methods: We performed a prospective cohort study in HIV/HBV treatment-naïve coinfected patients taking care at "La Raza" National Medical Center, Mexico City. Patients were treated with Efavirenz or Lopinavir-ritonavir, each with tenofovir/emtricitabine plus pegylated interferon alfa-2b (1.5 μg/kg/week) or pegylated interferon alfa-2a (180 μg/week) during 48 weeks. HBV genetic analysis was obtained. The study had a primary measure of effectiveness assessed at 24 and 48 weeks of treatment: suppression of HIV RNA to levels below 50 IU/ml. Secondary endpoints were increased in CD4+ cells count, HBV DNA to levels below 60 IU/ml, HBeAg seroconversion (defined by the loss of HBeAg and the presence of anti-HBe antibody) and HBsAg seroconversion (defined by the loss of HBsAg and the presence of anti-HBs antibody). Cumulative incidence with 95% confidence interval (95%CI) were calculated.
Results: We enrolled 18 subjects, 1 patient discontinued treatment because adverse events related to PEG-IFN. The mean (± SD) age was 30.3 ± 6.9 years old, all patients were men. The median (interquartile range) basal CD4+ cells count was 112 (61 to 300), RNA HIV 163,000 copies/ml (9,545 to 636,500 copies/ml), DNA HBV 20,200,000 IU/ml (627,500 to 480,500,000 IU/ml). All patients had positive HBeAg and were negative to HDV serology. HBV genotype distribution was H 9 (52%), G 6 (35%), A 1 (6%) and F 1 (6%). Primary endpoint (RNA HIV < 50 copies/ml) was present in 100% of our patient at 24 and 48 weeks; the median increased in CD4+ cells count was 231 cells/ml at 24 weeks and 322 cells/ml at 48 weeks; cumulative incidence of secondary endpoints were: DNA HBV < 60 UI/ml was present in 8 patients [47% CI95% 26-69%)] at 24 weeks and 17 patients (100 %) at 48 weeks; HBeAg seroconversion was in 8 patients [47% CI95% 26-69%)] at 24 weeks and 16 patients [94% CI95% 73-98%)] at 48 weeks, HBsAg seroconversion was in 0 patients (0%) at 24 weeks and 6 patients [35% CI95% 17-58%)] at 48 weeks.
Conclusions: Pegylated interferon alfa plus HAART were well tolerated and exhibited high viral effectiveness in HIV/HBV treatment-naïve coinfected patients.

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Sustained virological response in HIV/HCV co-infected patients without rapid virological response (RVR) on peginterferon-ribavirin therapy

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Background: Undetectable HCV-RNA at week 4 of therapy (RVR) is one of the best predictors of SVR in patients with chronic hepatitis C. However, there is scarce information about the variables influencing the achievement of SVR in patients without RVR.
Methods: A prospective study in which HIV-HCV coinfected patients were randomized to receive either pegylated IFNα-2a 180 μg/week plus ribavirin (RBV) at two different doses: i) 1000-1200 mg/day (arm A) or ii) 2000 mg/day plus erythropoietin (EPO) from baseline to week 4 (arm B), was conducted. Patients not achieving RVR prolonged therapy to 48 weeks for G2-3 and to 72 for G1-4. Liver fibrosis was measured using transient elastometry, being liver stiffness values ≥9.5 kPa as reflect of Metavir ≥F3. RBV trough concentrations at week 4 and pharmacogenetic studies including polymorphisms at the ITPA, ENT1 and IL28B genes were also performed. Variables associated to SVR in those not achieving RVR were examined.
Results: A total of 108 patients had reached the end of follow-up at the time the analysis (82% males; mean age, 43 years; mean baseline HCV-RNA, 6.4 log IU/mL; 91% HCV G1-4; 50% METAVIR ≥F3 estimates; mean CD4 count, 566 cells/μL; 93% on HAART and 84% with plasma HIV-RNA <50 copies/mL). In the on-treatment analysis 33% achieved SVR (31% vs 60% for G1-4 and G2-3; p<0.05; 42% vs 23% for patients with Hb drop at week 4 ≥2 vs <2 g/dL; p=0.04; 26% vs 43% for ≥F3 vs <F3; p=0.12; 57% vs 14% for patients with undetectable vs detectable HCV-RNA at week 12; p<0.001; 59% vs 18% for patients completing vs non-completing treatment prolongation; p<0.001). No differences in SVR rates were found comparing arms A vs B. Mean baseline HCV-RNA in patients with vs without SVR were 6.2 vs 6.5 log IU/mL, respectively [p=0.02]. The SVR rate was 57% vs 25% in IL28B CC vs CT/TT carriers [p=0.04]. No significant differences were found for other genetic polymorphisms examined. In the multivariate analysis (OR [95% CI], p) undetectable HCV-RNA at week 12 (5 [2-14], 0.001) and completing treatment prolongation (4 [1.5-12], 0.005) were the only independent predictors of SVR. IL28B CC was not included in the final analysis as it was only available for 42 patients.
Conclusions: Optimizing duration of HCV therapy (48 weeks for G2-3 and 72 weeks for G1-4) in HIV/HCV co-infected patients without RVR can clearly improve the SVR rate. Moreover, achievement of undetectable HCV-RNA at week 12 is a strong predictor of SVR in this population.

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Efficacy and safety of therapy of chronic hepatitis B with telbivudine (LdT) in patients with HIV-infection without HAART

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Introduction: According to the European recommendations (version 5.2., November 2009) at patients with the HIV-infection and chronic hepatitis B

(CHB), not receiving HAART, adefovir and LdT may be used as an alternative regime. In the Russian Federation adefovir is not registered and tenofovir was registered only in March 2010.
Objective: To study efficacy and safety Ltd at patients with HIV-infection and CHB (HIV/CHB).
Methods: 12 patients with HIV/CHB (men 10), middle age of 33,5 years, without HAART (CD4 + - 450-650 cells/mm^3), since 2009 received LdT (600 mg QD). All patients had HBsAg, HBV DNA. 9 from 12 patients had HBeAg. Duration of treatment has made 3-12 months.
Summary of results: At all patients had the positive result of therapy with LdT: 7 patients had disappearance of HBV DNA in 1-6 months; at 1 patient after 3 months of therapy observed disappearance of HBsAg and appearance anti-HBs and Ltd has been cancelled. At 5 patients through 6-9 months of treatment is marked a decreasing of level of HBV DNA on 2-3 log IU/ml. At 4 from 9 patients with HBeAg observed seroconversion to anti-HBe. In absence HAART registered fluctuations of level of HIV RNA was not statistically significant. The adverse events of therapy with Ltd have not been registered.
Conclusions: Therapy of CHB with Ltd at patients with HIV-infection was effective: at 58,3 % of patients had disappearance of HBV DNA, and at 4 from 9 patients with HBeAg observed seroconversion. Influence of therapy with Ltd on dynamics of HIV RNA it wasn't revealed.

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Efficacy and safety of TMC278 in treatment-naïve, HIV-1-infected patients with HBV/HCV co-infection enrolled in the phase III ECHO and THRIVE trials

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Introduction: TMC278 had a high virologic response rate, non-inferior to EFV, in two Phase III double-blind trials ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725) in treatment-naïve HIV-infected adult patients. As the use of NNRTIs, particularly nevirapine, has been associated with hepatic-related adverse events (AEs), especially in HIV/hepatitis B (HBV) and/or hepatitis C (HCV) co-infected patients, a subgroup analysis of these events was performed on the pooled Week 48 Phase III data.
Methods: Patients (N=1368) with alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 5x upper limit of normal received TMC278 25mg qd or EFV 600mg qd, plus TDF/FTC (ECHO) or TDF/FTC, AZT/3TC or ABC/3TC (THRIVE). HIV/HBV and/or HCV co-infection status was determined at baseline in 1335 patients by HBV surface antigen, HCV antibody and RNA testing.
Results: At baseline, 112/1335 patients (8.4%) had evidence of HIV/HBV and/or HCV co-infection (randomised to TMC278, n=49: 7.3%; EFV, n=63: 9.5%). Table 1 summarises the outcomes.
Compared with HIV mono-infected patients, co-infected patients had more hepatic AEs (clinical and laboratory) and lower virologic responses, which were similar across treatment groups. Hepatic AEs rarely led to treatment discontinuation (TMC278: n=3 vs. EFV: n=9 patients). There were no fatal hepatic AEs.
Conclusions: Overall, both TMC278 and EFV were well tolerated with no hepatic safety differences observed. Hepatic AEs were more common in co-infected than in HIV mono-infected patients (27% vs. 4%, respectively), but there were no differences between the two treatment groups. Virologic responses were similar for TMC278 and EFV within the co-infected and HIV mono-infected groups, and lower in co-infected than in HIV mono-infected patients.

