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Abstracts
ICAR 2009

Italian Conference on AIDS and Retroviruses

Teatro dal Verme
Via San Giovanni sul Muro, 2
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24 – 26 May 2009

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Italian Conference on AIDS and Retroviruses

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Sunday 24 May, 2009

PRE-CONGRESS COURSES

The pre-congress courses will take place at the following times: from 11.00 to 16.00

IMMUNOLOGY – The Challenge of Immune Hyperactivation in HIV/AIDS: from Natural History to Therapeutic Approaches, *with an educational contribution from Pfizer Italia s.r.l.*
Co-ordinator: *G. Antonelli* (Rome), *G. Marchetti* (Milan)

- Insights into HIV/AIDS immune pathogenesis: towards a better clarification of the role of immune hyperactivation
  M. Clerici (Milan)
- Mucosal immune dysfunction and contribution to immune hyper activation in AIDS pathogenesis
  G. Silvestri (Philadelphia)
- Translational research in HIV/AIDS: what is the role of the immunology laboratory in evaluating immune activation and function and how is this applied to clinical practice?
  A. Cossarizza (Modena)
- Insights into immune (and vaccine) therapy approaches in HIV/AIDS: can we turn off immune hyperactivation?
  G. Tambussi (Milan)

VIROLOGY – HIV viral minorities: clinical significance & impact
Co-ordinator: *M.C. Re* (Bologna), *S. Rusconi* (Milan)

- Dimension of the phenomenon
  M. Wainberg (Montreal)
- Technical critical issues
  F. Ceccherini Silberstein (Rome)
- Impact on clinical practice
  S. Rusconi (Milan)

CLINICAL – Osteoporosis in HIV infection
Co-ordinator: *A. Castagna* (Milan), *T. Quirino* (Busto Arsizio – VA)

- Osteoporosis and the risk of fractures
  D. Gatti (Verona)
- HAART and bone: toxicity of the old and new classes of antiretroviral drugs
  M. Borderi (Bologna)
- DEXA: from research to clinical practice
  G. Guaraldi (Modena)
- Osteoporosis and osteomalacia
  G. Mignogna (Milan)

14.00 **MEET THE EXPERT**, *with an educational contribution from Merck Sharp & Dohme s.p.a.*
The future of HAART: new scenarios and prospects regarding the use of new classes of drugs

14.30 **INVESTIGATOR'S MEETING**, *with an educational contribution from Bristol Myers Squibb s.r.l.*
HiVision

17.00 **OPENING OF THE CONGRESS WORK**

17.00 **Opening ceremony**
A. d'Arminio Monforte, *M. Galli*, *A. Lazzarin*
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F. Fazio (Rome)

18.00 **LECTURE**
HIV-AIDS: an infectious transmitted disease. New EU prevention policy for coming years.
W. Philipp (Luxembourg)
Chairmen: *A. Cerioli* (Bologna), *F. Crespi* (Rome), *P. Patanè* (Catania)

LECTURE
HIV: the stealth virus
L. Montagnier (Paris)
Chairmen: *G. Carosi* (Brescia), *M. Moroni* (Milan)

LECTURE
Access to drugs in countries with limited resources
Dedicated to Lucille Teasdale-Corti
M. Kazatchkine (Geneva)
Chairmen: *F. Mazzotta* (Florence), *G. Rizzardini* (Milan)

Monday 25 May, 2009

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K.T. Jeang (Rockville)
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09.30 **SYMPOSIUM: HIGHLIGHTS IN VIROLOGY**
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09.35 The problem of HIV subtype diversity in drug resistance: potential implications for treatment
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09.55 Virological monitoring of pediatric infection
A. De Rossi (Padua)
10.15 Gene therapy and cellular resistance to HIV
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10.35 **Discussion**
10.55 Conclusions
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11.30 **ORAL COMMUNICATIONS**

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15.00 **LECTURE**
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15.30 **ORAL COMMUNICATIONS**

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18.55 Conclusions
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Tuesday 26 May, 2009

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Evaluation of cardiovascular risk in HIV-positive patients

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16.25 Conclusions
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ANTIRETROVIRAL THERAPY: EFFICACY AND CLINICAL PHARMACOLOGY

CO 01

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48 WEEK EFFICACY OF FIRST LINE ANTIRETROVIRAL TREATMENTS FOR HIV INFECTION IN 1998 AND 2006: PRELIMINARY RESULTS OF A MULTICENTRIC INVESTIGATION

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Background. Several factors, that is better knowledge of drugs and pharmacological interactions, awareness of metabolic toxicities, support of adherence, have been invocated to explain the increased success of recent first line HAART regimens. Most of available data derive either from randomized clinical trials or from longitudinal cohort studies; little is known from unselected patients in ordinary clinical settings. We planned to retrospectively investigate the efficacy and tolerability of first line HAART regimens prescribed in institutions belonging to CISAI group in the 2 sample years 1998 and 2006
Methods. All consecutive patients starting their first HAART line in 1998 and in 2006 were enrolled on study entrance. We chose the sample year 1998 because of its proximity to the first availability of HAART; 2006 as a sample of most recent regimens. Age, sex, risk factors, comorbidities, CDC stage, treatment adherence, records of toxicity, any modification of HAART, basal, 24 and 48 week CD4 T-cell counts, HIV viremia, blood glucose, total cholesterol, triglycerides were considered. Here we elaborated on preliminary data from contributing centers. Statistical analyses were performed using Stata 10 software.
Results. 410 patients were included, 71.1 % males, with mean age of 38.7 years, mean basal CD4 T-cells 300/mm3 and mean basal HIV viremia 5,49 log10 copies/mL. 228 patients were considered in 1998; 181 in 2006. Patients in 1998 did not differ for age, sex, CDC state, % of AIDS presenters, immune and metabolic baseline parameters from patients enrolled in 2006. The proportion of drug users and hepatitis-coinfected patients was significantly decreased in 2006. Baseline CD4 T cell values were significantly higher and HIV viremia lower in 1998.
HIV suppression at 48 weeks was observed in 55.6% of patients in 1998 and in 92.3% in 2006, with a concomitant better immune recovery in the same year (ΔCD4 165 vs 226, p=.02). Analyses demonstrated a significant increase of fully adherent patients in 2006 (76.7% vs 90.5%, p=.02), without any significance in metabolic parameters. Toxicity was the major reason for changing HAART in recent regimens (10.9% vs 16.6%); virological failure was greater in 1998 (15.3% vs 2.2%, p<.001). Interestingly, however, neither HAART interruptions nor drug changes were significantly different in the 2 years.
In multivariate analyses, being treated in 1998 (OR 2.77, CI 1.35-5.55, p=.006) and being drug addict (OR 1.83, CI 1.08-3.10, p=.02) were independently associated with virological failure at week 48. Neither demographic nor basal immune parameters, nor adverse events independently altered the likelihood of virological failure.
Conclusions. Patients treated in 2006 had better chances of viral suppression and immune recovery than at the dawn of HAART. This would suggest a greater intrinsic potency and acceptance of first line HAART regimens prescribed in 2006.

CO 02

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RALTEGRAVIR, MARAVIROC, ETRAVIRINE, A PI- AND NRTI-SPARING REGIMEN FOR SALVAGE THERAPY: 48- WEEKS RESULTS

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Background: We previously showed 24-weeks results of raltegravir-based regimen in heavily pre-treated patients. 48 weeks outcome is here presented.
Methods: Perspective study including patients followed at San Raffaele Hospital and simultaneously screened in three Expanded Access Programs: raltegravir (MK0518-023, RAL), maraviroc (A4001050, MVC) and etravirine (TMC125-C214, ETR). Salvage therapy was prescribed according to: viral tropism, screening genotype and previous resistance tests. Patients are divided in two groups of treatment: Group A=RAL+MVC+ETR; Group B=RAL+OBT.ANOVA for repeated measures was performed and Greenhouse-Geisser probabilities calculated. Results as median (Q1-Q3) values.
Results: Up to date 103 patients (28 in group A and 75 in group B) have been included; BL characteristics: age 44.7(41.6-52.7) years, 22(21%) women, 15(15%) IVDU, infected since 15.8 (12.8-19) years, ARV exposure of 13.2(11.4-15.4) years, CDC C stage 43(41.7%); CD4: 230 (136-359) cells//μL; CD4%: 13.2(7.8-19.6), HIV-RNA: 4.12(3.6-4.9) log_{10} copies/mL and CD4 nadir: 94(27-181) cells/μL. No difference in BL characteristics were found according to the group regimen prescribed.85 patients (25 and 57 in group A and B respectively) reached week 48.All patients had HIV-RNA below 400 copies/ml; 23/25 (92%) and 53/57 (93%) had HIV-RNA<50 copies/ml in group A and B, respectively.

	Group	Baseline	Week 24	Week 48	p
CD4 cells/μL	A	254 (76-399)	492 (330-627)	517 (410-624)	0.0081
	B	215 (148-349)	355 (284-490)	419 (291-541)	
CD4%	A	13.6 (8.1-19.6)	20.5 (13.4-25.8)	21.1 (14.5-25.1)	0.7407
	B	13.2 (7.8-19.6)	17.7 (11.6-24.5)	19.7 (13.1-27.6)	
CD4/ CD8 ratio	A	0.21 (0.12-0.36)	0.42 (0.23-0.54)	0.44 (0.29-0.59)	0.6628
	B	0.19 (0.11-0.36)	0.33 (0.19-0.46)	0.36 (0.22-0.52)	
HIV-RNA log^{10} copies/ mL	A	4.16 (3.85-5.08)	1.69 (1.69-1.69)	1.69 (1.69-1.69)	0.3928
	B	3.98 (3.57-4.92)	1.69 (1.69-1.69)	1.69 (1.69-1.69)	

At W24 CD4 change was excellent in Group A and better than Group B (p=0.003). Over 48 weeks of follow-up this change was still significantly higher [Group A: 278(171-355); Group B: 198(111-264); (p=0.0081)]. Serious adverse events were diagnosed in 3 pts (11%) of Group A [spondilodiscitis (1), anal cancer (1), Hodgkin's lymphoma (1)] and 7 pts (9.3%) of Group B [esophageal candidiasis (1), bacterial pneumonia (1), worsening Kaposi's sarcoma (1), grade 4 rash (1), non Hodgkin's lymphoma (1), cutaneous squamous carcinoma (1), multiple foot fractures (1)]. (p=0.999)
Conclusions: 48 weeks results confirmed that raltegravir, maraviroc and etravirine represents a powerful option for salvage therapy. This

regimen is associated with a greater increase of CD4 absolute number than RAL+OBT.

CO 03

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HIV-DNA VIRAL KINETICS AND THERAPEUTIC DRUG MONITORING DURING RALTEGRAVIR-BASED SALVAGE THERAPY

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Background - Raltegravir (RAL) is the first antiretroviral which prevents HIV genome to integrate into host chromosomes. We hypothesize that RAL plasma concentrations can be associated to the decline of proviral DNA during RAL-based salvage therapy.
Methods - We evaluated 35 patients (pts), with multi-drug resistant HIV infection, treated with RAL. Of them, 17 pts completed a 12-week follow up period. CD4 cells, plasma HIV-RNA and proviral DNA were assessed at baseline and at day 14, 30, 60 and 90 of treatment.
Proviral DNA extracted from PBMC was used to quantify total HIV-DNA and unintegrated circular forms containing 2 adjacent LTR regions.
RAL Ctrough was measured by HPLC-UV at week 2 and 4 and reported as mean value between concentrations. The relationship between Ctrough and immuno-virological parameters was assessed by linear/univariate analysis as appropriate.
Results - Of 17 completed pts, 12 (70%) were male, with a median (IQR) age of 46 (41-48) years and a median HIV infection's length of 18 (14-20) years. At baseline, the mean (SD) HIV-RNA and CD4 were 4.4 (±0.7) log cp/ml and 224 (±159) cells/mmc. The mean RAL Ctrough was 156 (±135) ng/ml.
Pts were divided in 2 groups according to RAL Ctrough (group A, 11 pts: Ctrough <156 ; group B, 6 pts: Ctrough >156 ng/ml). Both groups had similar baseline demographic, clinical, immuno-virologic characteristics but different mean DNA load (789 vs 517 cp/PBMC).
At day 14, the mean CD4 cells increase was higher in group B than A (102 vs 14 cells/mmc, p=0.002), but no difference was found in RNA decrease (-2.6 vs -2.7 log cp/ml, p=0.7). The DNA decrease was higher in group A than B (- 498 vs -182 cp/PBMC, p=0.3).
At day 30 and 60, CD4 cells gain and RNA decrease were similar in both groups. The DNA reduction was persistently higher in group A than B (-546 vs +152 cp/PBMC, p=0.03 at day 30; -455 vs -76 cp/PBMC, p=0.04 at day 60, respectively).
At day 90, all pts achieved RNA <50 cp/ml. The mean CD4 cells increase was higher in group B than A (132 vs 42 cells/mmc, p=0.02). The DNA reduction was confirmed higher in group A than B (-571 vs +101 cp/PBMC, p=0.04).
At multivariate analysis, the mean RAL Ctrough was confirmed significantly associated to DNA decrease at day 30, 60 and 90.
In a subgroup of 10 pts, with detectable baseline unintegrated DNA, an increase of unintegrated DNA (mean 64,5 cp/PMBC, SD ±130) and of unintegrated/total DNA ratio (0.31,±0.55) was found.
Conclusions - RAL produces a significant decline in proviral DNA during a successful RAL-based therapy. This decline is significantly less pronounced in patients with higher RAL Ctrough and it is associated to an increase in unintegrated/total DNA ratio. Further studies are necessary to define the role of unintegrated proviral DNA and of therapeutic drug monitoring during RAL therapy.

CO 04

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DARUNAVIR AND RALTEGRAVIR IN THE PLASMA OF HIV-INFECTED PATIENT: TDM AND PHARMACOKINETIC VARIABILITY

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Background: Darunavir (DRV) and raltegravir (RTG) are recently introduced antiretroviral drugs, which have been shown to be highly effective against HIV-1. Their pharmacokinetic variability and relationships with virological response need to be adequately investigated in routine clinical practice.
Materials & methods: We enrolled HIV-infected patients that underwent therapeutic drug monitoring (TDM) of DRV or RTG trough concentration (C_{trough}) (12+2 hours after dosing) during routine outpatient visits. Plasma drug concentrations were measured by HPLC-UV assay. Interindividual (CV_{inter}) and intraindividual (CV_{intra}) pharmacokinetic variability were evaluated. Virological response was defined as: (i) reaching a HIV-RNA below 50 copies/mL after 24 weeks in patients with baseline (at TDM) detectable viral load; (ii) lack of rebound to above 50 copies/mL in two consecutive occasions or to above 1000 copies/mL on a single occasion in patients with baseline undetectable viral load. Genotypic inhibitory quotients (gIQ) were calculated by dividing the C_{trough} by the number of DRV resistance mutations (IAS-USA mutation 2008 list).
Results: A total of 49 patients were evaluated: 65.3% males, median age 44 years (IQR 39-51), 93.9% Italian born, 49% with past AIDS-defining events, median previous antiretroviral regimens prescribed 8 (IQR 5-10), median viral load 155 copies/ml (IQR 49-868) and median CD4 cells count 348/μL (IQR 212-415). Prior to DRV or RTG initiation, median PI resistance mutations were 12 (IQR 7-14), while median DRV resistance mutations were 1 (IQR 0-2).
DRV and RTG were measured in 90 and 19 pre-dose plasma samples, respectively. Median DRV plasma concentration was 3.98 mg/L (IQR 2.70-6.44) and median gIQ was 1.90 mg/L/mutation (IQR 0.99-3.53). Median DRV area under the curve (AUC), (n=19 patients), was 50.85 mg.hr/L (IQR 40.84-105.19) with an AUC-CV of 52.3%. DRV C_{trough} CV_{inter} was higher than CV_{intra} (52.9% vs 38.3%) and was lower than C_{trough} CV_{inter} calculated for other boosted-PIs in our cohort (lopinavir 62.3%[n=91], atazanavir 118%[n=33], fosamprenavir 88.3%[n=20], indinavir 77.9%[n=2], saquinavir 108.4%[n=7], tipranavir 129.8%[n=9]). Older age (B 1.06, *p=0.004*), foreign-born status (B -2.05, *p=0.018*) and HCV co-infection (B 1.60, *p=0.022*) were associated with DRV plasma concentration at univariate linear regression analysis but only older age was independently associated in the multivariate model (B 0.79, *p=0.040*). Concomitant antiretroviral drugs and other medications did not significantly influence DRV plasma levels.
Median RTG plasma C_{trough} was 0.20 mg/L (IQR 0.05-0.69); in 21.1% RTG levels were below the limit of quantitation of the assay (<0.05 mg/L). Interindividual variability was high (CV 91.7%). None of the tested variables, including DRV concentration, correlated with RTG C_{trough}.
A 24 weeks follow up was available in 27 patients on DRV-based regimens: 55.6% showed virological response. No association was found between the tested variables and virological response; in particular no relationship between DRV C_{trough} or gIQ and virological response could be demonstrated.
Conclusions: In clinical practice, DRV C_{trough} CV_{inter} was relatively limited as compared to other boosted-PIs and levels were higher in older patients. RTG levels showed a higher variability and were not related to DRV levels. Further pharmacokinetic studies of RGV and DRV are required to define the possible role of TDM of these drugs in the clinical context.

CO 05

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PHARMACOKINETICS AND PHARMACOGENETICS OF MARAVIROC IN THE CLINICAL SETTING

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Background: MVC can interact with several antiretrovirals due to CYP3A4-based hepatic metabolism. It is usually administered at 300 mg bid, 150 mg bid if co-administered with a boosted protease inhibitor, and at 600 mg bid with etravirine or efavirenz. The aim of our study was to investigate the influence of concomitant antiretrovirals on MVC plasma concentrations and to evaluate the effect of single nucleotide polymorphisms (SNPs) in *ABCB1*, *CYP3A4*, *PXR* and *SLCO1B1* on MVC plasma drug concentrations.
Materials and Methods: Patients receiving MVC as part of their antiretroviral regimen were recruited in Torino and Milan, Italy. Main inclusion criteria were written informed consent, no concomitant interacting drugs (non-antiretroviral), no hepatic or renal functional impairment and self-reported adherence > 95%. At each follow up visit, concentrations were measured in samples collected 10 – 14 h after dosing (Ctrough) by a validated HPLC-PDA method. Genotyping was conducted by real time PCR based allelic discrimination using standard methodology. Statistical analysis was conducted by Mann Whitney, Kruskal-Wallis or Spearman Rank to assess the effects of dose and co-administration of other antiretrovirals, weight, age, gender, and genotype on MVC Ctrough. Values are expressed as median (IQR), ng/mL.
Results: Fourty-one patients (76% males, median age 42 yrs) were administered with MVC 150 mg bid (*n*=7, all with DRV/RTV-containing regimens), MVC 300 mg bid (*n*=4, 1 with TPV/RTV-containing regimens, 2 with raltegravir + NVP, 1 with non interacting drug) or MVC 600 mg bid (*n*=30, all with raltegravir + etravirine). Median individual plasma MVC measurements was 4 (3-5). No associations between age, gender, BMI and MVC Ctrough were observed. However, subjects treated with 150 mg had higher Ctrough compared to the 300 mg and 600 mg group [127 (71 - 161) vs 51 (30 - 128) vs 59 (36 – 82) p=0.033. The sample size of the latter allowed genetic analysis. *PXR 63396 C>T*, *ABCB1 3435 C>T and CYP3A4*1B* were not associated with MVC concentrations. However, MVC Ctrough in *SLCO1B1* 521 heterozygote patients (TC) (n=8) were higher than in wild type homozygotes (CC) (n=22) [103 (69 - 124) vs 46 (28 - 66), p=0.003].
Conclusions. These findings indicate that, although associated with reduced MVC dosing, concomitant DRV/RTV lead to a significantly higher MVC plasma exposure as compared to standard dosing or increased dosing scheduled with CYP3A4 inducers. Moreover, we observed an association between SLCO1B1 *521 C>T* and MVC Ctrough, suggesting that MVC is a substrate for this hepatic influx transporter.

CO 06

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ANTIRETROVIRAL THERAPEUTIC DRUG MONITORING (TDM) AND NEWBORN BIRTH WEIGHT IN HIV-INFECTED PREGNANT WOMEN

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Objective: The minimal placental transfer of protease inhibitors has already been reported, but few data are available concerning the impact of transplacental passage of antiretroviral drugs on newborn outcome. The aim of this study was to evaluate the transplacental diffusion of antiretrovirals and the clinical assessment of the newborn.
Methods: Mother and cord lopinavir, nelfinavir, atazanavir, and nevirapine plasma levels were determined by high-performance liquid chromatography. Newborn gestational age, weight, and Apgar score were recorded. Cord-to-mother ratio (C:M) was calculated to estimate the placental passage of antiretrovirals. Pre-term birth was defined as delivery at <37 weeks gestation and low birth weight was defined as the birth weight <2500g.-
Results**:** Twenty-six HIV-infected pregnant women were studied. Nevirapine presented the highest C:M ratio (0.60$\pm$0.19), the C:M ratio of nelfinavir and atazanavir was 0.37$\pm$0.38 and 0.20$\pm$0.14, respectively. Considering the lack of lopinavir placental diffusion, the respective C:M was <0.004. Observed prevalence rate of neonatal low birth weight and pre-term delivery was 19,2% (n=5) and 15.4% (n=4), respectively. A significant linear regression analysis was reported between the C:M ratio and the birth weight of newborns (p = 0.01).
Conclusions: These data suggest a pharmacological rationale to the association between birth weight and highly active antiretroviral therapy during pregnancy. Although the role of HAART in the prevention of mother-to-child transmission is indisputable, further observations, including long term pharmacological and viro-immunological follow up, are warranted to clarify the outcome of these treatments on maternal and neonatal health.