Table 1 (abstract P210)

	HIV/HBV and/or HCV co-infected patients		*HIV mono-infected patients*	
	TMC278 25mg qd	EFV 600mg qd	TMC278 25mg qd	EFV 600mg qd
*Efficacy (Week 48 outcomes)**	N=49	N=63	N=621	N=602
% (95% CI) with viral load <50 copies/mL, ITT-TLOVR	73.5 (60.7-86.3)	79.4 (69.1-89.6)	85.0 (82.2-87.8)	82.6 (79.5-85.6)
Mean CD4 count (95% CI)	N=48	N=63	N=621	N=602
Baseline, cells/mm^3	230 (198-263)	246 (216-276)	262 (251-273)	274 (262-285)
Change from baseline, NC=F†, cells/mm^3	+137 (100-175)	+192 (147-238)	+197 (186-209)	+173 (161-185)
Change from baseline, NC=F†, %	+6.6 (5.0-8.3)	+7.7 (6.4-9.0)	+8.6 (8.1-9.0)	+8.4 (7.9-8.8)
Safety‡, §				
Treatment-emergent hepatic AEs of interest, n (%)	N=54	N=66	N=632	N=616
Any hepatic AE	15 (27.8)	17 (25.8)	23 (3.6)	28 (4.5)
Hepatobiliary disorders[Â¶]	3 (5.6)	7 (10.6)	6 (0.9)	9 (1.5)
HBV or HCV reported as an AE	3 (5.6)	5 (7.6)	-	-
Hepatic laboratory abnormalities reported as an AE	9 (16.7)	8 (12.1)	19 (3.0)	21 (3.4)
Grade 3 to 4 hepatic laboratory abnormalities, n (%)	N=54	N=66	N=631	N=604
ALT increased	9 (16.7)	11 (16.7)	1 (0.2)	12 (2.0)
AST increased	7 (13.0)	5 (7.6)	7 (1.1)	14 (2.3)
Hyperbilirubinaemia	0	0	4 (0.6)	1 (0.2)

ITT-TLOVR = intent-to-treat-time-to-loss of virologic response; CI=confidence interval; *Patients included in efficacy analysis were those with baseline HBV/HCV assessments; †NC=F = non completer = failure: missing values after discontinuation imputed with change = 0; Last observation carried forward otherwise; ‡Safety analyses performed using all available data, including beyond Week 48; §Patients who seroconverted for HBV/HCV during the study were included in the subgroup of HIV/HBV and/or HCV co-infected patients; Â¶Selection of preferred terms from System Organ Class as defined by MedDRA. Compared with HIV mono-infected patients, co-infected patients had more hepatic AEs (clinical and laboratory) and lower virologic responses, which were similar across treatment groups. Hepatic AEs rarely led to treatment discontinuation (TMC278: n=3 vs. EFV: n=9 patients). There were no fatal hepatic AEs.

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Response to treatment of hepatitis C in HCV/HIV co-infected patients is not influenced by either abacavir or tenofovir with weight-based ribavirin

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Background: Approximately 30% of HIV-infected patients are co-infected with hepatitis C (HCV). The current treatment standard of care for HCV, pegylated interferon and ribavirin (RBV), has demonstrated a sustained virologic response (SVR) in less than 50% of HCV/HIV co-infected patients, and only 17-35% in HCV genotype 1 patients. It has been previously shown that using a weight-based RBV dose results in favorable SVR rates. Prior studies suggest that HCV/HIV co-infected patients receiving a HAART regimen that included tenofovir (TDF) had higher SVR rates than those who received abacavir (ABC) in their nucleos(t)ide analogue (N(t)RTI) backbone.
Purpose of the study: At our specialty clinic for the treatment of HCV/HIV co-infected patients, we re-examined the efficacy of HCV treatment in patients receiving either agent in their regimen with weight-based ribavirin doses.
Methods: Patients with HIV/HCV co-infection (HCV genotype 1) met with a multidisciplinary team before therapy initiation for education and teaching. HCV treatment consisted of weekly injections of 180 mcg pegylated interferon subcutaneously and weight-based dosing of RBV (13mg/kg/day to maximum of 1200 mg/day). Treatment duration was 48 weeks with longer treatment in slow responders; side effects and adverse events were treated promptly. The HAART regimen consisted of a N(t)RTI backbone with either ABC or TDF and a protease inhibitor or non-NRTI. We retrospectively compared SVR rates in patients being treated with either ABC or TDF.
Results: Thirty-four patients met the inclusion criteria. In an ITT analysis, 20 of 34 (59%) patients receiving HAART demonstrated SVR with no significant differences between races (p=0.31). Among those twenty HAART patients with SVR, 9 patients were being treated with ABC and 11 were being treated with TDF (p=0.13). The length of treatment between ABC and TDF treated groups did not differ significantly (49.6 and 49.5 weeks, p=0.001). No significant difference in SVR rates was shown between the two groups.
Conclusions: The rate of SVR in patients with HIV/HCV genotype 1 dosed with weight-based RBV was significantly higher than generally reported. There was no difference in SVR rates in HIV/HCV co-infected patients receiving ABC or TDF in their HAART regimen with weight-based RBV. These results may give providers flexibility in their selection of N(t)RTI backbone while receiving treatment for HCV.

P212

Efficiency of HIV-1 PR-RT genotyping is not impacted by co-infection with HCV

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Background: Assays that are used for the diagnosis and management of HIV-1 infection are subject to assay interference(s) and co-infection with HCV may interfere with HIV-1 genotyping and/or phenotyping. Since a third of HIV-1 infected patients are frequently HCV co-infected, there is an increasing need to assess the effect of HCV co-infection on the accuracy of the HIV-1 protease (PR) and reverse transcriptase (RT) genotyping.
Purpose of the study: As a result, the efficiency and accuracy of Virco's HIV-1 PR-RT assay performance [1] was tested on a panel of HIV/HCV co-infected, clinical trial samples.
Materials and methods: A panel of confirmed 60 HIV/HCV-positive (Hep C antibody +), plasma samples (screening visit), that were collected as part of a HIV-1 clinical trial was PR-RT genotyped (virco®TYPE HIV 1; 1497 bp encoding 1-99 amino acids of PR and 1-400 amino acids of RT), phenotyped (Antivirogram®) and the Clade was determined. In addition, HCV subtyping was performed using NS5B sequence-based subtyping [2] along with NS3/4A genotyping [3] in all of the tested samples. All the 60 samples tested had externally determined plasma HIV viral loads that were >1000 copies/mL.
Results: For the 60 HIV/HCV + samples tested, the HIV PR-RT target genes were successfully (100%) genotyped, phenotyped and were confirmed to be Clade B. Subtyping (329 bp conserved fragment within NS5B) and genotyping (NS3/4A gene) of the HCV target genes was successful for 49/60 samples (81.6%) and 33 samples were identified as Genotype 1a, 10 samples as 1b, 5 samples as 2b and 1 as genotype 4a.
Conclusions: We demonstrated that there is no assay interference for HIV-1 genotyping/phenotyping in the presence of an active HCV co-infection. The HIV-1 PR-RT primers used within our certified, high-throughput laboratory is highly sensitive, specific, accurate and reliable to detect HIV-1 clade, genotype and phenotype in HIV/HCV co-infected samples.

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Relationship between dynamics of Epstein-Barr virus and immune activation in HIV-1 infected subjects in the HAART era

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Purpose of the study: HAART has greatly modified the course of HIV-1 infection; however, its impact seems to be less favourable on lymphoproliferative disorders associated with Epstein-Barr virus (EBV) than on other AIDS-defining illnesses. The aim of this study was to estimate the relationship between EBV levels and other viro-immunological parameters in HIV-1 infected subjects in the HAART era.
Patients and methods: 164 HIV-1 infected patients (pts) who attended the Infectious Diseases Unit of Rovigo Hospital, from July 2007 to December 2009 were included in this study. 28% of patients had HBV and/or HCV coinfections. HIV-1 RNA in plasma was quantified by COBAS Taqman HIV-1 test. HIV-1 DNA and EBV-DNA in peripheral blood mononuclear cells (PBMC) were determined by real-time PCR. Lipopolysaccharide (LPS), a marker of microbial translocation, was determined in plasma samples using a chromogenic assay (Limolus Amebocyte Lysate). B-cell activation was analyzed by flow cytometry using monoclonal antibodies CD19PerCP, CD86APC, and CD69PE.
Results: The median (IQR) EBV-DNA load was 41(1-151) copies/105 PBMC. 48% of pts had CD4 >500 cells/μl and 27% had undetectable HIV viral load. The EBV-DNA level was significantly higher in pts with CD4 below 500 cells/μl than in those with CD4 >500cells/μl [72(14-324) vs 18 (1-80) copies/105; p<0.0001] and in pts with detectable HIV-1 RNA than in those with undetectable viremia [49(7-315) vs 17(1-55) copies/105; p=0.001]. Levels of EBV-DNA were higher in the group of pts with CD4 cell counts >500 cells/μl and high HIV-1 viremia (>1000 copies/ml) than in pts with low viremia, regardless of the immunological status [48(5-153) vs 18(1-60); p=0.015). EBV-DNA was also significantly higher in pts with coinfections than in pts with no coinfections [85(10-527) vs 33(1-114); p=0.003]. Furthermore, pts with high EBV loads (up to 75th percentile) had higher levels of HIV-1 DNA [40(1-132) vs 10(1-76) HIV-DNA copies/105; p=0.050) and higher levels of LPS [130(88-244) vs 98(81-134) pg/ml; p=0.024) than pts with low EBV loads. B-cell activation in pts with high EBV loads was confirmed by immunophenotyping; two of these pts developed a B-cell lymphoma.
Conclusions: These findings suggest that HIV-1viremia, other coinfections, and immune activation play an important role in the B-cell stimulation and expansion of EBV-infected cells. Persistent HIV-1 viremia, despite immunereconstitution, may represent a risk factor for the onset of EBV-related cancers.

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Abstract withdrawn

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Detrimental clinical interaction between ritonavir-boosted protease inhibitors and vinblastin in HIV-infected patients with Hodgkin lymphoma

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Background: Pharmacokinetic interaction between Vinca alkaloids and antiretrovirals has been widely demonstrated, even though its clinical relevance is still debated. The incidence of Hodgkin's lymphoma appears to be rising in HIV-infected people, and vinblastine - containing chemotherapy regimens are widely recommended in these pts.
Purpose of the study: To evaluate the clinical interaction between HAART regimens and vinblastine in HIV-infected patients with HL.
Methods: Clinical charts of all HIV-infected patients followed at our center with a diagnosis of HL were reviewed. Differences in group proportions were assessed using 2 test. One way ANOVA test was used was to test for differences among independent groups. Potential risk factors for WHO III-IV neutropenia were analysed by step forward logistic regression analysis. The Hosmer and Lemeshow goodness-of-fit test was used to assess model fit. Statistical analysis was performed using the software program Intercooled Stata .
Summary of results: From June 2002 to July 2009 sixteen patients with HL were concomitantly treated with vinblastine-containing regimens (ABVD or Stanford V) and HAART, supported by G-CSF administration. (M/F: 11/5; median CD4 cell count: 189/µl , IQR 15-459; median HIV-RNA 5.8 log10 copies/ml, IQR 2.9-6.9 ; bone marrow was involved in 50% of cases. 43% of pts were in HL stage IV. 5 out of 16 pts were on PI/r, 2 on unboosted-PI, 7 on NNRTI (6 EFV and 1 NVP) and 2 on raltegravir. Mean nadir neutrophil count (+SD) for all cycles of PCT on the same HAART regimens were 0.218+0.343x10^6/L for patients taking regimens containing PI/r, 0.375+0.078x 10^6/L in patients taking PI-unboosted and 1.560+715 x10^6/L in patients on non PI-based regimens (P<0.001). After controlling for CD4 cell count < 200/µl, use of zidovudine and bone marrow involvement, the use of PIs were more likely to be associated with severe grade III-IV neutropenia (OR, 34.3, 95%CI 1.9-602.4; P = 0.02; McFadden R2:0.50). The mean nadir neutrophils count was 1.350x10^6/L (+SD 0.800) in patients not taking RTV, 0.850x10^6/L (+SD 0.091) in patients taking 100 mg of RTV, and 0.047x106/L(+SD 0.050) in those taking 200 mg of RTV as boosting, respectively.
Conclusions: The concomitant administration of vinblastine-containing chemotherapy regimens with PIs can lead to higher levels of neutropenia and in this set of patients HAART regimens containing different classes of drugs (NNRTI, integrase inhibitors) are more advisable.

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Cancer chemotherapy: early experience with combined chemotherapy for HIV-infected Kaposi's sarcoma patients at Lighthouse clinic, Lilongwe, Malawi

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Background: Kaposi's sarcoma(KS) is the most common AIDS related malignancy in Malawi. National guidelines recommend chemotherapy with vincristine, along with antiretroviral treatment (ART). Effectiveness of vincristine monotherapy is limited, is considered palliative and interrupted supply contributes to poor outcomes of KS patients. Lighthouse, a major provider of HIV related services, started 38 patients on ART due to KS in quarter 1, 2010 and overall, 1195 patients ever started ART due to KS.
Purpose of the study: To improve KS patient care,we introduced a combined treatment with vincristine(V), bleomycin(B) and doxorubicin(D), supplied by the central hospital pharmacy, developed standardized monitoring forms and trained providers in KS management.
Methods: Clinicians stage KS patients' tumor severity (T0-good risk, T1-poor risk)and presence of systemic illness (SO-good risk, S1-poor risk) using a standardized clinical assessment form and record information about prior chemotherapy and ART. The form guides clinical decisions on regimen selection and accurate dosage. From initiation of chemotherapy, clinical officers examine patients and record lesion size at each subsequent visit. Nurses administer the treatment. Doses vary depending on clinical findings and body surface area. A specialist physician reviews patients with side effects.
Results: Between 2nd June and 30th July 2010, 48 adult KS patients (35men) all of them with a prior history of vincristine monotherapy, started combined chemotherapy: 30(62%) received BV and 18(38%) received DBV. No patient developed side effects so far, and all of them are alive. Forty-six (96%) patients were already on ART at the time of chemotherapy initiation. 44 on d4T/3TC/NVP, one on d4T/3TC/EFV and one on AZT/3TC/TDF/LOP/r. All patients had severe KS manifestations (T1) with skin edema, pulmonary or gastrointestinal involvement, but only 5(10%) had systemic illnesses (S1), such as pneumonia, pulmonary TB or malaria requiring stabilization and co medication prior to chemotherapy. Bleomycin and vincristine were not available for 1 week.
Conclusions: Combination chemotherapy for KS patients appears to be feasible in a resource poor public health clinic setting and may be helpful to improve outcomes of patients non responsive to standard vincristine monotherapy and ART. Ensuring a continuous supply of all chemotherapy agents is a priority.

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Trends in human papillomavirus (HPV) infection among HIV-positive women in the pre-HAART and HAART era in a Nigerian clinic

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Background: The prevalence of HIV infection has been on the increase in Nigeria in recent times. HIV-positive patients frequently have anogenital malignancies due to HPV. HAART was introduced in Anti-retroviral (ARV) centers in Nigeria in the year 2002.
Purpose of the study: To determine trends in incidence of anogenital malignancies among HIV-positive women undergoing treatment in the clinic in the pre-HAART and HAART era.
Methods: A retrospective review of 541 case notes of HIV-positive female patients from January 1999 to December 2004 were analyzed by utilizing an on-going observational database at the ARV center. Rate ratios, comparing incidence rates (number of malignancies per 1000 person years) were calculated.
Results: Twenty-four (4.43%) of the patients had one form of anogenital manifestation of HPV or the other. The incidence rate for HPV rose from 2.28 in the pre-HAART era to 6.40 in the HAART era (Rate ratio = 3.15; 95% confidence interval (CI) =1.31 - 7.44; p= 0.0002).
Conclusions: There has been a significant rise in the incidence of HPV since the introduction of HAART. This may be due to the longer survival of HIV-infected patients, surpassing the latency period for the anogenital malignancies. Care providers should be more vigilant for HIV-associated malignancies as patients live longer in this part of the world.

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Review of HIV testing at a district general hospital in an area of high HIV prevalence following the introduction of new national guidelines

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UK national HIV testing guidelines were released in September 2008 and disseminated in our trust through emails to consultants and a grand round presentation. These aimed to promote patient HIV testing by all clinicians regardless of specialty and to trigger testing when specific indicator diseases were diagnosed. The guidelines also state that testing should be considered in all general medical admissions in areas where HIV prevalence exceeds 2 in 1000 of the population. Our audit looked at HIV testing at Blackpool Victoria Hospital (which is located in a region of high HIV prevalence) from October 2007 to September 2009. This represents 1 year before and 1 year after the publication of the new guidelines.
We used our laboratory database to identify proven cases of common diseases where HIV testing is indicated. We then cross referenced this against records of HIV tests performed. We also took the total number of HIV tests requested from the medical wards and compared this to the number of acute medical admissions. We found that in the year after guidelines were published and disseminated within the trust the rate of HIV testing for indicator diseases was as followed:- hepatitis B 6%, hepatitis C 28%, tuberculosis 9%, lymphoma 14%. In the case of hepatitis this represented a decrease on previous years. The overall rate of HIV testing in acute medical admissions was 0.5%.
Our results demonstrate that in our trust traditional methods of guideline dissemination did not lead to effective implementation on this occasion. We are now assessing alternative methods such as marking all positive laboratory results for indicator diseases with the phrase 'HIV TESTING SHOULD BE CONSIDERED' and the possible implementation of universal opt out screening in our Clinical Decisions Unit for all acute general medical admissions.