SESSION II
VIROLOGY

CO 07

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DYNAMIC VARIATIONS OF LYMPHOCYTE- AND MONOCYTE-ASSOCIATED HIV-1 QUASISPECIES AFTER DISCONTINUATION OF HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY AS ASSESSED BY MASSIVELY PARALLEL PYROSEQUENCING

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Background: During natural history of HIV-1 infection and during antiviral therapy, HIV-1 variants harboured by monocytes may evolve in segregated clusters from those harboured by T cells. We analyzed the dynamic variations of HIV-1 quasispecies in these two cellular reservoirs in a small group of chronically infected patients who interrupted HAART after long lasting successful HAART.
Methods: Proviral and viral quasispecies were analyzed at the time of therapy interruption and at subsequent time points. Antibodies targeting monocyte (CD36) and T lymphocyte (CD26) markers were used to sort the two PBMC subpopulations and the corresponding virion progeny released in the circulation. Then HIV-1 quasispecies archived in and released from the two PBMC subpopulations were analyzed with a high resolution technique, based on the next generation genome sequencer 454 GS FLX. Ultra-deep sequencing of a portion of *env* gene, encompassing V3 loop, was performed. By this approach it was possible to analyze thousands of clonally amplified PCR amplicons, increasing the probability of identifying minority variants. An original algorithm was developed to correct the sequences. V3 aminoacid sequences were used to establish heterogeneity parameters and to build phylogenetic trees by distance-based methods. Co-receptor usage was predicted by using position-specific scoring matrix (PSSM).
Results. The heterogeneity of proviral and viral genomes derived from monocytes was higher than that of T-lymphocyte origin. In some cases monocytes and T lymphocytes showed a clearly segregated HIV quasispecies at the time of therapy interruption. The analysis of circulating virions revealed that both sources might contribute to virus rebounding after therapy interruptions, but other sources might also be involved. In patients displaying a complete segregation of the two quasispecies at the time of therapy interruption, a bidirectional interchange of proviral quasispecies between monocytes and lymphocytes was observed already one month later.
In addition, both proviral and circulating viral sequences from monocytes and T lymphocytes were predictive of a predominant R5 coreceptor usage, but minor segregating variants, showing a predicted X4 phenotype, were detected.
Conclusions. This study provided a direct comparison between the HIV-1 quasispecies archived as provirus in circulating monocytes and T lymphocytes with that of plasma virions originating from the same cell types, as well as insights into the dynamics of variants interchange between cellular compartments after therapy interruption. The results indicate that therapy discontinuation was followed by the redistribution of HIV-1 quasispecies segregated into the two main reservoirs, increasing viral variability in each compartment. Ultra-deep pyrosequencing enabled the identification of minority variants that may have clinical and therapeutic relevance.

CO 08

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EVALUATION OF DRUG RESISTANCE EMERGENCE IN HIV-1 INFECTED PATIENTS FAILING A FIRST-LINE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY CONTAINING NNRTIS WITH OR WITHOUT THYMIDINE ANALOGUES

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Background. Highly active antiretroviral therapy (HAART) has reduced morbidity and mortality due to HIV infection since its introduction into clinical use. Current standard-of-care HAART consists of 2 nucleos(-t)ide reverse-transcriptase inhibitors (NRTIs) plus one a non-NRTI [NNRTI] or a ritonavir-boosted protease inhibitor. A proper first-line treatment maximizes the opportunity for successful second-line and subsequent therapies after viral rebound during first-line treatment, by minimizing drug-resistance to HAART. The aim of this work was to evaluate the emergence of drug-resistance in patients failing first line NNRTI-containing regimens administered with AZT+3TC or non-thymidine analogues (non-TAs, TDF or ABC, + 3TC or FTC).
Methods. One hundred and sixty-six HIV-1 infected patients (pts) failing a first line NNRTI-containing regimen (NVP: 81 pts; EFV: 86 pts) followed in different clinical centres in Italy were analyzed. For each patient, a genotypic resistance test at failure was available. The presence of drug resistance mutations in the HIV-1 reverse transcriptase was evaluated by comparing pts treated with NNRTI+AZT+3TC versus those treated with NNRTI+non-TAs. The statistical analysis was performed by Mann-Whitney test for the continuous variables, and by Fisher exact test for the categorical variables.
Results. One hundred and thirty-seven pts were failing with NNRTI+AZT+3TC and 29 with NNRTI+non-TAs (TDF+3TC:13 pts; TDF+FTC: 9 pts; ABC+3TC: 7 pts). No significant differences were observed among the two groups concerning the median time of first failure after six months from starting therapy (AZT+3TC group: 503 [IQR: 267-1128] days; non-TA group: 397 [IQR: 238-1183] days, p=0.719) and the median viral load at first failure (AZT+3TC group: 3.8 [IQR: 2.9-4.6] $\log_{10}$cps/ml; non-TA group: 3.9 [IQR: 2.9-4.9] $\log_{10}$cps/ml, p=0.705).
In the AZT+3TC group, the 3TC/FTC-resistance mutation M184V was present with a frequency doubled compared to those receiving non-TA+3TC (FTC) (68.6% vs. 34.5%, p=0.001). The incidences of ABC/TDF-resistance mutations K65R and Y115F were significantly higher in the non-TA-group than the AZT+3TC-group (K65R: 20.7 vs. 0.7%, p<0.001; Y115F: 10.3% vs. 0% p=0.005). The proportion of pts with at least one thymidine analogue mutation (41L, 67N, 70R, 210W, 215F/Y, 219E/Q) was higher in AZT-group than in non-TA-group (22.6% vs. 6.9%, p=0.071). Resistance to NNRTI (at least one mutation among the major EFV and NVP mutations 100I, 103N, 106A/M, 108I, 181C/I, 188C/H/L, 190A/S, 225H) occurred in 75.2% of AZT+3TC group and in 48.3% of non-TA-group (p=0.007).
Conclusions. Initial therapy with NNRTI+non-TAs resulted in less resistance compared to that observed under NNRTI+AZT+3TC, although no differences in viremia at failure were observed between the two groups. The results obtained confirm the importance of a proper choice of antiretrovirals in the initial therapy to minimize drug-resistance at failure.

CO 09

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ANTI-HIV-1 ACTIVITY OF NEW INTEGRASE INHIBITORS IN LYMPHOCYTES AND HUMAN PRIMARY MACROPHAGES

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Integrase inhibitors (INIs) are a novel class of antiretroviral drugs with potent anti-HIV activity in both antiretroviral treatment-naïve and experienced patients. Aims of our study were to investigate the anti-HIV-1 activity of new INIs (MK-2048, L870,70, IN2 and IN5) in monocytes derived macrophages (MDM) and in Peripheral Blood Mononuclear Cell (PBMCs), and to evaluate the capability of such compounds in preventing virus transmission from MDM to Ly and the related apoptosis. MDM, PBMCs and a CD4+T lymphocyte cell line (C8166) were infected with R5-using or X4-using HIV-1 strains in presence of different concentrations of INIs. HIV-1 p24 Ag gag-production was assessed by immunoenzymatic ELISA test. Effective drug concentration able to inhibit 50% (EC50) and 90% (EC90) of viral replication was calculated by linear regression of the log of the percent HIV-1-p24 production (compared to untreated controls) versus the log of the drug concentration.
Apoptosis was evaluated by FACS analysis in both HIV-1-infected C8166 and PBMCs co-cultured with HIV-1-infected MDM treated or mock-treated with INIs.
In MDM MK-2048 and L870,70 have shown a potent anti-HIV-1 with an EC90 of 4.8 and 37.5 nM, respectively. The values of EC50 in T CD4+ cellular line C8166 are 7.7 nM, for MK-2048 and L-870,70, as 26.8 nM and 9.6 nM are the EC50 values respectively for IN2 and IN5. The values of EC90 in C8166 are 43 nM, 38 nM, 194.3 nM, 19.7 nM, for MK-2048, L-870,70, IN2 and IN5, respectively. The capacity of INIs to prevent the cythopathic effect both in C8166 directly infected with HIV-1 as in C8166 co-cultured with HIV-1 infected MDM, was analyzed by microscopy. MK-2048, L-870,70 and IN5 (62 nM) are able to completely prevent the syncytia formation in C8166 infected with HIV-1. Moreover in the PBMCs cocultured with INIs pre-treated-HIV-1 infected MDM, the syncytia formation and the induction of apoptosis was prevented. In particular with MK-2048 and L870,70 (123.2 nM) the protection from apoptosis was 70% and 67%, respectively. At the same doses of compounds, the HIV-1 production due to the coculture was completely suppressed.
These results shown that INIs strongly reduce HIV-1 production both in MDM as in PBMCs and prevent the correlated damage and virus transmission from HIV-1 infected MDM to CD4+T lymphocytic cell line.

CO 10

Infection 2009; 37 (Suppl. II): 23

IN VITRO EFFICACY OF A NON-CONVENTIONAL (FOLDING) HIV-1 PROTEASE INHIBITOR WITHOUT SELECTION OF RESISTANCE.

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Aim. On the basis of theoretical approaches, we designed a peptide (BRU 83-92) able to interact with a highly conserved folding key sequence of HIV-1 protease. Because of that, the peptide should destabilize the active conformation of the enzyme in a way which is unlikely to bring life to drug resistance. To establish the pattern/rate of emergence of resistance to BRU, we passaged a wild-type clinical isolate in human peripheral blood mononuclear cells (PBMCs) in the presence of drug for up to 9 months.
Methods. *In vitro* "long-term" susceptibility was performed by passaging in PBMCs of a wild-type HIV-1 isolate in the presence of BRU 83-92 or Atazanavir (ATV). Cultures in the absence of drug were maintained as control. The p24 yield was monitored every 3 or 4 days by ELISA assay. In case of viral breakthrough, the concentration of drug was increased and the HIV-RNA at that time-point was extracted from the supernatant and used to detect appearance of mutations leading to resistance by Nested PCR and sequencing of the protease gene.
Results. After 11 months of *in vitro* passage, the experiments showed that the peptide was able to steadily inhibit the replication of HIV, whereas the ATV pressure caused increases of p24 production at different time-points. Thus, the amount of azapeptide was increased several times in order to lower the replication of the virus. By genotype sequencing, it was seen that BRU 83-92 did not select for any mutation that led to resistance. On the contrary, it was noted appearance of primary (I50L) and/or secondary mutations (L10I and Q58E) on the protease gene of the isolate under ATV.
Conclusions. The capacity to escape selection of resistance after several *in vitro* passages suggests that primary and/or secondary mutations on the protease gene able to overcome the inhibition of BRU 83-92 are likely to be incompatible with the regular activity of the enzyme. Resistance to protease inhibitors require specific or multiple mutations in discrete regions of the protease and BRU seems to avoid them so far. These data support the investigation of this peptide in the clinical setting.

CO 12

Infection 2009; 37 (Suppl. II): 24

PHENOTYPIC VARIATION IN A MOTHER-TO-CHILD TRANSMISSION COHORT

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Background HIV-1 variants with CCR5 usage are preferentially involved in transmission of infection and associated with progression of disease to overt AIDS. R5 viruses have an intrinsic variability demonstrated by their susceptibility to CC-chemokines as well as different capacity to infect macrophages or *ad hoc* engineered cell lines expressing CCR5/CXCR4 chimeric receptors. R5 viruses are not predictive of mother-to-child transmission (MTCT) of HIV-1. In this study we have explored the predictive value of R5 variability in MTCTand pediatric disease progression.
Materials and methods U87.CD4+ cells expressing the wild type receptor CCR5 or CXCR4, or one of the 5 different CCR5/CXCR4 chimeric receptors, in which subsequent part of CCR5 were replaced with corresponding parts of CXCR4, were used to determine the phenotype.
Virus isolates obtained from 24 transmitting mothers and their children obtained close to birth, and 171 biological viral clones of additional 5 mother-child pairs were tested for their ability to infect the U87.CD4+ cells.
Results 7 out of 24 transmitting mothers and carried viruses able to use both CCR5 and CXCR4 coreceptors.
All 10 mothers harbouring an R5narrow virus had children who displayed the same viral phenotype. Interestingly, the six mothers carrying R5broad viruses transmitted in all but one case a virus able to use chimeric receptors. The five mothers with an R5X4 virus transmitted the whole spectrum of virus phenotypes.
All the biological clones from the mothers have a R5 broad phenotype, able to use FC1, FC2 and/or FC4. None of the mothers carries a X4 virus. The virus of the infants is of R5 narrow phenotype only in 2 cases and mixed with R5 broad clones in the remaining 3 cases. Only 1 infant carries also R5X4 virus variants.
Conclusion Our results show that HIV-1 with broad chimeric receptor use can be transmitted from mother to child, even if this phenotype appears not to be predictive of MTCT. Moreover, the evolution of R5 phenotype to broad R5 broad usage occurs frequently.

SESSION III
ANTIRETROVIRAL THERAPY: TOXICITY

CO 13

Infection 2009; 37 (Suppl. II): 24

CORONARY AGEING IN HIV INFECTED PATIENTS

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Background. The objectives of this study were to assess the coronary age (CA) of a cohort of HIV infected patients based on the extent of coronary artery calcium (CAC) and to iden-tify the variables associated with it.
Methods. Observational cross-sectional study of 400 HIV patients receiving antiretroviral therapy (ART) attending a cardiometabolic clinic. All patients underwent CAC screening using computed tomography and CA was calculated based on CAC score tables generated by the Multi-Ethnic Study of Atherosclerosis (MESA).
Findings. Increased CA was observed in 162 patients (40.5%) with an average increase of 15 (range 1-43) years compared to their chronological age. In univariable analyses ad- vancing age, male sex, higher systolic blood pressure, longer duration of ART exposure, higher fasting glucose, fasting serum triglycerides, total cholesterol, LDL and HDL cholesterol, hypertension, and the presence of the metabolic syndrome were associated with CA. Among the 162 patients with with increased CA current CD4+ cell count was the only predictor of increased CA both in univariable (β=0.30, p=0.031) and multivariable linear regression (β=0.51, p=0.005) analyses.
Interpretation. Increased CA was highly prevalent in our cohort, and the current CD4+ cell count was the sole independent predictor of it. This hypothesis generating observation suggests that CA may be a surrogate of premature biological ageing in HIV infected patients and that the increase in CD4+ count due to ART may incite atherosclerosis development.

CO 14

Infection 2009; 37 (Suppl. II): 25

AN EXPLORATORY ANALYSIS TO ASSESS THE POTENTIAL EFFECT OF ART IN MODIFYING THE FRAMINGHAM RISK SCORE IN HIV- INFECTED PATIENTS ENROLLED IN THE ICONA FOUNDATION STUDY

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Background: The aim of this analysis was to quantify the potential effect of ART and other HIV-related factors in modifying the Framingham risk score (FRS) in HIV-positive patients living in Italy.
Methods: Baseline for the analysis was defined as the date of enrolment (for person years of follow-up (PYFU) while patients were still off-ART) and the date of starting ART (for the PYFU post-ART). We studied patients for whom data on smoking, blood pressure (BP), cholesterol (total, HDL) was available at baseline and their gender-specific FRS was 0% (the score was calculated at each subsequent clinical visit). The progression to a FRS ≥5% was analysed using KM curves and Cox regression; PYFU pre-ART were censored at the time of initiation of ART. Predictors studied included mode of HIV transmission, HCVAb-status, baseline CD4, baseline viral load (VL) and use of ART (intention to treat), after controlling for gender age and baseline FRS parameters (smoking, total and HDL cholesterol and BP).
Results: Of a total of 903 patients eligible for this analysis, 492 (54%) were excluded because they had a FRS of 1-4% at baseline. Of the 411 included, 151 contributed PYFU pre-ART (49% female, 30% smokers) and 260 post-ART (60% female, 30% smokers), none of the patients contributed to both. Median baseline parameters at enrolment and at ART initiation were: 31 vs. 34 years of age, 152 vs. 154 mg/dl of total cholesterol, 120 vs. 120 mmHg of BP, 48 vs. 45 mg/dl of HDL, 568 vs. 289 CD4 cells/µl and 4.17 vs. 4.32 VL log copies/mL. Overall, 40 patients experienced a FRS >5% over a median of 0.7 PYFU pre-ART and 2.9 PYFU post-ART. By 3 years from baseline FRS increased to a value ≥5% in 9% (95% CI:1-17) of patients over PYFU in which they were ART-naive and in 12% (95% CI:8-16) over PYFU in which they were ART-exposed (log-rank test p=0.62). Crude and adjusted relative hazards of a FRS ≥5% from fitting a proportional hazards Cox regression model are shown in the Table.

	Crude		Adjusted*	
Characteristic	**RH (95% CI)**	**p-value**	**RH (95% CI)**	**p-value**
Use of ART				
No	1.00			
Yes	1.23 (0.54-2.82)	0.62	0.51 (0.16-1.67)	0.26
Mode of transmission	1.00		1.00	
Heterosexual	1.51 (0.62-3.64)	0.36	0.74 (0.23-2.35)	0.61
IDU	1.94 (0.94-3.99)	0.07	1.02 (0.42-2.51)	0.96
Homosexual	1.21 (0.35-4.13)	0.76	0.68 (0.18-2.51)	0.56
Other/unknown				
HCV-coinfection	1.00		1.00	
No	0.89 (0.40-1.95)	0.76	0.75 (0.27-2.12)	0.74
Yes	0.82 (0.29-2.34)	0.71	0.68 (0.18-2.51)	0.67
Not tested				
Baseline CD4 count Per 100 cells/µl higher	0.92 (0.81-1.04)	0.18	0.86 (0.73-0.99)	0.04
Baseline VL Per log copies/mL higher	1.12 (0.86-1.44)	0.41	1.09 (0.82-1.46)	0.56

*Adjusted for gender, age, total cholesterol, hdl cholesterol, smoking status and blood pressure at baseline.

Conclusions: There was little evidence supporting that ART is implicated in a dramatic modification of parameters currently included in the FRS, although the power of our analysis was low. Besides the FRS parameters, a lower baseline CD4 count was the only factor associated with a higher risk of experiencing a FRS>5%.

CO 15

Infection 2009; 37 (Suppl. II): 25

ATTENUATED DIURNAL BLOOD PRESSURE RHYTHM IN NAÏVE HIV INFECTED PATIENTS. RESULTS FROM THE HERMES STUDY

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Background. In normal subjects, blood pressure (BP) decreases during sleep by 10% to 20% and increases promptly on waking. An abnormal diurnal variation pattern has been described when the nocturnal BP fall was <10% (non-dippers pattern). A less marked decrease in night-time blood pressure led to an increased risk of cardiovascular complications. Several cross-sectional studies reported that, non-dippers had more clinical and sub-clinical target organ damage in the heart, brain, and kidneys than dippers. In the general population the prevalence of non-dippers is expected between 10-35%.
Little is known about the relation between the circadian rhythm of BP, especially nocturnal BP, and HIV infection.
Objective. To identify an abnormal circadian blood-pressure profile in naive HIV-infected patients in ordinary clinical settings.
Design. This was a baseline analysis of data from HERMES, a prospective study including all treatment-naïve patients attending scheduled visits at the hospitals belonging to CISAI group in 2007.
Methods. Naïve HIV-patients were included. The 24 hours Ambulatory blood pressure (ABP) measurements were performed using an oscillometric device. Subjects with a nocturnal decline in systolic blood pressure <10% were considered as non-dipper.

Results. A total of 40 subjects was enrolled, median age 41.5 years, 87.5% of them males. The mean duration of HIV infection was 3.3 years (range 0-21 years), CD4 443±220cells/mm^3, HIV-RNA $\log_{10}$ level 4.2±1.1/mL. The mean of systolic and diastolic BP were 120±12 and 77±9 mm/Hg. Estimated 10-years global cardiovascular risk by new Framingham risk score was 9.9%±12.1%. The prevalence of the non dipping patients was 55%. Nocturnal systolic and diastolic BP fall was 14.2% and 18.6% in dippers and 5.0 % and 9.2% in non dippers.
Conclusions. In naïve HIV infected patients the prevalence of non dipping BP pattern, characterized by a limited nocturnal BP fall, was higher than expected. The consequences of this abnormal BP rhythm in HIV infected is unknown, but may significantly contribute to the increased risk of cardiovascular diseases.