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HIV testing in non-traditional settings: feasibility and acceptability in an acute admissions unit

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Purpose of the study: National guidelines recommend the routine offer of an HIV test to all acute medical admissions when the local diagnosed HIV prevalence exceeds 0.2%. We investigated the feasibility and acceptability, to staff and patients, of routinely offering HIV tests in an acute admissions unit (AAU).
Methods: Patients aged 16-65 admitted to the AAU over three months were identified using the electronic patient record. A researcher offered patients an HIV test, usually run on serum already collected. Questionnaires gathered attitudinal data from staff and a subset of patients.
Summary of results: Of 1388 age-eligible patients admitted, 716 (52%) were approached. 163 (23%) were clinically ineligible to test. Of the 552 patients offered an HIV test, 383 accepted (Uptake: 69%). Four patients were newly diagnosed as HIV positive (1.04% [95%CI: 0.29 — 2.66%]) and all were transferred to care. A further two individuals were diagnosed via contact tracing. Uptake was not shown to differ significantly by age, sex or sexuality, but did differ by ethnicity (p=0.04). There was agreement among the questionnaire respondents (107 patients, 43 staff) that HIV tests should routinely be offered to everyone (97%) and in settings other than sexual health and antenatal clinics (87%). Acceptability of the test offer among AAU patients was high (92%). However, only 42% of staff reported they were happy to offer tests and 62% felt they needed more training.
Conclusions: The routine offer of an HIV test to patients on the acute admissions unit was concluded to be feasible, acceptable and successful in identifying previously undiagnosed individuals. Training of relevant staff is advised.

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Clinical profile of HIV/AIDS patients admitted to a tertiary outpatient clinic in Istanbul, Turkey

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Purpose of the study: The clinical course of HIV/AIDS and pattern of opportunistic infections vary from patient to patient and from country to country. Hence, we aimed to study clinical presentation of HIV/AIDS patients according to their first admission sequence to our outpatient clinic.
Methods: Between the term of January 2006 and May 2010, 156 HIV infected patients were admitted to our center. Clinical data about patients were collected retrospectively from standardized HIV/AIDS forms filled at the time of admission.
Results: Out of 156 patients, 73 (47%) were admitted with obvious clinical signs and symptoms, whereas 83 (53%) had no signs and symptoms, and they were diagnosed through screens or check-up tests. The most frequent clinical symptoms on first admission were mucocutaneous manifestations of HIV infection (13,5%), weight loss (8%), persistent generalized lymphadenopathy (4,5%), pulmonary tuberculosis (4%), malignancies (4%), *Pneumocystis jirovecii* pneumoniae (2,5%) and chronic fever (2,5%). Screening tests were conducted most frequently during blood donations (12%), before surgeries (11,5%) and check-ups (7,7%). Among these cases 11,5% were diagnosed by volunteered HIV tests.
Conclusions: Turkey is among low prevalence countries in Europe for HIV/AIDS. Clinical profile of our patients is similar to the developed countries. More than half of the patients diagnosed through screens or check-up tests, which give satisfactory results at the early stages of the disease. Nevertheless, screening tests and encouragement of volunteered HIV tests for individuals within high risk groups may increase the number of early diagnosed cases and help to reduce the spreading of the virus.

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Aetiologies and factors associated with mortality among HIV-infected patients at Taraba State Specialist Hospital, Jalingo, Nigeria

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Background: Despite improved access to life-saving antiretroviral drugs, HIV associated mortality remains high in most settings in sub-Saharan Africa. Several studies have shown remarkable temporal distribution of these mortality figures, with a disproportionately higher number of patients dying within the first few months of commencing HAART.
Purpose of the study: To identify the aetiologies and factors associated with the deaths of HIV-infected persons enrolled into the HIV care program at our hospital.
Methods: The study setting is a 230- bed Hospital located in the north eastern region of Nigeria, with HIV prevalence of 5.2%. HIV services are supported by Management Sciences for Health through USAID. A cross sectional study was conducted. The case files of all recorded deaths were retrieved from the medical records department and information on age, sex, date of enrolment, date of commencement of anti-retroviral drugs, duration of HAART, W.H.O clinical stage, CD4 cell count and aetiologies/factors associated with the mortalities were extracted and analyzed.
Summary of results: A total of 1510 HIV positive patients were enrolled in our centre (63%F, 47%M) with 758 on HAART. 80 patients (5.2%) had died as at the time of the review. 63% of mortality cases were in patients<40yrs old and 82% presented with WHO stage 3 or 4 disease. The aetiology of death was TB in 40%, suspected TB in 16.25%, HIV wasting syndrome in 8.75%, septic abortion in 1.25% and HBV in 1.25%. In 30% of the cases however, the cause was not ascertained before death. 52% of mortality cases occurred before HAART commencement, 35% occurred within the first 3 months of HAART initiation. 60% of deaths occurred in patients with CD4+T-cell counts<200cells/uL.

Conclusions: Advanced HIV disease, severe immunodeficiency, TB co-morbidity and possibly delay in starting HAART were found to be associated with increased mortality in our centre. Thus, strategies to reduce mortality must include earlier diagnosis of HIV infection and timely initiation of HAART.

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Causes of death in patients infected with HIV from 1985 to 2008

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Introduction: Death rates and causes of death in patients infected with HIV seem to be related to the kind of ARV therapy they have been treated with and have altered the causes of death along the years.
Purpose of the study: To study the causes of death in HIV patients in the era before HAART, partial use of HAART, and HAART.
Methods: Retrospective study of the clinical history of the HIV patients who died in the HJU since 1985. The patients were dived into three periods in accordance with the kind of therapy: 1985 to 1995 (pre-HAART), 1996 to 1999 (partial use of HAART), and 2000 to 2008 (HAART). To accurately evaluate the causes of death 160 patients were eliminated as their causes of death have not been clearly conclusive.
Summary of results: Between October 1985 and December 2008, a total of 4362 HIV infected patients were examined in the HJU, of which 936 (21.05%) died. Of these 936, 85.3% were males, and 14.7% were females. The average age at the time of death was 36.8 (youngest 17, and oldest 80 years old). The average duration of the infection was 41.76 months. The identified mean of transmission were intravenous drug use (67.3%), heterosexuality (17.2%), homosexuality (6.5%), blood derivatives transfusions (0.3%), and in 8.7% of the patients the risk behaviour was unknown. Among all the dead patients, 32.5% were exclusively HIV infected, 35.7% HIV/HCV, 22.6% HIV/HCV/HBV, and 9.2% HIV/HBV. The average CD4 nadir value was 91/mm^3, and at the date of death was 112.2/mm^3. The average viral load at the date of death was 147.837 cop/ml. During the period 1985/1999 the death rate was 20.04%. During the period 1996/2000 this rate was 11.21%, and in the last 8 years it was 13.76%. As to the causes of death, 776 clinical histories have been studied.
Conclusions: We noticed a significant decrease of death rates between the first and the last years of HIV infection which is a consequence of the use of a more efficient therapeutics. The introduction of the use of HAART resulted in a relative decrease of deaths due to opportunistic infections and in a relative increase of deaths due to severe hepatic diseases, non opportunistic infections and malignancies.

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Syphilis infection is associated with an increase in plasma viral load in HIV infected patients: results from the FHDH cohort — ANRS CO4

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Background: The effect of syphilis on HIV infection remains controversial. Most studies involved small sample sized population and did not account for cART effects on HIV markers.
Purpose of the study: To assess the impact of syphilis infection on plasma HIV RNA (pVL) and CD4 cell counts.
Methods: In HIV-infected men followed in Paris between 1998 and 2006 in the FHDH cohort, we studied 2 matched groups of patients: the syphilis+ and syphilis-. The syphilis+ group consisted of men who were diagnosed with an incident primary or secondary syphilis during their HIV follow-up. Each syphilis+ patient was matched up to 5 men who did not contract syphilis (syphilis-) according to his age, sexuality, centre and date of syphilis diagnosis (index date), and to his immunologic and virologic status in the period prior to syphilis infection. We studied whether syphilis infection was associated with an increase in pVL in the 6 months following infection (rise of pVL ≥0.5 log or pVL ≥500 copies/mL in patients with prior undetectable pVL) by conditional logistic regression. Changes in CD4 cell counts were studied by linear mixed model.
Results: 282 syphilis+ (64 primary and 218 secondary) and 1233 syphilis- patients were included. 89% of the patients were MSM aged 38 years in median. 86% were on cART at the index date and 17% had a previous AIDS diagnosis. Median CD4 cell counts before syphilis was 480/mm^3, 58% of the patients had pVL<500 copies/mL. In the 6 months after infection, 40(14.2%) syphilis+ and 84 (6.8%) syphilis- patients exhibited a rise in pVL. Compared to syphilis- patients, syphilis+ patients had a higher risk of pVL increase (adjusted OR; 2.30 95%CI, 1.38-3.15). No statistical difference (p=0.20) was observed between syphilis patients with and without cART at the time of syphilis, (aOR; 1.89 95%CI ,1.16-3.08) and (aOR; 3.42 95%CI,1.59-7.37). Compared to the syphilis- group, the level of CD4 cell count in the syphilis+ group dropped of -28 CD4/mm^3 (p=0.001) during the episode of syphilis but did not differ significantly after the episode (-3 cells/mm^3, p=0.78). No change in the CD4 slopes was evidenced after the episode in both groups.
Conclusions: In this large prospective cohort study with adjustments for age and treatment, syphilis infection was associated with a transient drop in CD4 cell count, which was significantly regain at the end of the episode but exposed patients to a higher risk of increase of viral load.

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Low immunogenicity of whole virion, verocell-derived, inactivated, pandemic influenza H1N1 vaccine in HIV-infected patients

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HIV infected individuals face an increased risk of serious illness from influenza. Current guidelines recommend vaccination of all HIV infected adults. Several studies have analysed the immunogenicity of adjuvant H1N1 vaccines in these individuals. However, no such analysis exists for Celvapan (Baxter), an inactivated H1N1 vaccine without adjuvants, derived from verocells and based on whole virions. Celvapan contains A/California/07/2009 (H1N1)v virus strain. Vaccination was provided in two i.m. doses, at least three weeks apart. This vaccine has been used widely in Austria during the recent H1N1 pandemic.
Adult HIV-1 infected individuals scheduled for H1N1 vaccination where included in this study. Serum samples were taken before the first vaccination (baseline) and after the second vaccination. Antibody titers were determined by hemagglutination inhibition (HAI) assay using chicken red blood cells and the Influenza A/H1N1pdm virus A/California/7/2009 (NIBSC 09/146). Clinical and HIV-related data were taken from patient charts. Seroconversion was defined as a ≥4-fold increase in antibody titer between the pre- and post vaccination serum, and a post-vaccination titer of ≥1:40 was considered protective. 78 patients were included in the study. 42 patients provided serum samples after the second vaccination. 74 % of the patients were male. Median age was 38.5 years. 21 patients had a VL below the limit of quantification (BLQ) since more than 12 months, 27 patients received currently HAART therapy with a VL BLQ. The median CD4 cell count was 442 cell/mm^3 and the median CD4 nadir 209 cell/mm^3. 38 % of the patients seroconverted after receiving both doses of the vaccine. Only 7 patients had HAI titers <1:40 before vaccination; all of them showed post-vaccination titers of >1:40. There was no significant difference with regard to age, the recent CD4 cell count or the CD4 nadir between seroconverters and non-

responders and the share of patients with a recent VL BLQ or a VL BLQ for at least 12 months was roughly equal in both groups.
Seroconversion rates in HIV-infected individuals were significantly lower compared to those in otherwise healthy individuals in spite of a high percentage of individuals with well-controlled VL BLQ and high CD4 cell counts. In addition, seroconversion rate for HIV-infected individuals in this observational trial during 2009 pandemic flu season were lower than those recently published in studies using adjuvant H1N1 vaccines.

NEW TREATMENTS AND TARGETS

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No effect of a single supratherapeutic dose of lersivirine, a next-generation NNRTI, on QTc interval in healthy subjects

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Purpose of the study: Lersivirine (LRV) is a next-generation NNRTI currently under investigation in two Phase IIb studies at doses of 500 - 1000 mg QD. *In vitro* analyses suggest that LRV is a weak I_{kr} and CA^{2+} channel blocker. However, dose-ranging Phase I studies have not shown prolongation of QTc interval to date. This study was performed to investigate the effect of a supratherapeutic dose of LRV on QTc interval in healthy subjects, relative to matched placebo and active control.
Methods: A randomized, single-dose, placebo- and active-controlled 3-way crossover study was performed with 48 healthy adults. Subjects were randomized to receive either LRV (2400 mg), moxifloxacin (400 mg) or placebo for each treatment period with minimum washout of 7 days. Triplicate 12-lead electrocardiogram (ECG) measurements were performed and PK samples collected predose and at 1, 2, 3, 4, 5, 6, 9, 12, and 24 hrs postdose. Vital signs were measured predose, 3 hrs postdose and at discharge. Adverse event monitoring and safety laboratory testing were performed throughout.
Summary of results: All 48 subjects enrolled were white males (mean age 39.1 yrs, body mass index 25.6 kg/m^2) and completed the study. Following LRV administration, the upper bound of 90% CI for time-matched adjusted mean differences to placebo in QTcF at each of the time points postdose was below the regulatory threshold of 10 msec, thus satisfying the criteria for a negative thorough QT/QTc study. The highest upper bound of 90% CI occurred at 6 hrs for LRV (3.32, 90% CI 1.5, 5.1). The study was deemed adequately sensitive as the lower bound of the 90% CI for the adjusted mean differences between moxifloxacin and placebo at moxifloxacin's historical T_{max} of 3 hrs was >5 msec (15.29 msec, 90% CI: 13.5, 17.1 msec). No subjects receiving LRV or placebo had a QTcF ≥450 msec, nor did any experience a QTcF increase ≥30 msec from baseline at any time point. In subjects receiving LRV, no clinically significant changes in QRS complex, PR interval, heart rate or blood pressure were observed. PK analysis of blood samples indicated geometric mean (CV%) AUC_{last} 17750 ng.hr/mL (28%) and C_{max} 1727 ng/mL (33%), and median T_{max} 3 hrs. Adverse events were generally mild, with some moderate gastrointestinal events.
Conclusions: LRV administered as a single 2400 mg supratherapeutic dose did not prolong the QTc interval and no clinically relevant ECG or vital sign changes were observed in healthy subjects.

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Leukocyte extract reduces HIV replication and modulates cellular factors involved in HIV infection: therapeutic meant

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Background: The development of antiretroviral therapies to combat human immunodeficiency virus (HIV) infection has resulted in a decrease in morbidity and mortality associated with the acquired immunodeficiency syndrome (AIDS). Despite these therapeutic advances, problems of drug resistance, latent viral reservoirs, and drug induced toxic effects that compromise effective viral control point to the need for new classes of anti-HIV drugs with different modes of action. Dialyzable Leukocyte Extract (DLE) is a low molecular weight dialyzable material obtained from human leukocytes. A clinical trial of six years of follow-up was carried out using a DLE preparation in asymptomatic HIV patients. Twenty-eight percent of the untreated individual showed disease progression, while only progressed to AIDS 7% of DLE-treated patients. These results indicate that DLE delays disease progression. However, the molecular basis supporting this effect remained unknown.
Purpose of the study: To demonstrate anti-HIV activity in DLE and show DLE modulation on cellular factors involved in HIV replication.
Methods: Using an in vitro infection model on MT4 cell line we study the effect of DLE on HIV replication. We study the effect of DLE on important cellular factors like NFkB, Sp1 and TNF in MT4 cells or peripheral blood mononuclear cells.
Summary of results: DLE shows a significant inhibitory effect on HIV replication ranged from 80-90% according to the viral challenge (figure 1). In addition, others results shown DLE modulation of important endogenous factors involved in HIV immunopathogenesis like TNFa (figure 2) and transcription factors NFκB and Sp1.
Conclusions: DLE effect on cellular factors involved in HIV replication correlates with DLE inhibitory effect on HIV in vitro replication. The inhibition of HIV replication observed with DLE treatment could be mediated by inhibition of transcription factors that may promote replication of HIV. Also, it could be mediated or potentiated by modulation TNF and others endogenous factors involved in HIV replication. These finding could support the use of DLE on HIV patients.

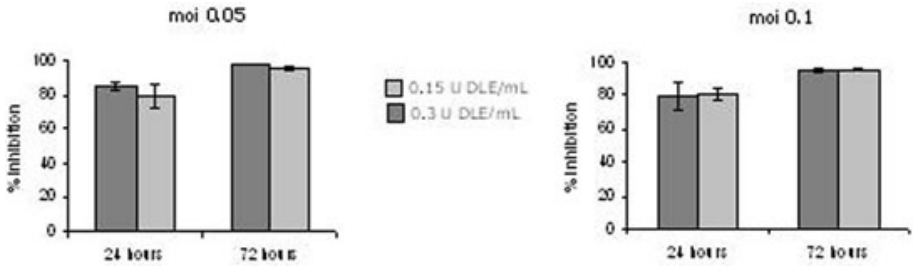

Figure 1 (abstract P226) 2.5×105 cell/mL were treated for 24 or 72 hours with 0.15 or 0.3 U/mL DLE. Leukocyte extract was removed and cells were infected with HIV-Bru isolate at moi 0.05 or 0.1 for 1 hour. Fresh medium containing DLE was added after virus challenge. p24 antigen was measured seven days after infection. Errors bars indicate SD, n=9.