CO 16

Infection 2009; 37 (Suppl. II): 26

ULTRASOUND AND LIPOATROPHY DIAGNOSIS: EXPERIENCE ON 295 HIV – POSITIVE OUTPATIENTS IN ANTIRETROVIRAL THERAPY

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Background: Ultrasound is an ideal imaging technique in the early assessment of lipoatrophy and in the follow up of affected patients because it is cost effective, widely available, easily accepted and without ionizing radiations risk. Aim of this study was to confirm ultrasound usefulness on HAART (Highly Active Antiretroviral Therapy) – related lipoatrophy diagnosis in HIV positive patients.
Methods: The thickness of the subcutaneous fat was assessed with ultrasound scan in correspondence of the deepest point of the Bichat pad for the face, 10 centimeters above the elbow for the arm and 10 cm above the rotula for thigh. We identified diagnostic cutoff values in males and females to assess moderate and severe degrees of lipoatrophy. They were 13.0 and 13.5 mm for moderate, 9.0 and 10.5 mm for severe facial lipoatrophy; 6 and 6.5 mm for moderate, 4.5 and 5.5 mm for severe brachial lipoatrophy; 6 and 10 mm for moderate, 4.5 and 7.5 mm for severe crural lipoatrophy in males and females, respectively. The ultrasound evaluations were performed in 295 outpatients on stable HAART (at least 1 year) attending the outpatient clinic of the Infectious Diseases Department – "L. Sacco" Hospital – Milan. The data were analyzed using ROC-*curve* analysis and compared to lipoatrophy clinical diagnoses according to the HIV Outpatients Study Grading Scale (HOPS-GS): not lipoatrophy (HOPS-GS 0), moderate lipoatrophy (HOPS-GS 1) and severe lipoatrophy (HOPS-GS 2-3).
Results: Compared to ultrasound technique, for all reference points severe lipoatrophy was assessed clinically in 80.9% of males and 88% of females whereas moderate lipoatrophy was detected only in 69% of males and 74% of females.
Discussion: This study confirms the validity of ultrasound technique in the assessment of lipoatrophy and in the follow up of affected patients. In moderate lipoatrophy the technique is able to detect minimal fat losses, not recognized by human eye. Due to these characteristics, ultrasound technique is useful particularly in the early diagnosis of body fat changes. Indeed, it is well known that a delay in therapy modification will restore normality only after several years.

CO 17

Infection 2009; 37 (Suppl. II): 26

PROTEINURIA OR GLOMERULAR FILTRATION RATE: THE IMPACT OF AIDS AND COMORBIDITIES ON THE PREVALENCE OF DIFFERENTLY MEASURED SUBCLINICAL RENAL IMPAIRMENT IN AN HIV-INFECTED POPULATION

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Background. Concern on long term toxicity of combination antiretroviral therapy (cART) comprises potential decline of renal function, which is however conditioned by other factors, including HIV itself and comorbidities. We assessed factors associated with mild renal impairment in an unselected cohort of HIV-infected patients on cART.
Methods. All sequential HIV-infected patients on cART attending the Infectious Diseases Unit of San Gerardo Hospital (Monza, northern Italy) who underwent routine examinations (including creatinine plasma level and urinary dipstick) between June 2008 and January 2009 were enrolled.
Two different outcome measures were considered: presence of proteinuria (any level) at urinary dipstick and mild glomerular filtration rate (GFR) reduction (i.e., <90 ml/min, estimated using Modification of Diet in Renal Disease [MDRD] formula). Possible associations with the following factors were assessed in both analyses: current CD4+ T cell counts, fasting glucose and insulin levels, total cholesterol, HDL, LDL, triglycerides (TG), HCV and HBV coinfections, diabetes, hypertension, previous diagnosis of any AIDS-defining illness, time of exposure to cART, use of tenofovir, boosted protease inhibitors or atazanavir. Moreover, age, gender, ethnicity and GFR were also studied for their possible association with proteinuria.
Association between categorical or continuous variables was assessed by Chi-squared, t-test or Mann-Whitney, as appropriate. All P-values are two sided. Results are expressed as means ± standard deviation or frequency (%), unless otherwise specified.
Results. Of 357 patients on cART, 71 (19.9%) had a reduction of GFR. Among all considered factors, only fasting glucose level was significantly higher in subjects with GFR reduction (101±55 vs. 93±20 mg/dL, P=0.050) and diabetes was more frequent (12.5% vs. 3.1%, P=0.007).
Proteinuria, detected in 47/357 patients (13.2%), was significantly associated with older age (50±11 vs. 46±9 years, P=0.003), lower GFR (98±34 vs. 109±22 ml/min, P=0.003), higher glucose (116±66 vs. 92±19 mg/dL, P<0.001), higher median [inter-quartile range] insulin (14.7 [8.9-29.1] vs. 11.2 [7.0-18.1], P=0.012), higher TG (256±231 vs. 191±161 mg/dL, P=0.016), lower HDL (39±16 vs. 46±17 mg/dL, P=0.005), presence of diabetes (19.5% vs. 2.8%, P<0.001), hypertension (26.8% vs. 12.6%, P=0.016) and AIDS diagnosis (51.1% vs. 27.9%, P=0.001).
Conclusions. A relevant prevalence of mild renal impairment has been documented in Monza HIV outpatient cohort. GFR reduction was neither associated with HIV-related nor with classical risk factors for renal impairment, except for diabetes. Conversely, proteinuria strongly reflected comorbidities commonly linked to renal damage, and was also associated with present or past AIDS diagnosis. Further studies are warranted to better define the role of proteinuria, possibly a better indicator than creatinine, in predicting the renal damage progression.

CO 18

Infection 2009; 37 (Suppl. II): 27

DIAGNOSTIC REASSESSMENT OF OSTEOPENIA AND OSTEOPOROSIS RATES IN HIV PATIENTS: ARE WE OVER-ESTIMATE THE PROBLEM?

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Introduction. It's well known that HIV infected patients have a higher rate of osteopenia than uninfected people. The most part of the studies diagnosed bone loss by means of T-score BMD, but the recent guidelines devised by the International Society for Clinical Densitometry (ISCD) have recommend to use the T-score only for women in menopause and men over the age of fifty; in the latter at least one major risk factor for osteoporosis must be present. As HIV patients are usually younger than 50 years, a T-score-based diagnosis appears not appropriate. For these a diagnosis by Z-score (that compares patient's BMD with that of a healthy age- and sex-matched population) is recommended.
The aim of this study was to investigate whether a Z-score-based diagnosis identifies a different rate of bone diseases rather than hat obtained by T-score.
Material and methods. In a retrospective study we considered 100 caucasian patients followed in the infectious diseases department of Bologna. Inclusion criteria were a documented HIV positive test, be older than 18 and younger than 50 years. Exclusion criteria were having a connate infection or, for a woman, being in menopause. We considered for each patient sex, age, years of infection. DXA scan was performed by means of an HOLOGIC 4500 QDR device. WHO criteria for diagnosis of osteopenia and osteoporosis (T-score) were applied. In order to conform Z-score and T-score we arbitrarily called in Z-score analysis the patients with low bone mass (Z-score lower than -1 and higher than -1,99) osteopenic and those with severe low bone mass (Z-score < -2) osteoporotic.
Statistical analysis was conducted by running the program SPSS (8.0 version), considering significant a P value lower than 0,05 A Chi Squared analysis was applied on contingency tables.
Results. Of 100 patients 55 were male and 45 women, the mean age was 41,1± 6.2 years, the mean of years of infection was 10,86± 6.1 years. The results of different rates of bone loss are visible in table 1.All the shown differences were statistiucally significant (P<0,0001).
Discussion. Our results revealed a significant difference between the T-score and the Z-score analysis, in the rates of normality, osteopenia and osteoporosis. This study suggests that a T-score-based diagnosis can possibly overestimate the rate of osteopenia and osteoporosis in HIV patients. By using a Z-score-based diagnosis a lower prevalence of bone diseases has been found and particularly a higher rate of osteoporosis has been identified. These preliminary results seem to suggest that a more sensible diagnostics criterion, like Z-score, can allow the identification of a higher risk population and therefore can help clinician both in reaching a more appropriate diagnostic assessment and a more effective therapeutic intervention.

Table 1

	Lumbar			Neck			Femur tot		
	Normal	**Osteopenia**	**osteoporosis**	**Normal**	**Osteopenia**	**osteoporosis**	**Normal**	**Osteopenia**	**osteoporosis**
T-score	35	51	14	24	62	14	36	58	6
Z-score	42	41	17	53	38	9	50	42	8

SESSION IV
CLINICAL IMMUNOLOGY

CO 19

Infection 2009; 37 (Suppl. II): 27

TOLL-LIKE RECEPTOR ACTIVATION PATHWAYS IN A COHORT OF HIV-1 EXPOSED SERONEGATIVE INDIVIDUALS

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Toll-like receptors (TLRs) trigger innate immunity against conserved motives of invading pathogens causing cellular activation and release of inflammatory factors. The influence of TLRs activation on susceptibility to HIV-1 infection has never been investigated in HIV-1 exposed seronegative individuals (ESN).
PBMC isolated from a cohort of 10 couples discordant for HIV-1 serostatus were stimulated with agonist specific for TLR3 (poli I:C), TLR4 (LPS), TLR7 (Iniquimod) and TLR8 (ssRNA). Expression levels of the factors involved in their signalling cascade, the downstream production of effector immune mediators, and TLR-expression on CD4+ and CD14+ cells were evaluated. Results were compared to those obtained in healthy controls (HC).
In ESN compared to HC we observed: 1) a lower percentage of CD14+/TLR4+ and CD4+/ TLR8+ CD14+/TLR8+ cells; 2) a higher responsiveness to Poly I:C, LPS, iniquimod and ssRNA stimulation, associated to a significantly increased production of IL1beta, IL6, TNFalpha, IFNbeta and CCL3; 3) an augmeted expression of mRNA specific for other targets (CSF3, CSF2, IL1alpha, IL8, Cox-2, Tak-1, TBk) as pointed out by a broader TLRs pathway expression analyses. These differences were particularly evident following incubation with ssRNA (TLR8) and iniquimod (TLR7) (stimulation of the Myd88-dependent pathways) than with poly I:C (TLR3) (Myd88 independent pathway).
These data suggest that TLR stimulation in ESN results in a more robust release of immunological factors that influence the induction of stronger adaptive antiviral immune response and may represent primary determinants in resistance to HIV-1 infection.

CO 20

Infection 2009; 37 (Suppl. II): 28

LONG-TERM NON PROGRESSING HIV-DISEASE ASSOCIATED TO COINFECTION WITH HTLV-2 IS ASSOCIATED WITH UNIQUE FEATURES OF NK CELL PHENOTYPE AND FUNCTION COMPARED TO MONOINFECTED LTNP PATIENTS

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The influence of human T-cell leukemia/lymphoma virus type 2 (HTLV-2) coinfection in HIV-1-infected patients has recently clarified as protective rather than potentiating HIV-1 disease progression. In this context HTLV-2 mechanisms of viral interference have been associated to increased CC-chemokine production and reduced STAT1 activation. NK cell function is usually profoundly affected during HIV infection, and relevant inhibition is also observed on CD8+CTL by de novo expression of inhibitory NKR
Here we studied whether viral interference could possibly affect also phenotypic or functional parameters in cytolytic cells (NK cells and CD8+ T-lymphocytes) in dually infected patients with non progressing disease compared to HIV-1 monoinfected LTNP.
Patients and Methods. PBMC were obtained from 2 cohorts of LTNP: HIV-1$^+$HTLV-2$^+$ LTNP and HIV-1$^+$HTLV-2$^-$ LTNP. In addition HIV-1$^-$HTLV-2$^+$ and viremic HIV-1$^+$HTLV-2$^-$ patients were considered for comparison. Negative separation using mAbs and magnetic beads and multiple-colour cytofluorimetry were employed: two-colour cytofluorimetry using specific monoclonal antibodies was performed on enriched or purified cell populations to analyze the expression of iNKRs on TCRαβ+ resting PBMC. Purified peripheral NK cells were analyzed to evaluate NK cell activation. In vitro activated NK cell cultures were generated in the presence of rIL-2 to evaluate cytokine production profiles.
Results. Data indicate that the expression of iNKR on T cells and the expression of activation markers on CD16+CD56+ NK cells is significantly different in the HIV-1+HTLV-2$^-$ patients compared to HIV-1 progressors. Both LTNP groups show limited functional iNKR inhibition on CD8+ CTLSs. Peripheral NK cells display relevant differences in the two LTNP groups, with reduced "exaustion", absent activation and higher levels of activatory receptors expression in HTLV2-coinfected LTNP. Cytokine and chemokine production patterns for IL-6,IL-8,IL-10, IL-17, IFNg, TNFa, MIP1a,MIP1b and RANTES were concordant for the two groups with relevant differences compared to viremic patients.
Some of the effects of viral interference of HLTV-2 on the progression of HIV-1 disease positively affect cytolytic cells of the immune system including CD8+ CTLs and NK cells in HTLV2-coinfected LTNP. Differential effects on NK cells in the two LTNP groups suggest relevance of different innate mechanisms for the control of disease progression in HIV-1 infected patients.

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LACK OF POLYFUNCTIONAL RESPONSE OF GAG-SPECIFIC CD4+ AND CD8+ T LYMPHOCYTES IN LTNP

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Polyfunctional CD8+ T cells specific for HIV are supposed to play a role in controlling the production of the virus, measured by the plasma viral load (VL), and thus in delaying the progression of the infection. Less is known about T regulatory cells (Treg) and HIV-specific CD4+ in "long-term non progressors" (LTNP), i.e., those infected from at least 10 years, with a stable number of CD4+ T cells (>500 CD4+T cells/uL), and who never took antiretroviral therapy.
We analyzed 10 LTNP, 8 treatment-naïve HIV+ patients with progressive disease (PROG) and 8 patients who underwent CD4-guided Structured Treatment Interruption and had to restart therapy (STI, 11-52 months without highly active antiretroviral therapy). By polychromatic flow cytometry (16 parameters flow cytometer CyFlow ML from Partec, Germany) in peripheral blood we evaluated HLA-DR+/- Treg (CD3+,CD4+,CD25+,FoxP3+,CD127-), and detected HIV-specific CD4+ and CD8+ T cells by simultaneously evaluating the expression of CD107a, CD40L, IL-2, IFN-gamma after stimulation with Gag overlapping peptides and exclusion of dead cells.
We observed that all groups displayed similar levels of Treg; in comparison with LTNP, STI patients showed a higher percentage of Treg and CD4+ that expressed HLA-DR+. LTNP had more CD4+ lymphocytes expressing CD127 if compared to PROG and STI patients. STI patients presented a higher HIV-specific CD4+ total response vs. LTNP, while HIV-specific CD8+ frequency was comparable in all groups. The overall quality of specific T cell response was similar in all patients. The majority of Gag-responding CD4+ cells were CD40L+ or CD107a+; cytokine production was detected in few responding CD4+. Gag-specific CD8+ response was dominated by CD107a+ cells, some of them producing also IFN-gamma+, while IL-2 was detected only in one LTNP. We could not highlight any association between the parameters we analyzed and CD4 count or VL, or between HIV-specific response and Treg frequency in LTNP.
The polyfunctionality of T cells specific for gag was very rare, even in LTNP. Most specific CD4+ cells did not produce TH1 cytokines, but were CD107a+ or CD40L+. The most striking difference between LTNP and PROG or STI patients was the expression of CD127 on CD4+ lymphocytes.

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DIVERGENT ROLE FOR DENDRITIC CELLS IN VIRAL CONTROL AND CHRONIC INFLAMMATION IN HIV DISEASE

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Background: Several studies suggest that plasmocytoid dendritic cells (pDCs) are crucial in the control of HIV replication and modulation of T-cell response. Although TLR recognition of viral components by pDC is crucial for antiviral immunity, TLR stimulation through of IFN-α secretion has also been implicated in the pathogenesis of

chronic immune activation and inflammatory response. Chronic inflammation might also be involved in the pathogenesis of some organ and metabolic disorders associated with HIV infection, including liver and kidney diseases, atherosclerosis and diabetes.
Objectives: To assess how DC analysis has a prognostic role not only in the control of HIV infection and disease progression, but also in the development of HIV-associated inflammatory pathology.
Methods: Circulating mDCs and pDCs were assessed in whole blood samples from 61 ARV-treated patients using single-platform TruCOUNT assay and monoclonal antibodies. 1 ml of whole blood were stimulated with imiquimod (10 μg/ml) for 18 hours and IFN-α levels (pg/ml) were measured in culture supernatants by ELISA. DC analysis was also correlated with biomarkers of inflammation, including plasma levels of high-sensitivity C-reactive protein (hs-CRP), tumour necrosis factor (TNF-α) and matrix metalloproteinases (MMPs). The carotid intima media thickness (IMT) was measured as surrogate marker for underlying atherosclerosis.
Results: Despite effective ART, patients exhibited a significant reduction of circulating pDCs and mDCs when compared with healthy donors ($p<0.001$). ARV-treated individuals with lower baseline pDCs (<5000 cells/ml) were more likely to have a virologic failure during the follow-up ($p <0.001$). On the other hand, the levels of CD4 count at baseline were not predictive of viral control over time. TLR-stimulating agent imiquimod, which is specific for TLR7, induces an up-regulation of IFN-α production by pDC in both viremic and aviremic treated patients, even if the mean levels of IFN-α in patients remained lower than healthy controls (28 pg/ml versus 179 pg/ml; $p<0.001$). The lowest levels of DCs, especially mDCs, were found in 36 patients who had a greater thickness in carotid IMT. The analysis of the correlation showed a statistically inverse association between the carotid IMT and the absolute number of mDCs (-0.34; $p=0.03$). Elevated plasma levels of hs-CRP and MMP-9 was also found, while TNF-α was undetectable.
Conclusions. The pDC dysregulation in the periphery could be associated with ongoing tissue activation and increased local production of IFN-α in lymph nodes and other inflamed tissues. Potential approaches based on the use TLR-targeted antagonist could be useful to limit the release of IFN-α by pDCs and to downregulate chronic inflammation. The dynamic measurements of DC numbers and biomarkers of inflammation may represent useful tools for the monitoring of HIV disease progression and metabolic-inflammatory conditions, such as atherosclerosis.

CO 23

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INCREASED THYMIC PRODUCTION OF REGULATORY T-CELLS (TREG) IN HIV-INFECTED PATIENTS: THE CONTRIBUTION OF THE THYMUS TO THE MAINTENANCE OF TREG LEVELS

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Background. Regulatory T cells (Treg) develop in the thymus and are critical for the control of immune responses. Treg may be beneficial by limiting non-specific immune activation, a hallmark of HIV infection. However, Treg may also be detrimental by suppressing HIV-specific immune responses, thus allowing more virus replication. The impact of HIV on the development of CD4+CD25+ T cells (Treg) in the thymus remains unclear.
Methods. We evaluated thymic tissue from 6 HIV-infected and from 6 HIV-negative adults who underwent heart surgery. The phenotype of thymocytes (CD34, CD1, CD3, CD4, CD8) was measured, together with the expression of activation/proliferation markers (CD69, CD27, Ki67). CD4+CD25+FoxP3+ T cells were analyzed by FACS. T-student test was used for statistical analysis.
Results. All thymopoietic stages were present in both HIV+ and HIV- thymic tissues, but these stages were skewed in HIV-infected compared to uninfected thymuses. Thus, whereas the percentage of immature triple negative cells (CD34+CD3-CD4-CD8-) was comparable in thymuses of HIV+ and in HIV- patients, a significant increase of double negative (DN) CD3+CD4-CD8- cells ($p=0.01$) and of CD3+CD4-CD8+ single positive (SP) cells ($p=0.05$) as well as a reduction of double-positive (DP) (CD3+CD4+CD8+) and CD3+CD4+CD8- SP cells were observed in thymuses of HIV+ subjects. Proliferation and activation, as evaluated by the expression of Ki67, CD27 and CD69, was significantly augmented in HIV+ thymuses both in DN/DP ($p<0.05$) and in SP thymocytes ($p<0.05$), with a predominant expression of CD69 in CD4+ SP cells. The expression of CD25 and FoxP3 on CD4+ SP cells was significantly increased as well in thymuses of HIV-infected individuals ($p=0.01$), whereas the expression of CD25 and FoxP3 on CD4+CD8+ DP cells was equal in HIV+ and HIV- thymuses.
Conclusions. HIV infection induces the reduction of intrathymic CD4+ precursors and an increased activation status of thymocytes at multiple stages of differentiation. The frequency of Treg is increased in HIV-infected thymus, particularly in already-committed CD4 single positive cells. HIV can induce the abnormal accumulation of Treg, either by direct infection and enhancement of their survival and function, or bystander effect, mediated by host-derived pro-inflammatory molecules.The enrichment of Treg in the thymus parallels a similar trend in lymphoid tissue and may lead to the suppression of pathogen-specific immunity and could contribute to the lack of immune control of HIV. The therapeutic manipulation of this subset may modulate pathogen-specific immune responses in HIV disease.

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OSTEOPENIA/OSTEOPOROSIS IN HIV INFECTED PATIENTS ARE ASSOCIATED WITH REDUCED EXPRESSION AND PRODUCTION OF IL-7RA IN CD8+ T CELLS

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Background: Much attention has been addressed to the role of activated T cells producing osteoclastogenic cytokines in the pathogenesis of bone resorption. Given the chronic hyper activation and the high prevalence of osteopenia/osteoporosis in HIV, we wanted to address whether osteopenia/osteoporosis in HIV+ patients (pts) was associated with a specific T-cell immune-phenotypes and cytokine milieu in peripheral blood.
Methods: Bone density was measured by dual X-ray absorptiometry (DEXA) at the femoral neck and lumbar spine. Osteopenia/osteoporosis were respectively defined by a T score <-1 and <-2,5 (WHO). Pts with pathologic DEXA (PD) were compared to pts with normal DEXA (ND) in terms of demographics (age, sex, BMI), HIV parameters (AIDS, time from HIV first positive test, current CD4 and nadir, HCV-Ab, HBsAg, time on HAART); T-cell phenotype (CD8+CD38+, CD4+ - CD8+CD95+, CD4+ - CD8+CD127+, CD8+CD38+45R0+). Variables with $p<0.05$ were studied by multivariable logistic regression.