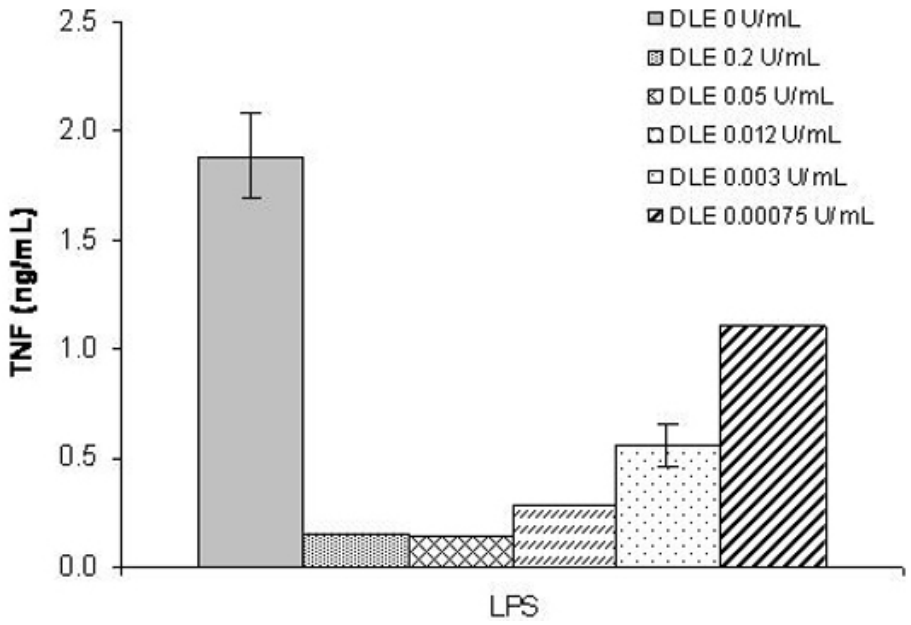

Figure 2 (abstract P226) Whole blood was treated with LPS (4 ng/mL) and DLE. TNF was measured using ELISA. Results are representative of six experiments using blood from different donors. Errors bars indicate SD.

P227

Therapeutics designed to neutralize soluble HIV tat protein could preserve IL-7 signaling and CD8 T-cell function in HIV+ patients

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Background: Interleukin (IL)-7 signaling is essential to CD8 T-cell development, homeostasis and function, and we have previously shown decreased expression of the IL-7 receptor alpha-chain (CD127) on CD8 T-cells in HIV+ patients. We have also shown that this down regulation of CD127 is mediated in part by soluble HIV Tat protein. By removing the IL-7 receptor from the cell surface, Tat is able to inhibit IL-7 signaling and impair both CD8 T-cell proliferation and cytolytic capacity.
Purpose of the study: To determine the molecular mechanism by which Tat down regulates CD127.
Methods: Histidine-tagged mutant Tat proteins were generated by sequentially deleting each of Tat's six domains and purifying the proteins over Nickel columns. CD8 T-cells were isolated from healthy HIV-negative volunteers and incubated in media alone or with purified Tat protein. CD127 surface and intracellular expression were measured by flow cytometry, fluorescence microscopy and by Western blot.
Summary of results: Soluble Tat protein is taken up from the medium by CD8 T-cells via endocytosis. Once inside the cell, Tat exits the endosomes during their normal acidification, enters the cytosol, and then translocates to the inner leaflet of the cell membrane where it binds directly to the cytoplasmic tail of CD127. Tat then induces receptor aggregation and internalization through a process dependent on microtubules and directs CD127 to the proteasome for degradation. While the basic domain of Tat is required for entry into the cell, the N-terminal domain of Tat plays a key role in removing CD127 from the cell membrane. Anti-Tat antibodies, heparin, and colchicine all block Tat's ability to down regulate CD127 on the cell surface.
Conclusions: Given the important role of IL-7 in CD8 T-cell function, down regulation of the IL-7 receptor alpha-chain by Tat likely contributes to the impaired cell mediated immunity and inefficient immunologic control of viral replication evident in HIV+ patients with progressive disease. This makes Tat an attractive target for the development of new therapeutics and vaccines. Drugs designed to disrupt the interaction between Tat and CD127, or neutralizing anti-Tat antibodies induced by vaccination could restore CD127 expression and thus preserve CD8 T-cell function.

P228

Novel monitoring technique to minimise the risk for patients participating in pilot studies of investigational compounds

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P228

Background: S/GSK1349572 is a new integrase inhibitor (INI) with in-vitro activity against INI-resistant HIV. Before dosing a large number of subjects in pivotal clinical trials, in-vitro findings were validated in a pilot clinical study (ING112961). At the outset of the study, the degree of susceptibility at which the drug no longer provides benefit was unknown. Planned enrollment for this study was 30 raltegravir (RAL)-resistant patients, incorporating a broad range of in-vitro susceptibility to S/GSK1349572. The clinical team developed novel stopping guidelines to minimise risk to study participants.
Methods: "Unacceptable" response rates were elicited for key numbers of recruited subjects (e.g. 5, 20, 30). These rates were translated statistically into a level of evidence for unacceptable efficacy, measured as a likelihood ratio (LR). The LR defined a stopping boundary. This boundary was defined for every assessment of response and was tested after each patient's results were observed.
Results: LR stopping guidelines are shown in Table 1 and compared with the rule "stop for >70% failures". A fixed 70% failure rate threshold does not allow for accumulating evidence. LR thresholds stop for lower rates of failure as more data are collected.
At Day 11, 21/27 (78%) of subjects with resistance to raltegravir and elvitegravir showed a virologic response. However, five of the six failures were from the nine subjects enrolled with decreased susceptibility to GSK1349572. The failure rate in this group (5/9) met the definition of "strong evidence of non-response" according to the LR thresholds and so enrollment into this group was halted early.
Conclusions: Monitoring response in a patient enables best treatment for that individual. In trials of new treatments, determining the best option for the next patient requires interpretation of accumulating data in

Table 1 (abstract P228) Number of observed treatment failures that would stop the study

Number of patients observed	4	10	16	20	26	30
70% failure stopping threshold	3	7	12	14	19	21
LR stopping threshold	4 (100%)	5 (50%)	7 (44%)	8 (40%)	9 (35%)	10 (33%)

population-level monitoring. This challenging task requires a combination of clinical insight and formal quantification of evidence. This case study shows that likelihood ratio thresholds define "strong evidence" of non-response and are suitable for constant monitoring. This approach enables additional safety checks for the best treatment for subjects when a new treatment has accumulated only limited data.

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Abstract withdrawn

Journal of the International AIDS Society 2010, **13(Suppl 4):**P229

NON-AIDS MORBIDITIES AND MORTALITY

P230

Prevalence of type 2 diabetes mellitus and its predictive factors in Italy: a comparison between HIV-infected and uninfected subjects

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Purpose of the study: We determined the prevalence of type-2 diabetes mellitus (DM) in HIV infected (HIV+) and uninfected (HIV-) subjects.
Methods: Cross-sectional analysis on HIV+ patients (pts), aged >18 years [median(IQR): 46(41-51)], who attended the Infectious Diseases Department of the San Raffaele Scientific Institute, alive or lost or dead after 2007 and HIV- subjects, healthy workers, aged >18 years [median (IQR): 47(40-53)], evaluated between 2007-2008, all over Italy (15 Italian regions), in a campaign for the assessment of cardiovascular risk factors, promoted by the Occupational Medicine of the H San Raffaele Resnati. Logistic regression used to determine the risk of DM; odds ratios(OR) and its 95% confidence intervals reported.
Results: 4249 HIV+ (3248 males) and 9148 HIV- (7052 males) individuals. HIV+ pts had a higher prevalence of DM than HIV- [N=172 (4.1%) vs N=225 (2.5%), p<0.0001; OR=1.68 (1.37-2.05)]. Prevalence of DM was still higher among HIV+ than HIV- after controlling for body mass index (BMI) [<25: 3.2% vs 1.1%; 25-29.9: 2.9% vs 3.1%; >=30: 12.7% vs 7.8%; OR=1.79 (1.29-2.50)], age [<=50 years old (yrs): 1.7% vs 1.2%; >50yrs: 10.8% vs 4.9%; OR=2.02(1.65-2.49)] or gender [Females: 2.7% vs 1.1%; Males: 4.5% vs 2.9%; OR=1.69(1.38-2.06)] or both factors [Females<=50yrs: 0.9% vs 0.8%; Females >50yrs: 11.1% vs 1.8%; Males<=50yrs: 2.0% vs 1.3%; Males>50yrs: 10.8% vs 5.6%; OR=2.02(1.64-2.48)].
Among subjects with DM, HIV+ pts were significantly different compared to HIV- as follows: were older(p<0.0001), had a lower BMI (p<0.0001), lower cholesterol(p<0.0001), lower HDL-cholesterol (p<0.0001), lower fasting glucose(p<0.0001) and higher triglycerides (p=0.019). HIV+ and HIV- pts with DM were similar with respect to LDL-cholesterol, systolic and diastolic pressure and smoking status. After adjustment for age (<=50yrs, >50yrs), gender, BMI (<25, 25-29.9, >=30), cholesterol, HDL- and LDL-cholesterol, triglycerides and hypertension (yes vs no), HIV+ pts had a higher risk of diabetes (OR=1.71(1.02-2.86), p=0.043). Increasing age [>50yrs vs <=50yrs: OR=4.10(3.01-5.59), p<0.0001] or BMI [25-29.9 vs <25: OR=1.87(1.28-2.74); >=30 vs <25: OR=4.67(3.08-7.10); overall effect: p<0.0001] were also predictive factors of a greater risk of DM.
Conclusions: Our findings suggest an increased prevalence of type-2 diabetes in HIV+ than HIV- subjects which was almost doubled in HIV+ than HIV- and up to 4-fold higher among obese subjects or those aged>50 years.