Plasma levels of osteoclastogenic cytokines, IL-7 and TNF-α, were measured by ELISA. IL7-Ra mRNA expression (cpsIL-7Rα/100ngTFRC) was measured by real time PCR in CD8+ and CD4+ T cells separated from PBMC trough magnetic beads.
Results: Seventy-nine pts were analysed: 23 had normal DEXA (29%) and 56 pathologic DEXA (71%): osteopenia in 48 pts and osteoporosis in 8 pts. PD and ND pts were comparable in terms of demographics and HIV parameters. T-cell immune-phenotyping resulted in significantly lower mean CD8+CD127+ % in PD respect to ND pts (13%[IC95% 11.2-14.5%] *vs* 16.3%[IC95% 13.3-19.4%],p=0.03), with no differences in any other phenotypes. This result was confirmed by multivariate analysis, adjusted for demographics and HIV parameters: CD8+CD127+ % resulted independently associated with pathologic DEXA (OR 0.9 for each 1% increase [IC95% 0.818-1.003]; p=0.05). Consistent with CD8+ IL-7Ra (CD127) expression, PD pts displayed lower mean IL-7Ra mRNA in CD8+ respect to ND pts, albeit not significant (18,5 *vs* 48, p=0,12). Interestingly, despite similar plasma IL-7 concentration, PD pts showed a trend to an inverse correlation between plasma IL-7 and IL-7Ra expression in CD8+ (rho=-0.29,p=0,10) and a significant inverse correlation between IL-7 and CD8+ IL-7Rα mRNA (rho=-0.78,p=0.01), whereas no significant correlation was shown in ND.
Conclusions: Our data show reduced IL-7Ra expression in CD8+ from HIV+ PD pts, independently of demographic, HIV and HAART conditions. Further investigation of IL-7/IL-7Ra axis resulted in an inverse correlation between IL-7 and IL-7RαCD8 production and expression. Given IL-7 osteoclastogenic activity, the findings of reduced receptor production and cell-surface availability, negatively correlating with free IL-7 in PD pts, might suggest altered cytokine-receptor balance and turnover at the cell surface ultimately resulting in differential signaling with possible implications in terms of bone resorption.

SESSION V
CO-INFECTIONS, OPPORTUNISTIC INFECTIONS AND TUMOURS

CO 25

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THE RISK AND DETERMINANTS OF MALIGNANCIES IN HIV- INFECTED PATIENTS ENROLLED IN THE ICONA FOUNDATION STUDY

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Introduction. It has been shown that the risk of death from non-AIDS defining severe events is higher in people with lower CD4 counts, even when the CD4 count is greater than 350 cells/cmm. There is less evidence that this is true for severe events non leading to death. We aimed to estimate the incidence of both AIDS (ADM) and non-AIDS defining (NADM) malignancies and to identify their predictors.
Methods. We studied patients of the Icona Foundation Study, with at least 1 CD4 count measurement, followed from enrolment to the minimum time between the last follow up date and the date of occurrence of a malignancy. Malignancies were divided into ADM and NADM, using the CDC93 definition and excluding in-situ cervicae carcinoma. Incidence rates of ADM and NADM were estimated as numbers of non-recurring malignancies per 1,000 person years follow up (PYFU) overall and by current CD4 strata (in a cause specific analysis). Multivariable Cox proportional hazard models were used to identify predictors of ADM/NADM malignancies in separate analyses. All covariates were fit as time fixed, using the value at enrolment, with the exception of current CD4 count, HIV-RNA load, and initiation of antiretroviral treatment (ART).

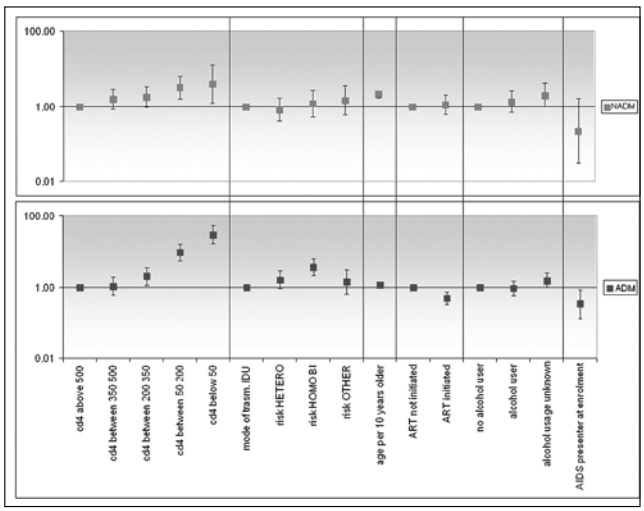

Figure 1

Results. 6691 patients were included in the study (71% male, 94% of European or North Americans, 37 years old on average, 41% HCV Ab positive, 7% HBV co-infected, 56% smokers, 40% alcohol users, 36% intravenous drug users, 1.1% with malignancies before enrolment). Overall, we observed 169/33517 ADM, corresponding to an incidence rate of 5.0 per 1000 PYFU (95% CI: 4.3-5.8). For NADM, we observed 83/33517 events, corresponding to an incidence rate of 2.5/1000 (95% CI: 2.0-3.1). Incidence rates of ADM were 2.2/1,000 (95% CI: 1.3-3.5) in patients with a current CD4 of 350-500 cells/cmm and 2.0/1,000 in those with a CD4>500 cells/cmm (95% CI: 1.4-2.8) (p=0.96), whilst for NADM the corresponding rates were 2.5/1,000 (95% CI: 1.6-3.9) and 1.5/1000 (95% CI: 1.1-2.2) (p=0.081). Adjusted relative hazards of ADM and NADM fitted from the Cox models are shown in Figure 1 (only RH for variables associated at 0.05 level with the risk of malignancies are shown). Models were adjusted also for HIV-RNA log10 cp/ml, nationality, sex, HCVAb positivity, HBV co-infection, smoking status, malignancies at anamnesis, and year of enrolment.
Conclusions. The incidence of NADM in our study population was relatively low compared to that of ADM. There was a tendency for the risk of both ADM and NADM to continue to increase even at CD4 count >350 cells/cmm, though not significant when comparing to CD4 count >500. Apart from the higher risk of both ADM and NADM produced by lower CD4 counts and age, there was a clearer increased risk of ADM for homosexual/bisexual mode of HIV transmission group, presumably due to the correlation with Kaposi's Sarcoma.

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LONG-TERM SURVIVAL AMONG HIV-1 INFECTED PATIENTS WITH AIDS AND NON AIDS RELATED MALIGNANCIES

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Background: 15-years or longer survival in HIV-1 infected patients with cancer has not been investigated.
We described long-term survival in a large cohort of HIV-1 infected subjects with AIDS defining (ADM) or non AIDS defining malignancies (NADM) .
Methods: HIV-1 infected patients followed at our department and with a cancer diagnosis were considered for the analysis. According to CDC 1993 classification, malignancies were divided into ADM and NADM. Survival was calculated from the date of cancer diagnosis and was censored to the last available visit or death or when lost to follow-up. Values are reported as medians (Q1-Q3) or frequencies (%) as appropriate. Survival curves were estimated according to Kaplan-Meier method and compared by the log-rank test.
Results: Among 6495 patients, 603(9.3%) patients developed a cancer during 75672 person-years of follow up (PYFU) corresponding to an incidence rate (IR) of 7.96./1000 PYFU (6.9-9.1%; 95% CI). Subjects characteristics: age at the end of follow up 44.4 (37.7-51.0) years, 95 (15.6%) females, 527 (87.4%) had an history of a CDC C event, 9.9 (4.5-15.2) years from HIV infection; 216 (35.8%) alive; 345 (57.2%) dead; 42 (7.0%) lost to follow up.
ADM were 424/6495 (6.5%) with an IR of 5.78/1000 PYFU (95% CI: 4.7-6.8) while NADM were 179 (2.8%) with an IR of 2.49/1000 PYFU (95% CI 2.0-3.0).
ADM were 228 (87.7%) out of 260 cancers observed in the pre-HAART era (<1998), while in the post-HAART era, ADM counted for 57.1% (196/343). In contrast NADM represented 12.3% (32/260) of cancers during pre-HAART era and increased to 42.9% (147/343) after 1997 (p< 0.0001).
Probabilities of death (expressed as percentages) at 1, 5,10,15, 20 years from the diagnosis of ADM or NADM were: [ADM= 43.9 (±2.5) at 1 year; 62.1 (±2.6) at 5 years; 69.8(± 2.7) at 10 years; 72.1 (± 3) at 15 years; not evaluable 20 years; NADM= 31.9 (±3.5) at 1 year; 51.5 (±4.4) at 5 years; 60.6 (± 5.7) at 10 years; 68.5 (± 8.4) at 15 years, 100% of patients died within 17 years].
Cause of death were tumor-related in 73/85 (86%) and 206/260 (79%) among NADM or ADM patients, respectively.
Probabilities of deaths in pre and post-HAART era for ADM and NADM were statistically different (p<0.0001) and are reported in Table 1.

Table 1

	1 year	5 years	10 years	15 years
NADM <1998(n=32)	32.0+3.9	65.6+8.4	68.8+8.2	75.0+8.6
NADM >= 1998 (n=147)	31.5+8.8	48.2+5.2	NE	NE
ADM <1998 (n=228)	47.4+2.7	74.9+2.9	80.1+2.7	81.6+2.7
ADM>=1998 (n=196)	23.8+5.4	43.4+4.0	52.0+4.9	NE

NE= not evaluable

Conclusions: Long term survival is poor both in patients with ADM and in those with NADM, although in HAART era survival seems to be higher compared to pre HAART era in both groups. After 1998 an increase of total number of cancer diagnosis was observed, which was basically due to an increase in NADM.

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SEVERE LIVER TOXICITY (SLT) IN A COHORT OF ITALIAN HIV- INFECTED PATIENTS TAKING COMBINATION ANTIRETROVIRAL THERAPY (CART) WITH A LONG PERIOD OF FOLLOW UP

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Background: cART may be limited by liver toxicity. Aim of the study was to investigate the rate and predictors of increased risk of severe liver toxicity in an observational cohort with a long follow up period.
Methods: We analyzed 1,719 HIV-infected patients enrolled in the Italian MASTER Database initiating cART from 1994 to 2005. cART was defined as a combination of three or more antiretroviral drugs with at least two NRTIs. Severe liver toxicity (sLT) was defined as ≥3 WHO grade of ALT or AST elevation. For subjects with baseline ALT or AST >40 IU/l, sLT was defined as an increase in baseline ALT/AST level ≥3.5. Poisson regression model was used to estimate crude and adjusted IRR.
Results: Among patients included in the analysis, 28.0% were HCV or HBV coinfected; 218 cell/mm^3 and 4.83 $\log_{10}$ cps/ml were baseline median value for CD4+ and HIV-RNA, respectively. During 5,232 p-y (median 3.0 years, IQR 1.2-4.7) of follow-up 136 episodes of sLT occurred (incidence rate 2.6 per 100 PYFU). At multivariable analysis the relative rate of sLT was higher in patients coinfected with HCV or HBV (ARR 3.12, 95%CI: 1.89-5.18), and with HCV and HBV (ARR 5.44, 95%CI: 2.39-12.38). The higher risk of sLT occurred after 3-6 months of cART (ARR 1.69; 1.64-4.42), whereas in a prolonged observation no increasing risk was observed. CD4+ cell count and higher HIV-RNA values, as time updated covariates, were associated with a reduced rate (ARR 0.96, 95%CI: 0.92-0.99 for 50 cells increase) and an higher relative rate of sLEE (ARR 1.11, 95%CI: 1.01-1.21 for each log10 increase), respectively. Age >35 years was found as associated with lower rate of sLT (ARR 0.70; 0.49-1.00). No significant association was observed with different ARV "third" drug class exposures. Only patients taking NNRTI plus PI tended to be associated with an increased risk of developing sLT (ARR 2.14, 95%CI: 0.68-6.70).
Conclusions: During long-term cART the incidence rate of sLT remains low. The risk of severe liver toxicity prevalently affects the first six months of cART, independently from drug-class received and line of therapy. HCV/HBV coinfection was confirmed as main predictor, whereas better viro-immunological conditions may have a protective effect on liver toxicity.

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CHARACTERISTICS OF LAMIVUDINE RESISTANCE PROFILES IN HBV REVERSE TRANSCRIPTASE FROM A NATIONAL COLLABORATIVE STUDY OF HIV+HBV INFECTED INDIVIDUALS ON LONG-EXPOSURE TO LAMIVUDINE INCLUDING REGIMENS

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Background: Nearly 10% of HIV-infected individuals worldwide suffer from chronic hepatitis B virus (HBV) infection, and given the widespread use of 3TC for anti-HIV therapy, many HIV+HBV co-infected patients (pts) have received prolonged 3TC therapy. The goal of this study is to provide new insights on 3TC resistance profiles in HBV reverse transcriptase (RT) and on factors affecting 3TC efficacy in HBV+HIV co-infected pts.
Methods: 89 full-length HBV RT and HBsAg sequences from 64 HBV+HIV co-infected pts, receiving 3TC including regimens were analyzed at baseline (BL) and at different time-points (up to 6 years) after starting 3TC therapy. All pts had detectable HBV-DNA at the time of starting 3TC and were not treated with other drugs effective against HBV. Virological-failure was defined by a rebound of serum HBV-DNA of >1logIU/ml from the nadir value. The association of mutations with 3TC treatment and with virological outcome was assessed by Fisher exact test and by calculating the dn/ds ratio at each RT/HBsAg position.
Results: Among 64 pts, 32(50.0%) and 27(42.2%) are infected with HBV-D and -A genotypes, respectively, while the remaining 5 (7.8%) are infected with HBV-G genotype.
3TC HBV-failure is observed in 47.3% of pts after a median time of 2.3[IQR:1.5-3.2] years with a median serum HBV-DNA of 6.0[IQR:4.6-7.2]logIU/ml, and is associated with lower CD4 cell count (344[IQR:258-488]cells/ul versus 704[IQR:550-770]cells/ul). Prevalence of 3TC resistance mutations progressively increases with longer duration of 3TC treatment: from 38.5% at 1 year to 77.8 at 2-3 years, and to 90.0 at >4 years. Of note, at 4 years, 60% of 3TC-failed pts harbors at least three 3TC resistance mutations, including the triple mutant (M204V+L180M+V173L) associated with vaccine escape. We also identified novel potential HBV RT mutations (V266R, W243G, M226L) significantly associated with 3TC treatment (P<0.05). Among them, W243G is completely absent at BL, and its frequency significantly increases up to 12.2% of 3TC failed pts, correlating with the presence of M204I/V at failure. No novel mutations associated with 3TC treatment are observed in the pre-S1/S2 and S domains of HBsAg.
Finally, we found that the presence of specific polymorphisms at BL significantly correlates with the achievement of HBV-DNA<12IU/ml at 1 year of 3TC treatment. In particular, the proportion of HBV-DNA<12IU/ml at 1 year is higher in pts with Q130P at BL compared to pts without this mutation (71.4% *versus* 18.2%, P=0.04), corresponding to a relative risk to achieve HBV-DNA<12IU/ml 3.1-fold (95%CI:1.2-4.8, P=0.04) higher in presence of Q130P compared to its absence.
Conclusions: Our study shows that the HBV-resistance profiles to 3TC are more complex than those currently known, and highlights the existence of HBV-RT polymorphisms able to modulate 3TC virological response. Their knowledge is crucial for a correct set up of antiviral therapy in both HBV mono-infected and HBV+HIV co-infected pts.

CO 29

Infection 2009; 37 (Suppl. II): 32

ROLE OF INTERFERON-Γ RELEASE ASSAYS (IGRAS) IN HIV- SSOCIATED TUBERCULOSIS: IN VITRO AND IN VIVO EFFECT OF ANTITUBERCULOUS DRUGS

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Background: The introduction in clinical practice of the interferon-γ release assays (IGRAs) has open new perspectives for the detection of tuberculosis (TB). However the value of these tests in patients with HIV/TB coinfection and their role in the monitoring the response to antituberculous treatment is still unclear.
Methods: A total of 167 HIV-infected individuals with suspected TB were tested with QuantiFERON-TB Gold (QFT-G) in response to *M. tuberculosis*-specific (MTB)-antigens ESAT-6 and CFP-10. In order to assess longitudinal changes of response to MTB antigens during treatment, individuals with active TB were followed over time. To evaluate the in vitro interference of the anti-TB treatment on the IFN-γ release, blood samples were incubated overnight with different concentrations of the following drugs: rifampicin, isoniazid, pyrazinamide and ethambutol. Statistical analysis in the patients was performed using Wilcoxon signed-rank and Spearman rank correlation tests.
Results: The QFT-G test was positive in all 33 (19%) subjects with active TB (mean CD4=195 cells/μl) and negative in 94 (56%) subjects with disease other than TB (mean CD4=365 cells/ml). 40 TST-negative subjects (23%) had an indeterminate QFT result (mean CD4=99 cells/μl), 10 of them developed an active TB within 2 months. Lower $CD4^+$ count was also associated with a reduced release of IFN-γ to TB antigens (p<0.005). Serial testing in patients with active TB showed a conversion to negative QFT-G results in all subjects and a parallel significant decline in IFN-γ levels (p<0.001) which correlated with clinical and microbiological response to treatment. In these patients, the median IFN-γ levels was 5,17 UI/ml at baseline, 3,98 UI/ml at month 2, 0,218 UI/ml at month 4 and 0,07 UI/ml at the end of treatment. The in vitro analysis showed for the first time that anti-TB drugs used at concentrations similar to those achieved in the serum of treated patients did not exert any inhibitory effects on IFN-γ release if compared to the control (p=0.071). A significant inhibitory effect (p<0.001) was seen only at concentrations 2-3 times greater.
Conclusions: Our findings suggest that advanced HIV-infected patients who had an indeterminate QFT-Gold result should be closely monitored for the potential risk of developing active TB. In addition the decrease of IFN-γ response to mycobacterial antigens in patients with successful treatment response is not due to a direct inhibitory of anti-TB drugs or to the variability of the IGRA, but it likely reflects the reduction in mycobacterial burden.

CO 30

Infection 2009; 37 (Suppl. II): 33

MUTATIONS OF AMINOACID RESIDUES INVOLVED IN CELL BINDING ARE PRESENT IN THE JC VIRUS (JCV) CAPSIDE PROTEIN-1 (VP1) FROM PATIENTS WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

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Background: PML has become the second cause of AIDS-related deaths and it is currently observed also in cART-treated patients, both during recently initiated and chronic treatment. JCV, the causative agent of PML, is ubiquitous in humans and, following primary infection, establishes a persistent infection in the kidney. The mechanisms leading to virus reactivation and PML, however, are not known. It is possibile that the major JCV capsid protein, VP1, plays a role in neuropathogenesis, because it is involved in cell entry, through binding with sialic acid residues on the cell surface. The aim of this study was to investigate whether JCV from PML patients carries mutations in VP1 and whether these may be associated with neurotropism and neurovirulence.
Methods: We amplified, cloned and sequenced the entire JCV-VP1 region from cerebrospinal fluid (CSF) samples of 26 PML patients (including 20 patients with HIV infection), and 11 paired plasma and 6 paired urine samples. From 9 patients, sequential CSF (n=7) or plasma (n=2) samples were also analysed . JCV DNA level was measured by real-time PCR. 3D modeling was used to map the mutations on VP1 structure.
Results: Almost all CSF clones from each of 25/27 (93%) patients carried one single mutation at specific aa in one of the three outer loops of VP1. These involved aa 51-52 (deletion; 1 patient), 55 (n=7), 61 (n=1), 122 (n=3), 124 (n=1), 265 (n=3), 267 (n=2) and 269 (n=7). Same mutations were recognized in all the paired plasma but in none of the paired urine samples. Analysis of the sequential samples showed persistence of initial mutation in four patients and onset of a new mutation in a patient showing PML relapse after remission of a first episode. By 3D modelling, all mutated residues clustered on the VP1 surface within or in the immediate proximity to the binding site with the sialic acid cell receptor.
Conclusions. JCV from CSF and plasma but not urine of PML patients consistently carry one of several specific VP1 mutation of aa residues located at critical sites for cell binding, and these mutations are maintained through the course of the disease. Overall, these findings support a model whereby VP1 mutations are selected during JCV replication in peripheral sites. These mutations might confer increased virus neurotropism and lead to progressive CNS infection.