P231

Smoking prevalence, cessation rates and relapse rates in the Swiss HIV Cohort Study (SHCS)

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Background: HIV-infected persons are at increased risk for cardiovascular disease and cancers due to various reasons. Smoking is the most prevalent modifiable risk factor for these diseases.
Purpose of the study: We studied the prevalence of smoking, cessation rates, relapse rates, and predictors of these events.
Methods: The Swiss HIV Cohort Study (SHCS) is a prospective observational database which semi-annually collects demographic, clinical and laboratory data, including on self-reported smoking status. Smoking cessation was defined by 2 consecutive visits without smoking (after 2 visits with smoking). We used Kaplan-Meier analyses to assess the probability of smoking cessation and relapse in different patient groups; and uni-/multivariable Cox models to study associations between such events and patient characteristics.
Results: Between 2000-2009, we followed 10,511 patients at 107,220 visits. Prevalence of smoking decreased from 60% (2000) to 44 % (2009). Prevalence of smoking was 84% in IDU, 42% in MSM, 50% in heterosexual men, and 47% in heterosexual women. Smoking prevalence differed in geographic/language regions of Switzerland (French speaking part 44%; Italian 57%; German 51%), and in different care settings (hospital outpatient clinics (51%), private practice (46%)). The incidence of smoking cessation was 4.0/100 ys of smoking without appreciable time-trends. The probability of smoking cessation was 31% (95% CI 29, 32%) after 10 ys. Hazard ratios for smoking cessation in multivariable models (ref. group: heterosexual men aged <30) differed significantly: IDU less likely stopped smoking (0.49 [0.42, 0.58]), whereas MSM (1.21 [1.02, 1.42]) and patients in care of private physicians more likely stopped (1.24 [1.09, 1.41]). No significant differences of cessation rates were found in different age groups, heterosexual women, or language regions. The probability of relapse 6 years after smoking cessation was 44%; half of relapses occurring within first 2 ys. HR for relapses in Cox models differed significantly in IDU (1.41 [1.06, 1.87]) and in private practice (0.75 [0.59, 0.94]) but not in MSM, age groups, heterosexual women, or in different language regions.
Conclusions: Smoking is highly prevalent in HIV-infected participants of the cohort, but decreased during the recent years. Relapse rates after smoking cessation were high. Counselling for smoking cessation, and prevention of relapse are important aspects of care for HIV-infected persons.

P232

Prevalence and risk factors for chronic obstructive lung disease in HIV-infected patients in the HAART era

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Purpose of the study: To evaluate the prevalence of respiratory symptoms and COPD in a stable HIV-infected outpatient population and

to further investigate the role of HAART and other possibly associated risk factors.
Methods: All participants completed a questionnaire for pulmonary symptoms and the MRC dyspnoea scale. A complete spirometry with evaluation of the residual volume was performed using the bodyplethismographic method. We considered the Total Lung Capacity (TLC), Forced Expiratory Volume (FEV1) at 1st second and the FEV1/FVC ratio (Tiffenau Index) for each patient.
Summary of results: We enrolled 111 HIV-infected patients with a mean age of 42.3 ± 8.1 years and 65 HIV-negative age and sex-matched controls. Seventy-seven (69.4%) HIV patients were male and 39 (35.1%) were in CDC stage C. Eighty-seven (78.4%) were receiving HAART. Mean CD4 cell count was 541 ± 243 cells/mm^3 and 79 (71.2%) had an undetectable HIV-RNA. Sixty-three (56.8%) patients were active smokers whereas 48 (43.2%) were non-smokers. No significant difference in age, sex, proportion of smokers and pack-year history of smoking was evidenced between HIV positive patients and controls. However, HIV-infected individuals had significantly lower FEV1 (p=0.002) and FEV1/FVC (p=0.028), whereas TLC was significantly higher (p=0.018). Furthermore, HIV-infected patients had a significantly higher proportion of any respiratory symptom (p=0.002), cough (p=0.006) and dyspnoea (p=0.020). HIV-infected patients had also a significantly (p=0.008) higher proportion (23.4%) of COPD in respect of HIV-negative controls (7.7%). In a multivariate regression analysis significant predictors of respiratory symptoms were current smoking (AOR 11.18; 95% C.I 3.89-32.12) and previous bacterial pneumonia (AOR 4.41; 95% C.I. 1.13-17.13), whereas the only statistically significant predictor of COPD was current cigarette smoking (AOR 5.94; 95% C.I. 1.77-19.96). HAART receipt was not significantly associated with respiratory symptoms nor with COPD.
Conclusions: Our results suggest a role for HIV infection itself and for current cigarette smoking in the development of respiratory symptoms and COPD in HIV-infected patients. HAART did not seem to reduce the risk of respiratory symptoms and COPD, in our cases. Thus, our results suggest that HIV-infected patients should be screened for chronic respiratory disease in order to early identify those at risk or those who need specific treatment.

P233

High plasma levels of parathyroid hormone (PTH) are associated with an increased cardiovascular risk among HIV-infected subjects

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Journal of the International AIDS Society 2010, **13(Suppl 4):**P233

Background: Elevated PTH plasma levels are associated to an increased cardiovascular risk (CVR) possibly due to a PTH effect on vascular calcification, myocardial impairment and hypertension.
Purpose of the study: To assess the association between CVR and PTH levels in HIV-infected patients (pts).
Methods: HIV-infected subjects followed at the Infectious Disease Department of IRCCS San Raffaele, with at least one PTH plasma value and a contemporary CVR determination. CVR was calculated according to Framingham 10-years equation (Anderson et al.) Cochran-Armitage test for trend and Spearman correlation were calculated at univariate analysis. Logistic regression was applied at multivariable analysis.
Results: Up to date 280 pts met the inclusion criteria; median (IQR) age was 48.4 (44.4-55.9) years, 205 (73.2%) male, 14.9 (9.3-20.4) years after HIV-infection, 104 (37.1%) smokers, 22 (7.9%) with a previous diagnosis of diabetes, PTH plasma level was 62.7 (49.5-81.5)pg/ml [82 (33%) pts > upper normal limit], vitamin D (25-OH D3) level was 22.5(14.8-31.0) ng/ml, systolic pressure was 120(110-135) mmHg, total cholesterol 192 (169-220) mg/dL, creatinine 0.83 (0.71-0.98) mg/dL, current CD4 cell count was 549 (391-740) cells/mm^3 and HIV-RNA< 50cp/ml in 235(83.9%) subjects. Overall CVR was 8 (4.3-13.8)% at 10 years. Eighty-four(30.0%) pts presented a CVR below 5%, 93(33.2%) between 5 and 10%, 46(16.4%) between 10 and 15%, 28(10.0%) between 15 and 20% and 29(10.6%) above 20% risk. PTH levels differed among classes of CVR [CVR <5%, 5-10%, 10-15%, 15-20, >20% had median PTH levels of 57.3, 63.6, 67.0, 73.3 and 65.3 pg/ml, respectively, (p=0.032)]. CVR was positively correlated with PTH (r=0.148, p=0.0134), creatinine (r=0.316, p<0.0001), triglycerides (r=0.300, p<0.0001) but not with vitamin D level (r= -0.102; p=0.123). After adjusting for PTH plasma levels, years of antiretroviral therapy (ART), years of HIV-infection, nadir and current CD4 cell count, detectable HIV-RNA, HIV transmission risk factor, triglycerides and creatinine levels, a CVR>10% was predicted by increasing PTH levels (OR=1.353 per 20-pg/mL increase, 95%CI: 1.074-1.802, p=0.028)as well as by increasing creatinine levels (OR=1.442 per 0.1-mg/dL increase, 95%CI:1.201-1.774, p=0.0002).
Conclusions: Among HIV-infected patients elevated PTH levels were related to increased CVR and independently predicted a 10-years CVR above 10%. The interplay between bone metabolism and CVR needs to be further investigated.