SESSION VI
ANTIRETROVIRAL THERAPY: IMMUNO-VIROLOGICAL OUTCOME

CO 31

Infection 2009; 37 (Suppl. II): 33

IMPACT OF MUTATIONS AT POSITION 135 OF HIV-1 REVERSE TRANSCRIPTASE ON VIROLOGIC RESPONSE TO A FIRST LINE NNRTI-CONTAINING HAART

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Background: Previous studies showed that mutations at RT position 135 can contribute to NNRTI resistance. Thus, the goal of this study is to investigate the impact of baseline (BL) mutations at position 135 on the virologic response to a first line HAART containing NNRTI.
Methods: We studied 373 HIV-1 infected patients (pts) who started a first line HAART containing NNRTI with a genotypic resistance test within the prior 6 months. Among them, 286 (76.7%) pts were treated with EFV and 87 (23.3%) with NVP. Endpoints were the proportion of patients with virological-success (VS: viremia <50cp/ml) at week-24, -48, and -96, and the evaluation of predictors of virological response to NNRTI regimens. Factors correlated with the achievement of VS were assessed by multivariate logistic regression in an intention to treat analysis (variables considered: subject demographic, year of treatment, drugs co-administered with NNRTI, BL viremia, not-B subtypes, and mutations at position 135).
Result: Among the 373 pts, 71 (19.9%) were infected with non-B subtype. At BL, pts with at least 1 transmitted drug resistance mutation were 21 (5.6%): 13 (3.5%) for NRTI, 15 (4.0%) for NNRTI. The proportion of pts who achieved VS at week 24 was 77.5%, and VS was maintained at week-48 and -96 in 79.2% and 74.8 % of pts, respectively. At BL, position I135 was mutated in 178 pts (47.7%), with the prevalence of mutations as follows: 29.2% with T, 9.7% with V, 3.5% with R, and less than 3% with other mutations (L/M/A/K/S). In particular, 135V was present in 24 pts (33.8%) with non-B subtypes, and in 11 pts (3.8%) with B subtype. The BL presence of 135V significantly correlated with a worse virologic response to first line NNRTI-regimen. In particular, the proportion of VS at week-96 was lower in NNRTI-treated pts with 135V at BL compared to pts without this mutation (46.6% *versus* 79.6%, P=0.008). Univariable logistic regression at week-96 showed that in pts without transmitted drug resistance the predictors associated with a reduced probability of VS were: 135V at BL (OR:0.23[CI:0.07-0.66], P=0.007) and TA use (OR:0.2[CI:0.1-0.6] P=0.002). Conversely, predictors associated with a increased probability of VS were: TDF use (OR:2.58[CI:0.5-6.4], P=0.03), EFV use (OR:5.2[CI:2.4-12.5], P=0.0001 versus NVP) and year of regimen starting (OR:1.25[CI:1.0-1.5],P=0.009 per more recent). Multivariable analysis confirmed the negative correlation of 135V (OR:0.16[CI:0.03-0.65], P=0.01) and the positive correlation of EFV (OR:6.4[CI:1.8-23.0], P=0.004 versus NVP) with VS at week-96. The other mutations at position 135 did not affect NNRTI VS.
Conclusions: This study shows that, among several natural polymorphisms at codon I135, only the 135V mutation may be an independent predictor of a worse virologic response of a first line HAART containing NNRTI. The identification of mutations able to predict the virologic response to HAART is crucial for a correct tailoring of the antiretroviral therapy.

CO 32

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DIFFERENT GENOTYPIC SENSITIVITY SCORE (GSS) APPROACHES FOR UNDERSTANDING THE IMPACT OF ARCHIVED RESISTANCE MUTATIONS ON HIV PROGRESSION

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Background: The correlation between extended resistance to antiretroviral drugs and HIV progression has been already assessed. However, the role of archived mutations is not still understood. To address this topic, we compared the predictive value for HIV progression of resistance detected in the latest genotypic resistance test versus those from resistance test history in multi-experienced patients.
Methods: From the data-base of our Institute, patients who underwent 3 genotypic resistance tests (GRT) in course of cART failure between 1999-2008 were included. The genotypic sensitivity score (GSS), using the latest REGA interpretation system (version 7.1.1), was assessed both for current GRT and for historic GRT (defined as combination of mutations detected in all 3 GRT).
Moreover, GSS was calculated with 3 different methods: the number of drugs predicted to be active among those received as salvage regimen after third GRT (effective GSS, GSS-E); the total number of drugs predicted to be active at the time of third GRT (total GSS, GSS-T) and the number of drugs predicted to be active among those approved for use at the moment of third GRT (weighted GSS, GSS-W). The predictive role of GSS-E/GSS-T/GSS-W for new AIDS events or death, as end-point, was assessed using adjusted Cox model.
Results: Overall, 209 patients were included: males 63.6%, median age 41, CDC-3 38.3%, median CD4 272, median log-HIV 4.28. After a median observation of 28 months (IQ range: 15-53), 21 events occurred (9 new AIDS events and 12 deaths).
The historic GSS-E, GSS-T and GSS-W were lower than the current ones (median 2.12 vs. 2.75, 14.5 vs. 18.5 and 11.25 vs. 13.6 respectively).
At Cox model, all GSS of current GRT were predictive of short term virological failure. In contrast, historic GSS-T/GSS-W predicted HIV progression: GSS-T was marginally associated to slower progression considering each score point (OR: 0.93, 95% CI: 0.86-1.00, p=0.073); GSS-T was also associated for a >16 score (OR: 0.19, 95% CI: 0.04-0.90, p=0.036) and GSS-W for a >13 score (OR: 0.20, 95% CI: 0.04-0.91, p=0.38).
A further analysis was performed after calculating GSS for each of the 3 main antiretroviral classes. Again, only historic GSS-T/GSS-W was associated with slower HIV progression if at least one active drug for each class was present (GSS-T: OR: 0.25, 95% CI: 0.06-1.07, p=0.062 and GSS-W: OR: 0.12, 95% CI: 0.12-0.91, p=0.04).
GSS-E was not associated to HIV progression in any model, while previous CDC-C diagnosis was associated to faster progression in all models tested.
Conclusions: Archived mutations play a major role in identifying the most impaired patients. All resistance mutations acquired during treatment history can influence future choices and survival, even though not detected by the latest resistance tests.
Thus, main challenge of antiretroviral treatment is to preserve future treatment options both avoiding loss of active drugs and maintaining active drugs in every drug class.

CO 33

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HIV PLASMA EARLY DECAY WITH TWO STANDARD FIRST LINE HAART: RELATIONSHIP TO IMMUNE-VIROLOGIC PATTERN, T CELL RECOVERY AND VIROLOGIC RESPONSE

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Objective: We characterized viral dynamics during the first week on therapy with two first-line standard HAART combinations and we investigated the relationship to immune-virologic pattern, T cell and virologic response at 12 weeks.
Methods: We conducted a pilot study including 11 naïve patients with baseline HIV plasma viral load (pVL) >50.000 cp/ml, randomised 1:1 to receive tenofovir/emtricitabine 245/200 mg backbone regimen plus efavirenz 600 mg once daily (arm E: 6 patients) or lopinavir-ritonavir 400/100 mg twice daily (arm L: 5 patients). The viral decay constant (VDc) during the first week and the reduction in pVL after 12 weeks of the two treatment arms were compared by Kruskall-Wallis test. Nonparametric Spearman's rank test was used for significance of correlations between VDc at day 7 and host specific factors (baseline pVL, CD4+/CD8+ T cell number and percentage, CD8+CD38+ percentage), T cellular restoration (the difference from baseline of CD8+CD38+/CD8+CD127+/CD8+CD95+/CD8+CD45Ro+ percentage at week 12) and virologic response (pVL reduction at week 12). All *P* values were two-tailed and were not adjusted for multiple testing.
Results: There was no significant difference in the baseline pVL (log10 cp/ml, [interquartile range, IQR]) between treatment arms (E : 4.8 [4.6-5.0]; L: 5.3 [4.6-5.7]). The median VDc during the first 7 days on HAART (log10 cp/day, [IQR]) was similar for E (0.19 [0.15-0.22] and L (0.19 [0.17-0.27]) as was the median reduction in pVL after 12 weeks (log10 cp/ml, [IQR]) (arm E: 2.78 [2.69-3.13]; arm L: 2.78 [2.51-3.59]). At baseline, mean CD4 T cell percentage (% [SE]) in arm L (11.3 [1.67]) were significantly lower than in arm E (21.8 [2.33]), despite comparable CD4 T cell count (cell/μL [SE]) (L: 229 [63]; E: 283 [26]), and no difference in the CD8 T cell panel. We found significant positive correlations between VDc and baseline percentage of CD8+CD38+ lymphocyte (rho=0.64; p=.043). No correlations were found between the decay rates and the baseline pVL nor the number of CD4+ and CD8+ T lymphocytes. The VDc at day 7 tended to correlate inversely with changes in the percentage of CD8+CD45Ro+ T lymphocytes (rho=-0.60, p=.08) and was significantly directly correlated with the reduction in pVL (rho=0.85, p=.0002) during 12 weeks.
Conclusion: Efavirenz and lopinavir/ritonavir in combination with tenofovir/emtricitabine showed similar virological efficacy in the short term. The early HIV decay with these regimens, either including NNRTI or boosted PI, is predictive of virological efficacy and reduced consumption of primed/activated CD38+45R0+CD8+, leading to the speculation of more preserved memory/effector CD8 pool. Moreover, our finding of an association of heightened baseline activated CD38+CD8+ and more elevated viral decay, might prospect the investigation of CD38 measurement as predictive marker of virological efficacy independently from baseline HIV-viremia.

CO 34

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CURRENT PATIENT-REPORTED DRUG HOLIDAYS ARE ASSOCIATED WITH LONG-TERM SUB-OPTIMAL TREATMENT OUT-COME IN SUBJECTS WITH CD4 NADIR <200 CELL/MMC INITIATING CART

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Objectives: Different patterns of non-adherence differently impact virological response to antiretroviral therapy. We studied the relationship between different non-adherence behaviours and long-term viro-immunological success in patients with CD4 nadir <200 cell/mmc.
Methods: Long-term viro-immulogical optimal response (defined as HIV-RNA<50 cp/ml and CD4>500 cell/mmc) was investigated in 235 subjects with CD4 nadir <200 cell/mmc who received cART for least 4 years. Adherence was assessed by a self-reported questionnaire that investigated the following patterns of non-adherence: <95% of therapy taken in the last month; <100% doses taken over the last week; timing deviation; drug holidays over the last month; interruption in drug refill over last 3 months. The relationship between different types of non-adherence and optimal viro-immunological response was assessed both in univariate and multivariate models.
Results: A total of 235 patients were included in the analysis: 24% women; mean age 47, 48% with a previous AIDS. Risk factors for HIV were: IDU in 45%, heterosexual intercourse in 32%, and homosexual in 12%. Participants were on cART for a median of 11 years (IQR 9-13) and had a median number of 5 (IQR:3-8) previous cART regimens.
Concomitantly with the adherence assessment, mean values of viro-immunological parameters were: HIV-RNA 2.00 log10/ml (range 1.70-5.70) and CD4 539/mmc (IQR 324-715). The current regimen contained a PI-boosted in 62%, and a NNRTI in 29% of cases.
Definition of viro-immulogical optimal response was recorded in 96 (41%) subjects.
Prevalence of reported deviations in adherence were: 25.0% for <95% of therapy taken in the last month; 26.6% for <100% doses taken over the last week; 43.8% for timing deviation; 16.2% for drug holidays, and 13.2% for interruption in drug refill.
At univariate analysis, all non-adherence behaviours were significantly associated with treatment success, and for each adherence deviation more a 60% lower probability of response was found. At multivariate logistic model adjusted for type of regimen, time of treatment, and HIV risk factor, number of non-adherence behaviours remained the strongest variable associated with treatment success (OR 0.56 for each more deviation; 95%CI 0.42-0.74; <0.0001). In particular, when all non-adherence patterns were included in the model, only self-reported drug holidays had an independent effect on optimal viro-immunological response (OR 0.16; 95%CI 0.04-0.61).
Conclusions: These data demonstrate that substantial CD4 gains are possible among highly advanced adherent patients. Our data suggest that patterns of incomplete adherence, namely unplanned short interruptions in treatment, may have a detrimental effect on immunorecovery. To optimize viro-immunological response in advanced subjects, a comprehensive investigation of all non-adherence behaviours is needed in clinical practice.

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PHENOTYPIC PROFILES OF HIV-1 INTEGRASE GENE EVOLUTION DURING RALTEGRAVIR FAILURE

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Background: Dynamic patterns of mutations have been observed during Raltegravir (RAL) failure, suggesting that they are the result of the equilibrium between drug resistance and enzyme function necessary for efficient HIV-1 replication. In this context, we investigated the phenotypic profiles of integrase gene evolution occurring in 11 triple-class failure HIV-1 infected patients failing RAL based regimens.
Methods: Phenotypic assays were performed on purified CD4+ T cells obtained from healthy donors. A specific recombinant vector with a cloning cassette for the integrase gene amplified from patients' plasma allowed viral clonal analysis and the generation of fully replicating recombinant viruses. RAL IC_{50} values were evaluated on 1-6 clones for each patient. Replication capacity (RC) of baseline and resistant variants (relative RC of resistant clones compared to wild type; RRC) were evaluated by a multiple cycle competition assay.
Results: RAL failure was associated with selection of resistance mutations in all patients but one, whose HIV-1 plasma load consistently remained above 500 copies/ml even if the virus resulted to be fully susceptible. RAL fold change resistance (FCR) of escape mutants varied from 10 to 700. Two patients had a rapid viremia rebound at week 4 associated with the selection of rare natural polymorphisms at position 143 (Y143K or Y143S+201I). These variants conferred moderate resistance level (20 and 10 FCR, respetively) to RAL and had no negative impact on viral RC, paving the way to major mutations (N155H+151I and Q148R+138K). Resistance mutations in position 143 (Y143C/G/R) had a variable impact on resistance and RC, possibly due to the presence of mutations in position 72, 74 and 97 that were always observed in combination. The majority of primary mutations caused a reduction of viral RC (78 to 7% RRC reduction) with a tendency, when treatment was maintained, to partially restore viral RC. The N155H mutation was associated with 42-200 FCR and to variable effects on RC from none (+151I) to 57% RRC reduction in combination with T97A. Y143R mutation was selected early, probably due to the high FCR (120) and a modest impact on RC (86% RRC). The G140S+Q148H combination had the highest FCR (231-700) and caused a 27% RRC reduction of viral RC. Selection of the G140S+Q148H combination was observed in either firstly selected variants, or as the population substituting the first escape virus bearing the Q148R+138K (90FCR, 87% RRC) or the G140S+143R (100 FCR and 50% RRC) combinations.
Conclusions: The driving force of selection and stabilization in the viral population was the level of RAL resistance. Many resistant variants showed a reduced RC compared to wild-type viruses as result of both the number and the combination of primary and secondary mutations. RC values tended to increase over time, but remained always below baseline levels during the follow-up.

CO 36

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REGULATORY T CELLS, IMMUNE ACTIVATION AND APOPTOSIS ARE INVOLVED IN PERSISTENTLY REDUCED CD4 COUNTS IN HIV- INFECTED IMMUNOLOGICAL NON-RESPONDERS.

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CD4 counts are persistently reduced and CD4 T lymphocytes are functionally-defective in a percentage of HIV-infected, HAART-treated patients (immunological non-responders –INR-). T regulatory cells (Treg), immuneactivation and apoptosis are suggested to play a role in such CD4 count defects. The PD-1/PD-L1 and the Fas/FasL pathways elicit apoptosis of antigen-specific cells; Treg down-regulate T cell function and induce apoptosis by PD1/PD-L1 interaction.
To verify possible role for these mechanisms in INR we enrolled 38 HIV-infected patients with comparable CD4 nadirs and HIV RNA <50 copies/ml who had undergone HAART for >1 year. CD4 counts were >500 cells/μl in 15 patients (full responders –FR-); in 23 other patients (INR) CD4 were <200 cells/μl. PBMC were stimulated with gag+env or with CMV peptides. Flow-cytometry was used to analyze intra and extracellular PD1 in CD4+ T lymphocytes as well as the expression of PD-L1, TLR2 and TLR4, and of Fas and FasL on immune cells. Treg lymphocytes (CD4+/CD25high/Foxp3+), IL-10 production, activation of caspases 8 and 9, and plasmatic LPS concentration were also examined in all patients.
Results showed that in INR compared to FR patients: 1) intra-and extracellular PD1 positive CD4+ T lymphocytes, 2) Fas- and FasL-expressing CD4+T lymphocytes, 3) Treg and IL-10 production, and 4) the percentage of apoptotic cells are increased. Additionally, in INR patients CD14+/TLR2+ TLR4+ cells are augmented, plasmatic LPS concentration is higher, and CD4+ T cells are hyperactivated. These increases are seen both in gag+env- and CMV-stimulated PBMC. Notably, PD-L1 expression was comparable in CD14+ and CD19+ cells of both groups of patients.
The augmented plasmatic LPS concentration detected in INR could explain immune activation and presence of higher Treg cell function. PD1/PD-L1interaction results in an increased apoptosis of antigen-specific CD4+ T lymphocytes. IL-10 is also increased in INR, this observation could explain the functional T helper impairments also seen in these patients. Apoptosis plays an important role in the defective immune reconstitution seen in INR.

POSTER PRESENTATIONS
SESSION I

PP 01

Infection 2009; 37 (Suppl. II): 37

TEMPORAL CHANGES IN COST OF FIRST LINE COMBINATION ANTIRETROVIRAL THERAPY (CART) FOR PATIENTS WITH HIV IN ITALY, 1997–2007

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Background: The introduction of combination antiretroviral therapy (cART), in 1996, caused a dramatic reduction of mortality and morbility for Human Immunodeficiency Virus (HIV) infected subjects. The resulting decrease in the hospitalization costs more than offset those for antiretroviral (ARV) drugs. The changes in treatment costs that have taken place since then for subjects accessing cART for the first time has not been sufficiently described.
Objectives - The objective of the study was to analyze the temporal changes in the average cost of first line cART regimen through the period 1997-2007 in participants in the Italian Cohort of Antiretroviral-Naïve Patients (ICoNA).
Methods: We studied subjects who started a cART regimen (defined as a combination of at least three drugs that included a PI or a NNRTI). Inclusion criteria required: 1) age>=18 years; 2) availability of a CD4 cell count and a HIV RNA viral load measurement in the 6 months before starting treatment. The monthly cost of each regimen was calculated based on: 1) the average prices applied to the public hospitals of Lazio region in 2007; 2) the standard dosage used in the same year. To analyze the temporal trend in monthly cost we used linear regression models. The hypothesis of a trend in the proportion of subjects reaching viral suppression (a viral load<500 copies ml) within 6 months from cART initiation was tested by the LR test.
Results: Among 4359 subjects starting a cART regimen, those satisfying inclusion criteria were 3796. 71% were males and the median age at cART initiation was 37 years (Interquantile Range (IQR) 32.8-42.6). The mean monthly cost for first line regimen increased from 590.5 € in 1997 to 755.9 € in 2007, with an estimated average annual increase of 15.1€ (Confidence Interval (CI) 14.2-16.0). At the multivariable analysis, characteristics significantly associated with an increase of monthly cost were: lower CD4 cell count; having experienced an aids defining illness, older age and not being ARV naïve at cART initiation. After taking into account clinical and demographic characteristics of the subjects, the average annual increase of monthly cost remained statistically significant (14.7€; CI 13.8-15.7). In the same period, the proportion of subjects experiencing viral suppression showed a significant increase, from 23.8% in 1997 to 66.9% in 2007 (Likelihood Ratio test for linear trend p<0.001). As a result, the cost to reach a viral suppression in the first 6 months of treatment went down from 12180€ in 1997 to as much as 5890€ in 2007.
Conclusions: Changes in clinical and demographic characteristics of patients did not explain the increase observed for the average cost of first line cART regimen in the (ICoNA) cohort. Nevertheless we saw a parallel increase in the effectiveness of first line cART as measured by the proportion of subjects reaching viral suppression that more than offset the higher costs incurred in the more recent years.

PP 02

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INCIDENCE OF SYPHILIS IN A COHORT OF HIV INFECTED SUBJECTS, ITALY

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Background and objective: Syphilis is re-emerging worldwide, especially among HIV infected persons. In this population syphilis is a behavioural marker that reflects the potential for further spreading of the HIV virus through sexual activity. We measured factors associated with increased odds for syphilis among HIV infected persons at a single clinical site.
Methods: All consecutive HIV infected persons registered at the Department of Infectious Diseases, Spedali Civili, Brescia from 1 January 2001 to 30 June 2008 were included. All demographic, behavioural, and syphilis treponemal tests (TPHA) results were extracted from the electronic database where information is prospectively entered. Syphilis prevalence and incidence were measured as a positive TPHA test at the first determination after cohort entry and during follow-up screening tests, respectively. Logistic regression was used to identify the variables independently associated with syphilis.
Results: During the study period 1966 new HIV infected subjects were entered in the database. They were predominantly male (1409, 71.7%), Italian (1473, 74.9%), infected by the heterosexual route (789, 40.1%), with mean CD4+ T cell count of 364 (SD± 277.11) and HIV-viral load of 119,427 copies/mL (SD± 496.27). A TPHA test was performed in 1492 subjects (75.9%). Positive TPHA results were documented in 240 persons, with a syphilis prevalence of 16.1%. In the multivariate analysis model the factors which were independently associated with an increased probability of syphilis infection were male gender (OR= 2.7, 95% C.I.:1.56 – 4.57; p< 0.005), being foreign born (OR= 3.0, 95% C.I. 2.04 – 4.41; p< 0.005), omo-bisexual orientation (OR= 4.4, 95% C.I: 3.15 – 6.16; p< 0.005), and older age (OR= 1.05; 95% C.I.: 1.03 – 1.06 for each year of age; p< 0.005). After a mean follow-up period of 2.49 years, at least one new TPHA test result was available for 660 patients. Sixty-one (9.2%) new cases of syphilis infection were diagnosed, for an incidence rate of 3.71 cases/100 person-year (95% CI: 2.85 – 4.74).
Comments:Syphilis prevention strategies are important among HIV infected persons, and should be primarily directed towards male subjects with omo-bisexual orientation. An older age and being foreign borne are additional criteria for targeted interventions.

PP 03

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ECONOMIC EVALUATION ON TWO TYPES OF HIV-POSITIVE PATIENTS (FAILING HAART AND VIROLOGICALLY CONTROLLED) FROM LOMBARDIA REGION HEALTH CARE SYSTEM PERSPECTIVE

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Background: The use of HAART led to dramatic decreases in the morbidity and mortality of patients infected with HIV. This conversion of HIV disease from fatal condition into chronic disease made pharmaceutical expenditure related to this pathology hugely increase, within a system with limited resources. There is, therefore, the need to evaluate whether the costs introduced by the newest therapies can be compensated by the reduction of the expenditures due to the clinical management of patients failing viral suppression and exposed to the risk of developing AIDS disease.
Objective: The aim of this study is to evaluate the budget impact on Lombardia Region Health Care System of different categories of public health costs (Hospitalizations, HIV-drugs, Nonantiretroviral drugs, Out-patient care) related to two HIV-positive patient typologies: "failing HAART" and "virologically controlled".
Methods. The study is a retrospective observational one based on a HIV-patient cohort from 1st and 2nd Department of Infectious Diseases of Luigi Sacco Hospital, identified from years 2004 to 2007; differences by calendar timeframe were assessed. Patients moving from one category to another during the period of observation were weighted in the analysis according to the time spent in each category. "Failing HAART" patient definition: a treated HIV-subject with two consecutives detectable plasma HIV-RNA. The analysis will be performed considering the four aforementioned cost categories, within a four-year time horizon (2004-2007) using the two patient typologies, line treatment and the year in which the cost occurred as drivers.
Results: Public health yearly mean costs per patient (total cost and costs divided per category) are reported in the table below. A sample of 304 patients was taken into consideration. Except for year 2004, the number of hospitalized patients was higher in failed subjects than in controlled ones.

€	Total Costs	HIV-drugs	Other drugs	Hospitalizations*	Out-patient care
FH 2004	10505	7817	242	2221	2754
VC 2004	9083	7097	424	3835	1827
FH 2005	11938	8097	985	4827	2482
CV 2005	9373	7659	539	3882	1722
FH 2006	12671	7694	393	4564	3313
VC 2006	9402	7570	524	4679	1520
FH 2007	15556	9105	2465	7666	2447
VC 2007	10529	8111	706	7207	1573

FH=failing HAART; VC=virologically controlled; *mean hospitalization costs were calculated on admitted patients.

Conclusions. From the payer perspective, the total costs of a "failing HAART" patient are higher than a "virologically controlled" one. The difference between the total costs of the two patients typologies are mainly due to HIV-drugs and Out-patient care costs.

PP 04

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CLINICAL COURSE OF JCV-POSITIVE CSF AND JCV-NEGATIVE CSF DEMYELINATING LEUKOENCEPHALITIS IN HIV INFECTED PATIENTS

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Background: demielinating leukoencephalopathies in HIV patients encompass classical JCV-DNA CSF positive form, named progressive multifocal leukoencephalopathy (PML) and a recently described syndrome named not-defined leukoencephalopathy(NDLE) characterized by absence of JCV in CSF.
Methods: HIV-selected patients were either neurologically asymptomatic, with at least7-years lasting infection or neurologically symptomatic with demyelinating lesions. At the enrolment and thereafter once-a-year, patients underwent neurological evaluation and CNS-MRI scan, real-time PCR on CSF (HSV1, HSV2, VZV, EBV, HCMV, HHV6, JCV, HIV). Neurological assessment was evaluated using Scripps Neurological Rating Scale (SNRS). Data are reported as median (range). Survival was estimated using Kaplan-Meier method and the groups were compared in survival by using the log-rank test.
Results: study was conducted between 2002 and 2008, 23 subjects with demyelinating lesions were detected: 9 (4PML-5NDLE) out of 166 asymptomatic randomly selected patients; 13 symptomatic patients (5PML 9NDLE). Prevalence of demyelinating lesions in asymptomatic HIV-infected patients was 5.4% (95%CI2.5-10). Length of follow-up was 39.2months (0.7-56.8). All patients, except 3, were on HAART at the enrolment. In each patient, CSFanalysis was performed 3 times in median (1-8); JCV-DNA CSF was negative in NDLE while it resulted positive at least once in PML. At the enrolment NDLE *vs* PML CD4+ were 309 cell/mm^3 (233-401) and 106.5 cell/mm^3 (75.5-166) (p=0.008); $\log_{10}$ plasma HIV-RNA and nadir CD4+ were not significant. SNRS score was 100% (90-100) in NDLE and 75% (37-100) in PML(p=0.057).
Cumulative survival in NDLE was 100% at month 48, in PML it was 67% at month 24 and 53% at month 48 (p=0.017). Among PML asymptomatic patients, during follow up 2 out of 4 subjects died, and 2 remains neurologically asymptomatic; among NDLE, none died and one developed mild neurological symptoms.
Conclusion: Higher CD4+ and better neurological assessment characterize NDLE which shows a benign outcome with better survival compared to PML. Prevalence of demyelinating lesions in otherwise asymptomatic patients suggest repeated neurological/neuroradiological evaluation in long lasting HIVinfection.

PP 05

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CEREBROSPINAL FLUID (CSF) SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR (UPA) RECEPTOR (SUPAR) IS ELEVATED IN AIDS DEMENTIA COMPLEX AND CORRELATES WITH VIROLOGICAL, IMMUNE ACTIVATION AND NEURONAL CSF MARKERS

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Background: The urokinase plasminogen activator (uPA) system may be involved in the pathogenesis of AIDS dementia complex (ADC) through interaction with HIV-1 and subsequent dysregulation of uPA system functions - extracellular proteolysis and chemotaxis. The aim was to investigate this hypothesis through measurement of CSF and plasma level of uPA molecules and comparison with levels of other HIV-1, immune activation and neuronal markers.
Methods: Cross-sectional study of antiretroviral-untreated patients, including patients with neurologically asymptomatic HIV infection and no AIDS (n=19); neurologically asymptomatic HIV infection and AIDS (n=18); ADC (n=17); and HIV-negative healthy controls (n=16). CSF and plasma were assessed for uPA system molecules (suPAR, uPA, PAI-1, tPA); immune activation markers (CSF cells and protein and the following cytokines and chemokines, measured by the Luminex technology - Bio-Plex, Bio-Rad Laboratories, Inc.: IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, basic FGF, eotaxin, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF); and neuronal markers (NFL, t-tau, p-tau, $A\beta_{1-42}$, α-sAPP and β-sAPP).
Results: ADC patients had significantly higher CSF and plasma levels of suPAR compared to each of the other groups ($p<0.0001$ for all), slightly higher levels of uPA, and no different levels of PAI-1 or tPA. ADC patients had CSF levels of HIV-1 RNA, IL-6, MCP-1, MIP-1α, MIP-1β, NFL and t-tau significantly higher and of α-sAPP and β-sAPP significantly lo wer than each of the other groups. In the whole group of HIV-infected patients, CSF suPAR correlated significantly with CSF and plasma uPA, and with CSF HIV-1 RNA, MIP-1α, MIP-1β, NFL and t-tau (direct correlation); and with blood CD4 cells and CSF α-sAPP and β-sAPP (inverse correlation).
Conclusions: These findings strongly support the role of the uPA system in the pathogenesis of ADC. The relatively low CSF levels of uPA and the unaltered CSF levels of PAI-1 and tPA do not favor proteolysis dysfunction as prevalent mechanism. Rather the correlation between CSF suPAR, HIV-1 and chemokines favor a mechanism by which suPAR itself may promote migration of inflammatory cells into the CNS and further enhance viral replication. In addition, the strong association between CSF suPAR and neuronal markers suggests that suPAR might also be directly or indirectly involved in neurotoxicity.

PP 06

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RAPID DETECTION OF MDR-TB TO GUIDE PATIENTS' MANAGEMENT: A FEASIBILITY STUDY IN BURKINA FASO

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HIV patients have higher risk to develop tuberculosis (TB) and co-infection with Multi Drug- or Extensively Drug-Resistant (MDR, XDR, respectively) *M. tuberculosis* strains is more frequently associated with fatal outcome. Drug-susceptibility testing (DST) is critical for the management of patients. Mycobacterial culture and DST capacity are severely limited in resource-poor countries and results are available within weeks to months meanwhile inadequate treatment may occur, promoting resistance development. New develop genotyping techniques relying on the detection of mutations involved in resistant phenotype to anti-TB drugs allow to perform rapid DST in selected population at higher risk of MDR-TB.
The GT-MTBDR*plus* (Hain Lifescience) allows to identify mutations responsible of RIF and INH resistance. Reported sensitivity for rifampin- (RIF) and isoniazid- (INH) resistance for the GT-MTBDR*plus* are ≥ 97% and ≥ 90%, respectively. We evaluate the feasibility of a more accurate management of TB patients in Burkina Faso (a country with a high TB-HIV co-infection prevalence) by detecting drug resistant TB directly in clinical specimens using the molecular assay.
Samples were collected in Burkina Faso where culture and DST are not currently available and chronic cases are classified and treated based on clinical evaluation and sputum smear microscopy results. One hundred eight patients undergoing category IV treatment, including 17 HIV-*M. tuberculosis* co-infected individuals, were enrolled from Dec-2006 to Oct-2008. Two early morning sputum samples were collected from each patient and sent to Italy. Upon arrival, samples were decontaminated and processed for smear microscopy and DNA extraction. Culture was attempted on MGIT960 (Becton Dickinson) and decontaminated specimens were analyzed for presence of mutations conferring resistance to RIF and INH by the molecular assay GT-MTBDR*plus*.
Fifty-one samples were not reconfirmed as sputum smear positive. We obtained a valid molecular test result in 56/57 smear-positive and 51/51 smear-negative samples.
Among 108 chronic TB cases we identified patients who (i) harboured RIF- and INH-sensitive strains (n 24), (ii) were negative for *M. tuberculosis* complex DNA (n 29), and (iii) had non-tuberculous Mycobacteria infections (NTM, n 15).
Concerning 17 HIV patients, the molecular assay allowed to identify 6 MDR (all confirmed by culture DST), 1 RIF-monoresistant and 3 RIF- INH-sensitive *M. tuberculosis* co-infections. In 7 out of 17 HIV patients the molecular assay didn't detect the presence of *M. tuberculosis* complex DNA. Culture analysis allowed to confirm the molecular data (3 culture-negative samples, and 4 NTM).
The MTBDR*plus* assay performed directly on specimens improves the management of TB cases offering timely access to more appropriate anti-TB regimens and contributing to limiting the emergence of resistance, especially in selected population at higher risk for MDR-TB.

PP 07

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PRESCRIPTION PATTERNS AND COST OF COMBINATION ANTIRETROVIRAL THERAPY (CART) IN AN ITALIAN CLINICAL CARE SETTING

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Objectives: The objective was to investigate prescription patterns and treatment-related costs in HIV-infected patients in an Italian managed care setting.
Methods: Cross-sectional analysis based on a standardized survey carried out at the Italian National Institute for Infectious Diseases in December 2008. Total and treatment-specific direct costs per day were calculated according to patient profiles and therapeutical characteristics. Comparisons of mean costs between group of patients were performed by t-test and AN.O.VA., and predictors of higher costs were assessed by a multiple linear regression model. Cost analysis considered the discount rate applied by Pharmaceuticals to public hospitals in Italy on antiretroviral sale prices.
Results: A total of 3101 patients receiving ARVs at December 2008 were included in the analysis: 71% were males, median age was 45 (range, 17-87), 29% co-infected with hepatitis viruses. The median CD4 count was 521 (IQR 346-718), 83.3% had HIV-RNA <50 cp/ml, 50.2% did not have experienced previous virological failure (VF), and 2NRTI+PI/boosted (48%) was the most commonly prescribed regimen. Variables associated with higher mean daily costs were: CD4 count (+€0.51 for each 100 cell decrease; P<0.001), HIV-RNA >50 cp/ml (yes: €27.4 vs no: €24.6; P<0.001), hepatitis co-infection (yes: €25.6 vs no: €24.7; P=0.001), number of virological failure (0 VF: €22.8; 1 VF: €25.0 e >1 VF: €28.4; P<0.001). At multivariable linear regression, lower CD4 count (β=13.7 for 100 cell decrease P<0.001), younger age (β=-9.8 P=0.04), and 1 or more previous failures (1 VF β=67.9 P<0.001; >1 VF β=171.1 P<0.001) were associated with higher mean costs.
Regimen-specific costs per day were significantly different between drug classes: €20.2 for 2NRTI+NNRTI, €25.6 for 2NRTI+PI/b, €50.5 for regimen containing new classes (P<0.001). A total of 204 prescription patterns were recorded with a great heterogeneity effect (Gini heterogeneity index=95.4%). The 10 most frequently prescribed regimens with single prevalence between 11.3% and 2.7% accounted for 64% of total patients and covered 60% of total costs. cART regimens with single prevalence <0.5% were prescribed to 19% of patients and determined the highest cost component (23%).
Conclusions: Within an Italian unselected patient population in a tertiary care setting, higher daily antiretroviral costs were associated with lower CD4, previous virological failures, and younger age. An extremely high variability in prescription patterns has been recorded and the most uncommon types of cART regimens accounted for the greatest cost component. Prescribers and decision makers have the difficult task to investigate whether cART heterogeneity in prescription patterns is necessary because of treatment "tailoring" or can be addressed in planned interventions to reduce drug-associated health care costs.

PP 08

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IMPACT OF ANTIRETROVIRAL TREATMENT WITH PROTEASE INHIBITORS TREATMENT ON CAROTID WALL STRUCTURE IN HIV- INFECTED PATIENTS

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Background: The study of atherosclerosis in HIV-infected patients is highly relevant due to the longer life expectancy and disturbances in metabolic parameters. Uncertainty exists, however, on whether this is typical of HIV per se or it is due to the adverse metabolic effects of antiretroviral treatment (cART) including proteas inhibitors (PI). Aim of our study was to provide information on this issue measuring common carotid artery intima-media thickness (IMT) in HIV patients on treatment on PI or not in their therapy.
Methods: We cross-sectional studied 44 HIV-patients: 29 (26 men and 3 females) with continuous use of PI regimens and 15 PI-*naïve* subjects (13 men and 3 females). The groups were matched for age, race, body weight and duration of antiretroviral treatment ($\geq$ 2 years). All patients were normotensive and had no history or evidence of cardiovascular disease or diabetes. Their total cholesterol was 161.3$\pm$46.3 mg%, while serum triglicerydes value were 165.7$\pm$117.0 mg% Visualization of carotid artery IMT was obtained via non-invasive high-resolution B-mode carotid artery ultrasonography and integrated backscatter analysis (IBS) has been performed. IMT values were correlated to use of PI-regimen, duration of HIV infection (mean 47.7$\pm$33.2 months), duration of cART.
Results: The average IMT was 0.64$\pm$0.22 mm (RCCA) and 0.68$\pm$0.26 mm (LCCA) values, which were similar of those of age, sex and blood-pressure matched controls. There was not significant difference between the IMT value in HIV patients treated or not treated with PI. In HIV patients there was a significant correlation between the duration of the disease and IMT value. The slope of the relationship (r=0.36, p<0.01) was similar in the two subgroups (PI-treated or untreated) which also showed a similar carotid wall composition as assessed by IBS. Moreover, no significant differences were found in IMT values between smokers and no smokers and cholesterol levels.
Conclusions: Although the present finding do not show a straightforward carotid abnormality in HIV patients, the correlation between IMT and the duration of the disease suggests that a relationship does exist. Current or past use of PI does not seem to contribute substantially to the rate of carotid IMT, but the HIV-related chronic inflammatory state could be the leading cause for development of atherosclerosis.

PP 09

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IMPACT OF HAART (HIGHLY ACTIVE ANTIRETROVIRAL THERAPY) ON THE OUTCOME OF PREGNANCY IN A RESOURCE-LIMITED SETTING

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Background: The increasing use of HAART (Highly Active Antiretroviral Therapy) among HIV-infected pregnant women raised the question of the safety of this drugs regimen on the health of mothers, foetus and infants. Controversial data from industrialized countries suggested that use of combined antiretroviral therapy can be associated with adverse outcomes of pregnancy like prematurity and low birth weight. Our aim was to explore the association between HAART administration on HIV-infected pregnant women and risk of adverse outcome of pregnancies and low birth weight. Our study takes place in a resource-limited setting, where an increasing use of HAART is actually recommended.
Material and Methods: The study analyzed pregnancies of HIV-infected women enrolled in the program of Prevention of Mother-to-Child Transmission (PMTCT) between January 2003 and December 2007 at the Saint Camille Medical Centre, in Ouagadougou, Burkina Faso.
Data collected for observational retrospective study included age, HIV-status, CD4+ T lymphocyte count, type and timing of ARV drugs administration, outcome of pregnancy and birth weight of live-born infants.
Univariate analysis was used to examine the relationship between variables. Multiple logistic regression analysis was performed using age, type and timing of antiretroviral administration and CD4+ T lymphocyte count as predictive variables for adverse outcome of pregnancy and low birth weight.
Results: 678 pregnant HIV-infected women (means of age= 29.1 ± SD 4.9 years) with largest prevalence of HIV 1 mono-infection (97.6%) were followed by the program of PMTCT: 395 received prophylaxis regimen (principally using single dose of Nevirapine during labour), 115 on HAART regimen started before conception and 168 on HAART regimen started after the first trimester.
An advanced immunocompromised status (CD4+ T cell count<200/ mm^3) was found as the only significant predictive factor for an adverse outcome of pregnancy like abortions, maternal deaths and stillbirths (A.O.R. = 3.9, C.I. = 1.08-14.00).
Women on HAART started later in pregnancy presented the major incidence of low birth weight infants (34%). In this group HIV infection was diagnosed during ante-natal voluntary screening and it contains the largest percentage (73.6%) of women with advanced immunodepression (CD4+ T cell count<200/ mm^3).
Conclusion: HAART administered during pregnancy did not represent a significant risk factor neither for an adverse outcome of pregnancy nor for low birth weight. Advanced immunocompromised status was the most important predictive factor for an adverse outcome of pregnancy. Unknown HIV-status before conception and CD4+ T cell count lower than 200/ mm^3 were significantly associated with a low birth weight of newborns delivered by women on HAART. Implementation of strategies for active offer of HIV test among women of childbearing age should be emphasized.

PP 10

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GREATER IMMUNOLOGICAL RECOVERY ASSOCIATED WITH ADDITIONAL ENFUVIRTIDE IN THE TREATMENT OF NAÏVE HIV- INFECTED PATIENTS AT VERY ADVANCED DISEASE STAGES: 24-WEEK RESULTS OF A RANDOMIZED, CONTROLLED, PILOT STUDY

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Background: Patients starting antiretroviral therapy at advanced disease stages (late presenters) often have a suboptimal response to antiretrovirals, which prompts toward new therapeutic strategies. We carried out a randomized controlled pilot study to investigate whether the addition of enfuvirtide (ENF) to a conventional PI-based HAART could improve the immunological recovery in late presenters.
Methods: Naïve HIV+ patients presenting with CD4 cell count < 50/ µL, without tuberculosis and neoplasms, gave informed consent to be alternatively allocated to 2 NRTIs + LPV/r with (ENF arm) or without (SOC arm) ENF 90 mg bid. ENF was planned to be administered until achievement of viral load (VL) < 50 copies/ml and for at least 24 weeks, and thereafter discontinued. Primary endpoint was CD4+ recovery at week 24. Secondary endpoints were early CD4+ recovery and VL decay. HIV-RNA was intensively (day 1,2,3,4,5,6,7,14,28) monitored in the first month, and thereafter monthly throughout week 24 as for clinical data, CD4+ cell count and %. Data were expressed as median (IQR).
Results: 22 patients were enrolled. At baseline (BL) no significant differences were found between ENF (n=11) and SOC arm according to race (caucasian 81% vs. 81%), sex (male 90% vs. 81%), age (43.9 vs. 40.5), concomitant AIDS-defining illnesses (63% vs. 81%), TDF-containing backbone (100 vs. 81%), VL (5.7 vs. 5.4 log), CD4+ cell count (20 vs. 15 cell/µl), CD4+ % (3.3 vs. 3.1%). 18 patients completed the study (10 in ENF arm): 1 in the SOC arm died on day 8, 1 was dropped out and 2 were lost to follow-up. VL decay at week 4 was higher in the ENF arm (-2.9 vs. -2.1 log, p=0.01) while proportion of patients with VL<50 copies/ml at week 24 was comparable (80% vs. 62,5%, p=0.42). CD4+ gain was comparable at week 4 (94 vs 80 cell/µl, 6,7% vs 4,5%; p=ns), showing a higher value in the ENF-arm at week 8 (160 vs. 48 cell/µl, p=0.07; 7.6% vs. 3.6%, p=0.02). At week 24, CD4+ gain was significantly higher in the ENF arm (207 vs. 134 cell/µl, p=0.04; 10.7% vs. 5.9%, p=0.02), and a significant higher proportion of patients achieved CD4+ > 200/µL (70 vs. 12.5%, p=0.01) in the latter.
Conclusion: In this pilot study, addition of ENF to a LPV-based HAART was shown to be associated with a significantly faster and greater immunological recovery in newly discovered HIV+ patients with very low CD4+ cell count. Induction strategies using an ENF-based approach in such subjects warrant further investigation.