COST-EFFECTIVENESS

P234

Cost-effectiveness of atazanavir-ritonavir versus lopinavir-ritonavir in HIV patients initiating first-line antiretroviral therapy

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Purpose of the study: Selection of initial antiretroviral therapy (ART) may be informed by factors such as efficacy, adverse effects, and cost. This study assessed the lifetime cost-effectiveness of atazanavir-ritonavir (ATV/r) versus lopinavir-ritonavir (LPV/r) in HIV patients initiating first-line ART.
Methods: A Markov microsimulation model was developed to project lifetime health-related outcomes, costs, quality-adjusted life years (QALYs), and cost-effectiveness of ATV/r versus LPV/r, both with tenofovir-emtricitabine, as first-line ART. Virologic suppression, baseline characteristics, state transition probabilities, cholesterol changes, and adverse effects were based on 96-week CASTLE results. HIV-related mortality, opportunistic infection (OI) and AIDS rates, coronary heart disease (CHD) risk, treatment adherence, costs, and utilities were obtained from published sources. Costs were reported in 2009 US dollars. Sensitivity analyses were conducted to assess the robustness of study results.
Summary of results: Compared with patients initiating LPV/r, patients initiating ATV/r were estimated to have longer time in first-line therapy, fewer cases of AIDS, OI, CHD, and diarrhea, more cases of hyperbilirubinemia (HB), and higher costs. While absolute survival was similar, patients initiating ATV/r were predicted to have longer quality-adjusted survival. Overall, ATV/r added 0.26 QALYs at a cost of $6,826, producing an ICER of $26,421 per QALY gained. Sensitivity analyses indicated that at a willingness to pay threshold of $50,000 per QALY, ATV/r was cost effective 94% of the time. Table 1.
Conclusions: Accounting for both lifetime costs and QALYs, ATV/r is cost effective (less than $50,000 per QALY) compared with LPV/r in HIV patients initiating first-line ART.

P235

Cost-efficacy analysis of the MONET trial using Spanish antiretroviral drug prices

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Background: In virologically suppressed patients, switching to DRV/r monotherapy maintains HIV RNA suppression, and could also lower treatment costs.
Methods: In the MONET trial 256 patients with HIV RNA <50 copies/mL on current HAART for over 24 weeks (NNRTI based (43%), or PI based

Table 1 (abstract P234)

Health-Related Outcomes							
	Time on First-Line Treatment (months)	AIDS cases (per 1000 patient years)	OI cases (per 1000 patient years)	CHD cases (per 1000 patient years)	Diarrhea cases (per 1000 patient years)	HB cases (per 1000 patient years)	Absolute Survival (life years)
LPV/r	70.7	20.054	0.519	5.511	6.262	0.247	18.51
ATV/r	97.3	19.081	0.443	5.437	1.272	6.986	18.52
Cost, QALY, and Cost-Effectiveness							
	Cost	Incremental Cost	Quality-Adjusted Survival (QALY)	Incremental QALY	Incremental Cost-Effectiveness		
LPV/r	$269,160	–	10.761	–	–		
ATV/r	$275,986	$6,826	11.020	0.258	$26,421		

(57%)), switched to DRV/r 800/100 mg once daily, either as monotherapy (n=127) or with 2NRTI (n=129). The Spanish costs per patient with HIV RNA below 50 copies/mL were calculated, using a "switch included" analysis at Week 96, to account for additional antiretrovirals taken after initial treatment failure. Published prices were used.
Results: In the ITT switch included analysis, HIV RNA <50 copies/mL by Week 96 was 92.1% versus 90.7% in the DRV/r monotherapy and control arms. No patients in either arm developed phenotypic resistance to DRV. Before the trial, the mean annual cost of antiretrovirals was €4612 for patients on NNRTI based HAART, and €9217 for patients on PI based HAART. During the MONET trial, the mean annual per-patient cost of antiretrovirals was €9915 in the triple therapy arm, of which 45% was from NRTIs and 55% from PIs. The mean per-patient cost in the monotherapy arm was €5915, a saving of 40%. We estimated 65,000 people treated with antiretrovirals in Spain (50% NNRTI based, 50% PI based) and 15% of patients (9,750) eligible for PI monotherapy. A switch to DRV/r monotherapy could cut the two-year cost of antiretroviral treatment for these patients, from €137 million to €115 million, a saving of €22 million over two years.
Conclusions: Based on the MONET results, the lower cost of DRV/r monotherapy versus triple therapy in Spain would allow more patients to be treated for a fixed budget, or a saving of up to €22 million over two years, if all eligible patients were switched, while maintaining HIV RNA suppression below 50 copies/mL.

P236

Late versus non-late presentation of HIV/AIDS: an economic impact analysis

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Background: In Austria up to 25% of newly diagnosed HIV infected patients present with less than 200 CD4 cell/mm^3 and/or AIDS (late presenters). Late diagnosis not only adversely affects individual health and survival but may also be associated with higher need for care, thus resulting in higher expenses for the healthcare system.
Purpose of the study: To assess the marginal costs of late presentation of HIV-infection in Austria.
Methods: Direct costs incurred during follow-up, demographic and clinical data were retrospectively collected for all late presenters (=cases) and an age- and risk-group matched cohort of controls (>350 CD4 cells/mm^3 and never AIDS at presentation) presenting at the HIV-unit of the Medical University of Vienna between July 2006 and November 2008. Calculation of costs was based on official standard reimbursement systems for in-patient care, out-patient consultations, diagnostic procedures, and drug prices paid by the social insurance company or the hospital.
Results: 24 cases and 27 controls were followed over a mean of 15 months. Cases and controls were well matched with regards to age, gender, risk group, migrational background, and follow-up time (p=NS). Median overall costs for late presenters incurred during the observation period were nearly 5 times higher for cases than for controls (21.166 vs. 4.329 Euros; p < 0,05). This difference was driven by higher costs for out-patient consultations (p<0,005), in-patient care (p<0,0001), diagnostic procedures (p< 0,02) and ART (p < 0,005). Costs for non-antiretroviral drugs did not differ significantly between the groups.
Conclusions: Late presentation of HIV-infection is associated with a significant economic burden for the health system during the initial period of care. Higher costs for ART due to the immediate need for treatment account only for part of these costs. Interventions promoting earlier diagnosis of HIV in Austria may therefore prove to be cost-effective.

P237

Cost-effectiveness of 2NRTI+NNRTI versus 2NRTI+PI as the initial cART regimen

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Purpose of the study: To compare ART initiation with 2NRTI+NNRTI versus 2NRTI+PI through a retrospective analysis and incorporate these results in a cost-effectiveness analysis.
Methods: Time to regimen switch (discontinuing at least one ARV) due to VF (two consecutive viral loads >50 cps/ml after viral suppression or 6-months unreached viral suppression), time to regimen switch due to any other reason and time to resistance development were calculated using survival analysis. Log-rank test for equality of survivor functions was used for comparison. Average 4-months absolute increase in CD4 cell count was compared using weighted linear least squares. Cost-effectiveness analysis was performed using a microsimulation discrete events model with a lifetime time horizon and 5% discount rate. All resources valued at 2009 prices. The hospital's perspective was assumed.
Summary of results: The retrospective analysis was performed on a cohort of 317 HIV-1 infected naïve to ART individuals followed at an HIV Unit in Portugal (Centro Hospitalar de Cascais). All (unrandomized) patients in the analysis initiated ART between 2000 and 2008 with either 2NRTI+NNRTI (158) or 2NRTI+PI (159). Median age was 39 years-old, 33% were women, and 29.7% were HCV co-infected. Median (IQR) CD4 count and $\log_{10}$ viral load were 229 (121–350) cells/mm^3 and 5.0 (4.3–5.5) log cp/ml. Groups were identical with respect to these characteristics. Equally of Kaplan-Meier survival curves could not be rejected with respect to:

time to switch due to VF, time to viral suppression and time to resistance development. In the first 3 years, no statistically significant difference between groups was found in CD4 cell count change. Median (95% CI) time to any ARV switch due to reasons other than VF, was 6.7 (3.5-7.1) and 2.7 (2.3-3.7) years in the NN and PIr groups, respectively (p=0.0078). The median difference (95% CI) in first regimen monthly ART costs and in monthly non-ART costs was, respectively, 348€ (287€-410€) and 23€(11 €-35€), with lower costs for the NN group. Initiating therapy with 2NRTI +NN reduces the average number of switches by 17%, saves 18,943€ per individual and increases life expectancy by 1.3 months due to the impact of the accumulated number of regimens on future events.

Conclusions: This study suggests that, when clinically valid, initiating therapy with 2NRTI+NN is a cost-saving strategy and equally effective when compared to 2NRTI+PI as the first regimen.

Cite abstracts in this supplement using the relevant abstract number, e.g.: Aragão *et al.*: Cost-effectiveness of 2NRTI+NNRTI versus 2NRTI+PI as the initial cART regimen. *Journal of the International AIDS Society* 2010, **13** (Suppl 4):P237