POSTER PRESENTATIONS SESSION II

PP 11

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DECREASING TEMPORAL TRENDS OF CLASS RESISTANCE IN A MULTICENTER NATIONAL-BASED STUDY (START STUDY) OVER THE 2003–2007 PERIOD

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Background: Studies of the prevalence of resistance in patients failing antiretroviral treatment have shown that class resistance is decreasing over time, although at low rate. We evaluated the time trends of class resistance of HAART-treated patients according to regimens at time of failure in a multicenter national-based study.
Methods: We analysed 4,333 HIV-1 *pol* sequences stored in the ARCA (Antiretroviral Resistance Cohort Analysis) database, participating in the START study during 2003-2007. Patients (n=3,496) with viremia >1,000 copies/mL received a genotypic test while on treatment. Resistance mutations were identified from IAS-USA 2008 tables. Time trend have been analyzed by Cochran-Armitage.
Results: Sequences were obtained from 49 Centres (64.9%, 30.9% and 4.2% from North, Center and South Italy, respectively). At genotypic testing, 80.6% of patients were receiving an HAART with an NRTI backbone accompanied by PIs and NNRTIs in 47.5% and 27.5%, respectively.
Among patients on NRTI resistance to this class decreased from 85.8% in 2003 to 72.1% in 2007 (p<.0001). PI resistance went from 60.9%, 59.0%, 51.6%, 44.7 to 56.3% (p=.025) in unboosted PI (unbPI) treated subjects and from 71.3%, 65.7%, 61.7% 61.2% to 51.8% in those receiving boosted PIs (bPI) (p<.0001) in the 5-year interval, while bPI regimens increased from 28.5% to 54.1% (p<.0001). Thymidine analog (TA)-sparing regimens increased from 27.5% to 62.8 % (p<.0001). TA-sparing regimens containing bPIs but not unbPIs were associated with marked reductions of mutations overtime (from 84.4% and 64.5% to 54.8% and 60.6% (p<.0001, p=ns, respectively). NNRTI mutations in NNRTI treated individuals decreased from 86.0% to 81.1% (p=.04). NRTI+NNRTI and NRTI+PI resistance changed from 62.4% to 59.0% and from 38.9% to 24.1%, showing a significant decrease only for the latter association (p<.0001). NRTI+NNRTI usage went from 28.4% to 17.2% overtime.
TA mutations declined in TA-assuming patients from 64.9% to 48.5% (p<.0001). K65R rose from 3.6% to 6.3% (p=.030) in subjects receiving any of TDF, ABC, ddI, 3TC, FTC. However, no association was detected with any pair thereof. M184I/V decreased significantly from 73.2% to 65.3% (p=.0009) in patients on 3TC or FTC or ABC.
Among major protease mutations, 30N and 48V decreased from 10.0% and 5.3% to 2,3% and 2.7% (p<.001 and p=.03, respectively), while 33F, 84V, 54M/L and 50L showed a significant increase (from 14.2%, 14.4%, 5.7% and 0% to 22.2%, 20.5%, 11.3% and 3.0%, p=.0004, =.014, =.0008 and <.0001, respectively) with no association with specific PI usage.
Conclusions: A noteworthy reduction of NRTI+PI resistance was observed in patients treated with these drugs over time, due to TA sparing therapy, NRTI backbone enhanced protection by bPIs or their combined effects. In addition, NNRTI mutations slightly declined as a likely consequence of changes in the proportions of NRTI+NNRTI combining regimens. Nevertheless, NRTI+NNRTI resistance did not decline despite a less frequent use of this association.

PP 12

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TEMPORAL TRENDS AND CHARACTERISTICS OF RECENTLY ACQUIRED HIV INFECTIONS AMONG NEWLY DIAGNOSED CASES IN ROME

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Objective: The application of new laboratory techniques to identify recently acquired infection of HIV in HIV/AIDS routine surveillance systems can be a tool for better measuring the changing patterns of HIV epidemic. The aim of this study is to assess the proportion of recent HIV infections among the persons diagnosed with HIV, between 2001 and 2007, at the National Institute for Infectious Diseases "Lazzaro Spallanzani", in Rome.
Methods: We used the avidity assay (AA) – an approach that investigates the maturity of the HIV antibody response by investigating its avidity – to distinguish recent (< 6 months) from long-standing HIV infection**.** An Avidity Index (AI) of 0,80 was used to identify recent infection (RI). We analyzed residual serum and/or plasma specimens collected from individuals which received a new diagnosis of HIV infection between, between 2001 and 2007.
Results: During the study period 1796 newly diagnosed HIV infections were observed. Overtime, the number of the diagnoses per year was stable (average 256, range 210-303). Of the persons considered, 1329 (75,4%) were males; 728 (43%) were heterosexuals (395 male and 354 female), and 688 (38,39) were men who have sex with men (MSM). The median age were 36 years (range 18-86 years). One third (31%) were foreign born (33% from sub-Sahara countries, 33% from Latin America, 20% from Eastern Europe); 929 (52%) had a CD4 cell count of <350 lymphocytes/μl, and 624 (35%) had a more advanced HIV infection (<200 cell/μl).
Residual samples were not available for approximately 30% of new diagnoses; compared with individuals who had a sample available for AA, those who had not a sample available, were more likely to be foreign born, heterosexuals, and in a more advanced stage of disease.
Overall, the proportion of RI was 17,4%. We observed an increasing temporal trend: <10% in the period 2001- 2002, 18,2% in 2003, 16,4% in 2004, 22,4% in 2005 and >25% in the years 2006- 2007. The proportion of RI was higher among Italians (20%) than foreigners (9,5%), among MSM (21%) than heterosexuals (14,6%), and decreased with the age (20,6% among 18-29 years old vs 11,9% among >=50 years old). In multivariable analysis, older age and being foreign born were associated with a lower probability of a RI, while diagnosis in more recent years was associated with a higher probability of RI.
Comment: The proportion of individuals diagnosed with HIV within six months from infection increased in the last years, and was around 25% in 2006-2007. Older persons and those born abroad should be primary targets for interventions aimed at promoting early HIV diagnosis.

PP 13

Infection 2009; 37 (Suppl. II): 43

HIV-1 INTEGRASE MUTATIONS, FOUND AS MINORITY QUASISPECIES IN PATIENTS NAÏVE TO INTEGRASE INHIBITORS, ARE ASSOCIATED WITH DECREASED SUSCEPTIBILITY TO RALTEGRAVIR AND ELVITEGRAVIR IN VITRO

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Background: Two HIV-1 integrase inhibitors (INI), raltegravir (RAL) and elvitegravir (EVG), have been shown promising in clinical trials, and the first has been recently made available for clinical practice. However drug resistance to INIs has been shown to occur both *in vitro* and/or *in vivo.* By performing a clonal phenotyping assay, the goal of this study was to investigate in INIs-naïve patients (pts) the presence of IN resistance mutations as minority quasispecies, and evaluate their effect on susceptibility to RAL and EVG and on replication capacity.
Methods: The RT-RNAseH-IN region was PCR-amplified from plasma viral RNA obtained from 49 HIV-1 B subtype infected pts (21 drug-naïve and 28 failing HAART not containing INIs), and recombined with an RT-IN-deleted HXB2-based backbone. Recombinant viruses (RVS) were tested against RAL and EVG. Preliminary biological cutoffs (BCO) were determined as the 97.5-percentile of all fold changes (FC) values. On this basis, FC values >1.97 for RAL, and >2.21 for EVG were considered associated with resistance to the INI. In addition, to evaluate the replication capacity of resistant RVS, cytopatic effects and p24-gag-antigen production in human C8166 T-lymphocytes were also analyzed after 5 days of infection.
Results: 349 RVS from 49 pts were successfully analyzed both phenotypically and genotypically. 3 out of 21 drug-naïve pts (14.3%) and 2/28 HAART-treated pts (7.4%) carried 1 or more clones with a FC >cutoff for at least 1 INI and with INI resistance mutations. G140S, a secondary resistance mutation to RAL and EVG, was observed in a single RVS (out of 10) in 1 HAART-treated pt, showing FC values for RAL 2.44 and for EVG 5.6. The RAL-secondary mutation T97A, was observed in 2 RVSs (out of 10) in 1 drug-naïve pt, showing FC>BCO only for EVG (2.74 and 2.46, respectively). Finally, a novel mutation, E92G, was found in 2 RVSs in 2 different pts, with FC measurable only in 1 RVS and >BCO only for EVG (11.6). The p24-gag-antigen production of RVSs containing G140S or T97A mutations was not statistically different from what observed by the wt HXB2 virus in C8166 cells. Differently, the two RVSs carrying the E92G mutation, showed a drastic decrease of viral production (one virus: 63.7% versus 100% of HXB2, P=0.03; the other virus, with no FC measurable, showed undetectable p24 production).
Conclusion: Secondary mutations associated with resistance to INIs are present at very low frequency as minority quasispecies in INIs-naïve pts. A novel mutation, E92G, also found as minor species, was associated *in vitro* with decrease susceptibility to EVG and with low viral replication. The potential role of these preexisting mutations to the *in vivo* development of INIs-resistance needs further investigation.

PP 14

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GENOTYPIC ANALYSIS OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 IN BLOOD MONOCYTES, CD4 T CELLS AND PLASMA FROM NAÏVE AND TREATED INDIVIDUALS

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Several studies showed that peripheral blood monocytes can harbour genetically diversified HIV-1 variants that are distinguishable from those present in blood CD4+ T cells. The present study was aimed to characterize the patterns of resistance of HIV-1 in CD14+ monocytes, CD4+ T cells and plasma.
Blood samples were collected from 42 HAART-experienced patients. At the time of blood sampling, 32 patients were failing a current antiretroviral therapy and 10 patients were maintaining undetectable level of viremia. CD14+ monocyte and CD4+ T cells were isolated using magnetic beads for positive selection (Miltenyi Biotec). Genotyping of the reverse transcriptase (RT) and protease gene (pro) of HIV-1 was performed using fluorescent dideoxy-terminator method (TRUGENE HIV1-Siemens Heathcare Diagnostics). HIV drug resistance was defined according to the HIV-1 genotypic resistance interpretation algorithm of the GUIDE LINES™ RULE 12.0-BAYER.
The analysis of the mutation patterns associated with drug-resistance detected in plasma HIV-RNA and in HIV-1 from CD14+ monocytes and from CD4+ T cells, revealed that eight of the 32 patients' samples analysed showed virological failure, without showing any resistant mutations in both cellular compartments and plasma. Careful anamnesis by the clinicians revealed that these patients were not adherent to antiretroviral therapy.
Twenty-four of the 32 patients' samples (75%) showed resistance mutations in at least one compartment analyzed. Of these 24, in only 2 (8%) the number and type of mutations in HIV from blood monocytes was the same of that detected in CD4+ T cells and in plasma. In 17 of the 24 samples (71%) the virus harboured in monocytes showed a number and/or a type of drug resistance mutations different from those detected in plasma virus and in CD4+T cells-associated virus. In 5 patients (21%), HIV-1 sequence in blood monocytes was identical to that detected in plasma. As far as concern the ten patients with virological suppression, sequence analysis was performed only on cell-associated viruses, being the plasma viremia undetectable. In three of ten patients no drug resistance mutations were found in both cellular compartment. Seven patients exhibited drug resistance mutations in HIV-1 sequence from CD4+T cells and/or from blood monocytes. Specifically, the mutations at the codon recognized as important in the genotypic resistance pattern differed between monocytes and CD4T cells in five patients (71%), while only 2 (29%) showed the same number and type of mutations in both compartments.
Circulating monocytes may harbour a viral dominant population different from the viruses circulating in the blood and archived in other cellular compartments. HIV-infected monocytes can be an indirect source of HIV-1 by carrying virus and differentiating into tissue macrophage where HIV may productively replicate. Hence, blood monocytes might serve as an indirect source of drug-resistant viral variant.

PP 15

Infection 2009; 37 (Suppl. II): 44

DEVELOPMENT OF ALLELE-SPECIFIC PCR (AS-PCR) ASSAYS TO INVESTIGATE MAJOR HIV RESISTANCE MUTATIONS TO NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS) AND NON NUCLEOSIDE RT INHIBITORS (NNRTI).

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Background: HIV-1 resistance mutations are routinely identified by direct sequencing of target viral regions. This approach, however, does not enable detection and quantification of minor resistant populations, which may be important for therapy management. The aim of this work was to develop allele-specific (AS)-PCR assays for relevant HIV RT resistance mutations, including M184V/I, conferring resistance to lamivudine and emtricitabine, and K103N and Y181C, conferring resistance to non nucleoside reverse transcriptase inhibitors. We evaluated the sensitivity of these assays for the detection of minor viral variants, and also assessed the utility of the AS-PCR for quantification of resistant variants.
Methods and Results: AS-PCR assays were based on amplification of the full RT region, followed by amplification of shorter fragments by both "universal" (U) PCR, flanking wild-type (WT) sequences and AS-PCR. For AS-PCR, a reverse primer was designed to recognise the mutated nucleotide at the -1 position of the 3' end and contained a mismatch at the -2 position. For each assay, a panel of 19 samples, each containing different proportions of mutated/WT plasmids (from 0.01/99.9% to 99.9/0.01%), was prepared, and a standard curve generated by calculating the difference between U-PCR and AS-PCR cT values (Ct). The results were expressed as the relative proportion (%) of mutant virus. The lower sensitivity limit of the assays to detect mutant virus was defined by calculating the mean ΔCt value plus three standard deviations on 20 replicates of wild-type virus and it was 0.4% for the M184V assay, 0.1% for the M184I, 0.1% for the K103N (aat), 0.4% for the K103N (aac), and 0.1% for the Y181C. To assess the value of AS-PCR for quantification of resistant mutants, we examined, by the 184V AS-PCR, plasma samples collected every fourth week from 15 cART failing patients carrying the M184V mutation who underwent complete treatment interruption as part of the "E184V" study. Following interruption, the proportion of M184V decreased progressively, with different trends among patients. M184V% achieved the low detection limit after 8-36 weeks, with a mean slope of -14.83% (SE, ±2.43%) over 48 weeks. In patients with slower M184V% decays there was a less marked decrease of CD4 counts (r=0.582, p=0.029), whereas no relationship was observed between M184V% decay and changes of VL, CD8 counts, CD4%, CD8% or CD4/CD8.
Conclusions. The high sensitivity, together with the ability to accurately quantify the proportion of mutant virus, make AS-PCR a promising additional tool for the study and management of HIV resistance mutations in cART treated patients. The application of AS-PCR to the study of the M184V dynamics in patients interrupting cART showed an association between slow M184V decay and smaller loss of CD4 cells, which adds support to the hypothesis that M184V mutant virus might be less pathogenic for CD4 cells than wild-type virus.

PP 16

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PIN1 PROMOTER POLYMORPHISMS ARE RESPONSIBLE FOR THE UPREGULATION OF APOBEC3G EXPRESSION IN HIV-EXPOSED SERONEGATIVE (ESN) INDIVIDUALS

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Pin1 is a peptidil-prolil-*cis*-trans isomerase that specifically binds phosphorylated Ser/Thr-Pro protein motifs and catalyzes the *cis/trans* isomerization of peptides. Mitotic proteins, cytoskeleton, transcription factors and apoptotic proteins are Pin1 substrates and targeting sites. Recent data show that Pin1 interacts with APOBEC3G (A3G). The Pin1/A3G interaction results in a reduced A3G expression and a diminished A3G-mediated restriction of HIV. Two single nucleotide polymorphisms (SNPs) in the promoter region of the Pin1 gene (-842 G/C and -667 T/C) modulate PIN1 expression; in particular, the -842 GC genotype or CC haplotype are associated with reduced protein levels (*Neurobiol. Aging, 28;69-74, 2007).*
The -842 C/G and -667 T/C polymorphisms in the promoter of Pin1 gene as well as Pin1 protein levels were analyzed in 30 Exposed Seronegative Individuals (ESN), heterosexual partners of HIV-infected patients; 40 HIV-infected patients (HIV) and 40 Healthy Controls (HC).
The genotype and allele distributions of the -842 SNP was skewed in ESN (genotype: p= 0.008; allele: p= 0.013). In particular ESN showed a significantly lower frequency of the -842 GG genotype compared to HIV and HC (p=0.017 and p=0.019, respectively) and consequently a lower G allele frequency (p=0.026 and p=0.028, respectively). No significant differences were found for the -667 SNP. These SNPs are in linkage disequilibrium and combine to form haplotypes. The haplotype distributions were different in ESN compared to the other two groups of individuals (p=0.032 vs. HIV and p=0.047 vs. HC). Pin1 protein concentration was significantly lower in ESN compared to HIV patients and HC, Finally, a trend toward higher A3G expression was seen in ESN showing the presence of the Pin1 -842 SNP
ESN show a significantly lower frequency of the -842 GG genotype and lower G allele frequency in comparison to HIV patients and HC; as a consequence Pin1 protein concentrations are reduced in ESN compared to HIV and HC. The down-modulation of Pin1 in ESN is associated with an upregulated A3G expression and might be involved in the resistance to HIV infection observed in ESN.

PP 17

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EFFECT OF HLA EPITOPES ON HIV-1 INFECTION PROGRESSION IN THE ABSENCE OF HAART

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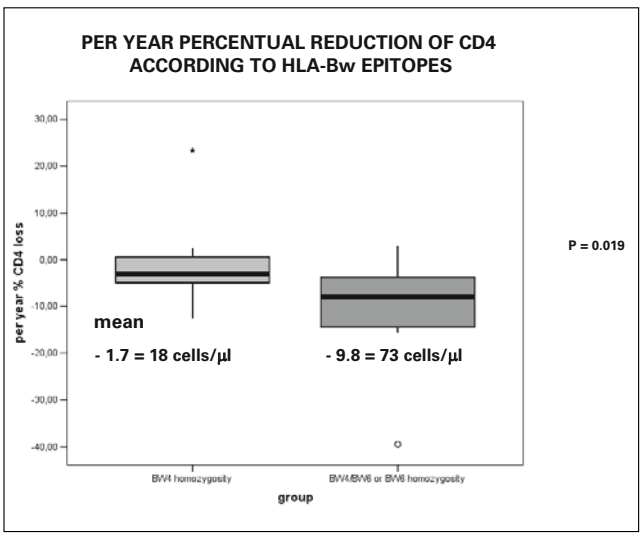
Objective: Understanding why some people establish and maintain effective control of HIV-1 and other do not is a priority. Major Histocompatibility Complex (MHC) class I genetic variation has been definitively associated with either clinical disease progression or HIV-RNA levels as well as immunological decay.

Methods: host genetics were examined in a case control study including untreated HIV-1-infected patients with steady HIV-RNA levels < 50 copies/ml (elite controllers, EC, N = 6), with low replicating virus (HIV-RNA 50-1000 copies/ml, low viremic, LV, N = 12) and with steadily high viral load (HIV-RNA > 1000 copies/ml, high viremic, HV, N = 12).
Results: Over time, the CD4 decrement was of - 0.5% cells/year in EC (- 5 cells/μl); -2.9 cells year in LV (-25.9 cells/μl) and of –11.9% cells/year in HV (-90.9 cells/μl). Differences were statistically significant between EC and HV (P < 0.01) and LV and HV (P < 0.03), but not between EC and LV. Polymorphisms of the HLA class I alleles significantly associated with a slower progression were HLA-A*24 (allele presence: 25% EC/LV vs 4.2% in HV; P = 0.04) and HLA-B*27 (allele presence: 19.4% vs 0%; P = 0.03), while a more rapid decline of CD4 counts was present in patients showing alleles HLA-A*1 (allele presence: 2.8% vs 20.8%; P = 0.03) and HLA-B*35 (allele presence: 2.8% vs 25%; P = 0.01). According to logistic regression analysis being HLA-A*24 positive lowered the risk of being HV 2.5 times and being HLA-B*27 positive 20.8 times. By contrast HLA-B*35 positivity increased this risk 2.6 times. HLA-A*24 and HLA-B*27 were not associated (phi coefficient 0.36; P = 0.84) while the linkage between HLA-A*1 and HLA-B*35t was strong (phi coefficient 0.71; P < 0.001). There was a negative association between alleles HLA-A*24 and HLA-B*27 with HLA-B*35 (phi coefficient –0.32; P = 0.07), too. HLA-Bw4 homozygosity was present in 83% of EC, 50% of LV and 25% of HV. Being homozygotes for HLA-Bw4 significantly (P = 0.019) reduced CD4 decline over time (figure).



Conclusions: These data support an important role of the presented epitope in mediating relative control of HIV replication and immunological decay. We confirm the beneficial role of HLA-B*27 allele and of Bw4 homozygosity on HIV infection progression as well as the detrimental one of HLA-B*35. We describe two new alleles of the HLA-A complex possibly influencing HIV disease progression.

PP 19

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CX3CR1 I249M280 HETEROZYGOSITY IS ASSOCIATED TO CONTRACTION OF HIV-SPECIFIC IMMUNE RESPONSES IN HIV- INFECTED PATIENTS FAILING TO RECOVER CD4 T-CELL COUNT FOLLOWING LONG-TERM HAART

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Background: Patients failing to recover CD4 counts following long-term HAART represent a critical clinical issue, yet the pathogenetic mechanisms and long-term immune competency are still poorly understood. Recently, the expression of fractalkine receptor CX3CR1 gene has been shown to associate to a different rate of HIV progression because of its role in lymphocyte trafficking and function. We hypothesised that CX3CR1-V249I and T280M polymorphisms might contribute to defective functional immune responses in patients with no CD4 recovery on HAART.
Methods: We cross-sectionally analyzed frequencies of CX3CR1-V249I and T280M mutations by PCR-RFLP analysis in 37 HIV+ subjects with different responses after at least 12 months stable HAART: 24 *immunologic non-responders*, (INRs: CD4≤200, HIV-RNA≤50) and 13 *full responders*, (FRs: CD4≥400, HIV-RNA≤50). As controls, genetic analysis were performed in 204 HIV- healthy subjects. The percentage of Gag- and CMV-specific IL-2/INF-γ producing CD4/CD8 T-cells and IFN-γ ELISpot responses were studied in 17 INRs and 16 FRs. Student T-test and Fisher's exact test were used for statistics.
Results: No CX3CR1-280M homozygotes were found in HIV+ patients as compared to 4/204 (2%) HIV- subjects. Interestingly, as compared to FRs and HIV- subjects, INRs displayed a trend toward a higher frequency of heterozygous genotype, albeit statistically not significant: INRs: V249I 13/24 (54%), T280M 10/24 (42%); FRs: V249I 5/13 (33%), T280M 2/13 (15%); HIV-: V249I 84/204 (41%), T280M 58/204 (28%) (V249I: p INRs vs FRs=0.495, p INRs *vs* HIV-=0.223, p FRs *vs* HIV-=0.847; T280M: p INRs vs FRs=0.149, p INRs *vs* HIV-=0,180, p= FRs *vs* HIV-=0,523). Given the role of the CX3CL1/CX3CR1 system in polarizing Th1 and cytotoxic T-cell responses, we analyzed HIV and CMV-specific T-cell responses. Interestingly, INRs displayed significantly fewer Gag-specific IFNγ/IL-2 T-cells, in particular for IL2/CD8 (p=0.05); a trend toward a predominant IFNγ-producing T-cell pattern was shown in response to CMV as compared to FRs (p>0.05). Accordingly, INRs presented significantly weaker ELISpot responses to Gag (p=0.02), whereas no differences were observed in CMV responses (p>0.05) *vs* FRs.
Conclusions: HIV+ patients failing to recover CD4 on HAART show a higher frequency of heterozygous 249I and 280M mutations, likely translating in reduced receptor activity. This genotype corresponds to a significant HIV-specific functional impairment with preserved, although IFNγ-shifted, recall immune function. Given the protective Th1 phenotype in HIV/AIDS, our findings suggest altered CX3CL1/CX3CR1 as a pathway of hampered CD4 rescue on HAART.

PP 20

Infection 2009; 37 (Suppl. II): 46

CCL3L1 AND HTLV-2 MEDIATED HIV-1 PROTECTION: THE KEY ROLE PLAYED BY TAX-2

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Background: A substantial percentage (10-20%) of IDUs dually infected with HIV-1 and HTLV-2 are associated with a LTNP condition. Leukocytes of individuals co-infected with HTLV-2 and HIV-1 secrete chemokines that prevent CCR5-dependent (R5) HIV-1 infection of $CD4^+$ T-cells and macrophage, with HTLV-2-induced MIP-1α as dominant HIV-1 inhibitory molecule. Independent studies have demonstrated that an increased copy number of CCL3L1 gene results in enhancing the secretion of the corresponding protein CCL3L1, an isoform of CCL3 with potent inhibitory activity for R5 HIV-1 strains. Here, we investigate whether CCL3L1 up-regulation, observed in co-infected patients, is attributable to CCL3L1 gene dose or Tax-2 transactivator function.
Methods: By real-time PCR, CCL3L1 gene copy number as well as mRNA expressions were evaluated in the following cohorts: HTLV-2/HIV-1^{MEU} (multiply exposed-uninfected seronegative) (n=8), HIV-1 mono-infected LTNPs (n=8), and HTLV-2/HIV-1 co-infected LTNPs (n=7). In order to check Tax-2 ability to control CCL3L1 promoter, Jurkat Tet-On cells, selected to be showed 1 copy number pdg of CCL3L1 and no expression of its mRNA, were transiently nucleotransfected with a responsive plasmid expressing tax-2 (derived from HTLV-2 Gu isolate) and AcGFP as reporter gene. After turning on tax-2 by the addition of doxycycline, both tax-2 as well as CCL3L1 relative mRNA expressions were determined by real-time PCR.
Results: Unexpectedly, a median *CCL3L1* copy number corresponding to a high susceptibility to HIV-1 infection, was observed in HTLV-2/HIV-1^{MEU}. In contrast, a median *CCL3L1* gene dose indicating a low risk of HIV-1 infection, was detected in both HTLV-2/HIV-1 co-infected and HIV-1 mono-infected. Relative *CCL3L1* mRNA expression was up-regulated in *ex vivo* PBMCs from all groups. Thus, we hypothesized that a specific Tax-2 induction, rather than gene copy number, drives the up-regulation of *CCL3L1* mRNA expression observed in HTLV-2/HIV-1^{MEU}. By *in vitro* transfection of *tax-2*, we demonstrated that *tax-2* and *CCL3L1* mRNA expression occurred nearly simultaneously (peak at 8 and 24 hours, respectively), and that a low level of *tax-2* induction (20-fold increase relative to unstimulated control) is sufficient to induce a strong *CCL3L1* expression (700-fold higher than that detected in unstimulated culture).
Discussion: These findings demonstrate that in HTLV-2/HIV-1^{MEU} and LTNP co-infected subjects, the up-regulation of CCL3L1 expression, is independent by *CCL3L1* genotype but triggered by HTLV-2 infection via a post-genomic mechanism, in which Tax-2 plays a lead role. Because CCL3L1 and CCR5 host factors influence HIV-1 pathogenesis, we are currently exploring the Tax-2 role on a CCL3L1 controlled expression as a new preventive and therapeutic approach to counteract HIV-1 infection.

POSTERS

PO 001

Infection 2009; 37 (Suppl. II): 47

HIV AND HCV COINFECTED PATIENTS: DEVELOPING OF CIRRHOSIS, ROLE OF PROTECTIVE HAART AND SURVIVAL

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Aim of the study: 411 HIV/HCV coinfected patients consecutively enrolled in the last 8 years at Cotugno Hospital were observed for developing cirrhosis. For each subject were analyzed type of diagnosis, mean time from first observation (or first anti-HCV antibody positivity) and the onset of cirrhosis, effects of CD4 cell counts and HIV viremia at baseline on the natural history of HCV infection and the efficacy of previous HAART on fibrosis progression. We also evaluated mean time for developing decompensated cirrhosis and overall survival after cirrhosis developing.
Subjects and methods: 76 of the 411 coinfected patients (18.4%) developed cirrhosis during the period of study. Of the 76 patients 50 were males and 26 females, most of them (61%) were intravenous drug addicts, 20% were heterosexuals. 72/76 subjects (94.7%) had symptomatic HIV infection (class B and C CDC): Mean age at diagnosis of cirrhosis was 41,4 years (ranging from 27 to 70). Mean CD4 cell count and mean HIV VL log10 at diagnosis of cirrhosis were 265,8 cells/mcl and 4,1 log10 respectively. All patients were regularly observed both for HIV and HCV infection with virological, immunological and biochemical test as necessary. Ecotomography of abdomen was performed every 6 months.
Results: All the cases had a clinical and ultrasonography diagnosis of cirrhosis; no one performed liver biopsy. Mean time from first observation (or first anti-HCV antibody positivity) and the onset of cirrhosis was about 5 years (59,4 months). 14 of the 76 subjects had diagnosis of cirrhosis at the moment of their first observation. A non statistical difference on developing cirrhosis was observed when patients were stratified into two groups regarding CD4 cell counts (less than 200 or more than 200 CD4/mcl) and HIV viremia at baseline (detectable or undetectable). In contrast, efficacy HAART prior the developing of cirrhosis, significantly delayed the progression of fibrosis towards cirrhosis. More than 30% of cirrhotic patients (26/76) developed decompensated cirrhosis after one year from diagnosis and 19/76 died, after a mean of 16,7 months from the diagnosis.
Comments: Our observations confirm that HIV/HCV coinfection accelerates the progression of HCV disease towards cirrhosis. We do not observed faster progression of HCV infection towards cirrhosis in subjects with detectable HIV viremia and low CD4 cell counts baseline as reported from other Authors. Coinfected HIV/HCV patients have an increased rate of decompensation (more than 30% at one year) and increased rate of mortality (25% at 2 years). HAART has been associated with significantly decrease of liver disease progression, liver decompensation and liver related mortality in coinfected HIV/HCV patients. So, we believe that ideal strategy in the management of this setting of patients is to start HAART early, maintain CD4 cell count >500 cells/mcl and closely monitor patients for HAART-related liver injury.

PO 002

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HIV/HCV CO-INFECTION AND RISK OF LIVER STEATOSIS: THE ROLE OF TENOFOVIR

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Background: Liver steatosis is a common and important histological finding in hepatitis C, and is associated with an increased progression of the disease. In HIV co-infected patients steatosis was independently associated with d-drugs, such as stavudine, especially in non-3 HCV genotypes. We investigate the safety of tenofovir disoproxil fumarate (TDF) in determining hepatic steatosis in HIV-HCV co-infected patients.
Methods: All consecutive HCV-infected patients who had undergone a liver biopsy have been included in this study. Primary outcomes were the presence or absence of steatosis, or the presence of fibrosis. Results: 370 HCV infected patients underwent liver biopsy; 182 co-infected with HIV. Steatosis (> 5% in liver biopsy) was diagnosed in 33.0% of HCV mono-infected and in 47.3% in HIV co-infected patients (OR: 1.82; p=0.005). 50 HIV patients (27.5%) were naïve to antiretroviral therapy. In 89 patients received stavudine for a median of 38 months (IQR 17.5-58) while 36 patients received tenofovir for a median of 23 months (IQR 8.8-32). Duration of HCV infection (x 5 yrs OR. 1,10; 95%CI 1.10-1.17 p=0,001), HCV RNA levels (x log: OR 1,92; 95%IC 1,28-2,89; p=0,002), BMI >25 (OR 2,30; 95%IC 1,23-4,28; p=0,009) and use of d4T in HIV patients (OR. 3.00; 95% CI 1.18-7.59; p=0,021) were variables associated with steatosis in multivariate analysis. Since infection by HCV genotype 3 was independently and strongly associated with the presence of steatosis (OR: 3,14; 95%CI 1.89-5.20; p<0,001), we stratified patients according to this genotype in order to analyse the factors associated with steatosis. In HCV genotype other than 3 the risk of steatosis was related to fibrosis (OR, 3,95; 95% CI 1,65-9,47; p=0,002), BMI >25 (OR 2,62; 95%IC 1,15-5,97; p=0.023), older age (OR, 1,09;95% CI 1,02-1,17; p=0,014) and use of d4T (OR, 4,98; 95%CI 1,39-17,80; p=0,014). In all cases use of TDF was not associated with steatosis. . HIV characteristics such as the nadir of CD4+ T cell count, CD4+ count and HIV-RNA levels at biopsy were not related with risk of steatosis.
Conclusion: As previously described the risk of steatosis is mainly associated to HCV genotype 3 in patients infected by HCV. HIV co-infected patients with genotype other than 3 are at risk of developing steatosis with stavudine but not with tenofovir.

PO 003

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ETRAVIRINE SAFETY AND TOLERABILITY PROFILE IN HBV AND/OR HCV CO-INFECTED PATIENTS. DATA FROM THE POOLED DUET STUDIES

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Analysis of the safety and tolerability profile of the next-generation NNRTI etravirine (ETR) has been conducted in HBV and/or HCV co-infected patients over 48 weeks as part of the DUET 1 and DUET 2 studies. We report results from the pooled analysis, according to baseline hepatitis co-infection status.
HIV-1-infected patients on stable but virologically failing therapy were randomised to receive either ETR 200mg twice daily or placebo, both in combination with a background regimen (BR) consisting of darunavir with low-dose ritonavir (DRV/r), investigator-selected NRTIs and optional enfuvirtide (ENF). Hepatitis B and/or C virus (HBV and/or HCV) co-infection status was confirmed by hepatitis B surface antigen or HCV antibody and qualitative HCV ribonucleic acid (RNA). Co-infected patients were eligible if they were clinically stable, with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <5 x the upper limit of normal and did not require anti-hepatitis treatment.
At baseline, HBV and/or HCV status was known for 1130 HIV-1-infected patients. Of these, 140 patients (12.3%) were co-infected with HBV and/or HCV; the sample size was too small to compare HBV and HCV groups separately. Median treatment duration for this analysis was 52.3 vs 51.0 weeks in the ETR + BR and placebo + BR groups, respectively. In co-infected patients, grade 3 or 4 AEs, serious AEs and deaths were less frequent with ETR than with placebo. Grade 3 or 4 AST/ALT elevations were more frequent in co-infected patients receiving ETR, however the differences between the ETR and placebo groups was small. The incidence of grade 3 or 4 hepatic AEs was similar in both treatment groups.

	HIV and HBV and/or HCV co-infected patients		Non co-infected patients	
Incidence, %	**ETR + BR (n=72)**	**Placebo + BR (n=67)**	**ETR + BR (n=495)**	**Placebo + BR (n=495)**
Any AEs	95.8	97.0	95.7	95.8
Grade 3 or 4 AEs	31.9	44.1	32.8	33.5
Discontinuation due to AEs	8.3	8.8	6.7	5.1
Serious AEs	26.4	33.8	18.2	21.8
Deaths	2.8	4.4	1.4	2.8
Hepatic AEs*	12.5	8.8	5.5	6.0
Grade 3 or 4 hepatic AEs	6.9	7.3	2.4	2.4
Discontinuation due to hepatic AE	1.4	2.9	0.8	0.4
Selected treatment-emergent grade 3 or 4 laboratory parameters				
ALT	11.1	7.3	2.4	1.4
AST	9.7	5.8	2.2	1.4

HBV and/or HCV status was not recorded in 40 placebo- and 33 ETR-treated patients. *Data also includes hepatic laboratory abnormalities reported as AEs.

In general, the incidence and severity of AEs with ETR was similar to placebo, irrespective of co-infection status. The incidence of hepatic AEs was higher in co-infected patients than in non-co-infected patients in both treatment groups, consistent with the underlying chronic hepatitis condition. ETR did not increase hepatic toxicity in patients with hepatitis co-infection and was generally well tolerated in all patients.

PO 004

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USE OF ONCE-DAILY DARUNAVIR/R (800/100MG) IN TREATMENT– NAÏVE PATIENTS CO-INFECTED WITH HEPATITIS B AND/OR C. DATA FROM THE ARTEMIS STUDY.

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The Phase III ARTEMIS trial was conducted in HIV-1-infected treatment-naïve patients using once-daily darunavir/r (DRV/r 800/100mg). Its use was generally well tolerated, and had a lower incidence of treatment-related, moderate-to-severe diarrhea and triglyceride elevations versus lopinavir/r (LPV/r). This analysis examined the safety and tolerability of once-daily DRV/r (800/100mg) and LPV/r (800/200 mg total daily dose) in treatment-naïve HBV/HCV co-infected ARTEMIS patients.
Patients with HIV-1 RNA ≥5,000 copies/mL received DRV/r 800/100mg qd or LPV/r 800/200mg total daily dose, plus a fixed-dose combination tablet of tenofovir (300mg qd) and emtricitabine (200mg qd). Patients with chronic HBV/HCV co-infection were permitted to enter the trial if their condition was clinically stable and they would not require treatment for their hepatitis. HBV was determined by HB surface antigen testing and HCV by HCV antibody and PCR testing. 343 and 346 patients were randomized to DRV/r and LPV/r, respectively; 43 (13%) of DRV/r and 48 (14%) of LPV/r patients had HBV/HCV co-infection. The overall incidence of liver-related adverse events (AEs) was higher in co-infected patients (7/43, 16% DRV/r; 18/48, 38% LPV/r) than in non-co-infected patients (9/300, 3% DRV/r; 13/298, 4% LPV/r). In co-infected patients, the most common events (>5%) were liver-function abnormalities reported as AEs: increased ALT, increased AST and increased transaminases. These AEs were reported in ≤1% of non-co-infected patients. There were few clinical AEs, with the exception of HCV, which was reported in three (6%) LPV/r co-infected patients; all other AEs were reported in at most one co-infected patient.
Regarding laboratory abnormalities, the observed incidences of increases in ALT and AST were higher in patients with HBV/HCV

co-infection compared with those without co-infection in both treatment groups. The incidence of Grade 3 increases in ALT or AST was comparable in both co-infected groups. Grade 4 increases in ALT or AST were not observed in DRV/r patients with co-infection but were seen in 6/48 (13%) and 4/48 (8%) co-infected LPV/r patients, respectively. In the LPV/r group, the overall incidence of hyperbilirubinemia was higher in co-infected patients (6/48, 13%) versus non-co-infected patients (13/298, 4%), while this was low and comparable for co-infected and non-co-infected DRV/r patients (1/43 and 5/300, 2%).
Although HBV/HCV co-infected patients had a higher incidence of liver-related AEs compared with non-co-infected patients, the most commonly observed were liver-function abnormalities reported as AEs. There were no Grade 4 ALT or AST elevations in DRV/r co-infected patients, while these occurred in LPV/r patients. These results support previous findings and suggest that safety monitoring of HIV-1-infected patients with HBV/HCV co-infection treated with once-daily DRV/r 800/100mg is appropriate.

PO 005

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INCREASED RISK OF DEATH AMONG HIV/HCV CO-INFECTED PATIENTS WITH NON-HODGKIN'S LYMPHOMA

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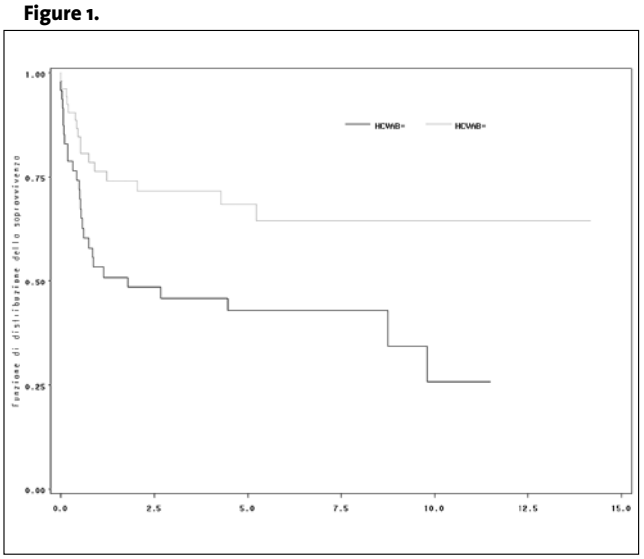
Background: Hepatitis C virus (HCV) infection has emerged as a risk factor of non-Hodgkin's lymphoma (NHL). No studies evaluated the long-term survival after lymphoma diagnosis according to HCV infection.
Methods: HIV-positive patients recorded in the Infectious Disease Database (IDD-HSR) with a diagnosis of Hodgkin's disease (HD) or AIDS-defining NHL and available data for HCV infection were analysed. Results are presented as median (Q1-Q3) or frequency (%). Survival and the corresponding standard error were calculated as the time interval from the date of lymphoma diagnosis to the last available visit or death. Kaplan-Meier and Cox-proportional hazard model were applied.

Survival for NHL is also shown in
Figure 1.



Results: 128 patients met the inclusion criteria: 99 (77%) had NHL, 47 (47%) of whom with HCV co-infection; 29 (23%) had HD, 13 (45%) of whom with HCV-co-infection.
HCV co-infected compared to HCV uninfected patients were younger [42.5 (38.8-45.3) vs 45.1 (40.2-55.9) years, p=0.006], more frequently IVDU (79% vs 5%, p<0.0001) and had a longer exposure to HIV infection [17.1 (10.7-21.2) vs 10.8 (4.8-15.5) years, p<0.0001]. No differences were detected in relation to sex, HBV coinfection, year of lymphoma diagnosis, previous AIDS diseases, nadir CD4, time of exposure to HAART.
Overall, 53 patients (41%) died: 33/60 (55%) of HCV co-infected patients and 20/68 (29%) of HCV uninfected patients (p=0.004).
Probabilities of death at 5,10 and 15 years from diagnosis of lymphoma were higher in HIV/HCV co-infected patients: [HCV+=49.7(+6.8) at 5 years; 67.8(+8.9) at 10 years, not evaluable (NE) at 15 years; HCV-=27.7(+5.9) at 5 years, 34.1(+6.9) at 10 years and 47.3(+13) at 15 years (p=0.0054)]. Death probabilities estimated according to HD and NHL diagnosis are reported in

Table 1.

	1 year	5 years	10 years	15 years	p-value
HCV+/HD+	7.7+7.4	24+12	49.2+16.7	NE	NS
HCV-/HD+	0	14.3+9.3	31.4+17.1	65.7+25.7	
HCV+/NHL+	46.7+7.5	57+7.6	74.2+10.5	NE	0.008
HCV-/NHL+	23.7+6	31.7+7	35.7+7.6	NE	

Among patients with HD, the risk of death was comparable in HCV infected and uninfected patients (HR=1.602, 95% confidence interval 0-426-6.024, p=0.49); in patient with NHL the hazard ratio of death was significantly higher in HIV/HCV co-infected patients (HR=2.257, 95% CI 1.215-4.201, p=0.009).
Conclusions: Probability of death in HIV/HCV co-infected patients with NHL was nearly twice than in HCV uninfected patients. Reasons for this difference, including severity of cancer, exposure to chemotherapy and hepatotoxicity of chemotherapics need to be investigated.

PO 006

Infection 2009; 37 (Suppl. II): 49

HEPATIC IRON ACCUMULATION IN LIVER OF HUMAN IMMUNODEFICIENCY VIRUS-AND HEPATITIS C VIRUS-COINFECTED PATIENTS

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Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are both transmitted by parenteral routes, and coinfection with these 2 viruses is common, particularly among patients with a history of injection drug use or transfusion. Increasing knowledge on the management of adverse events under hepatitis C therapy and optimized selection of antiretrovirals in HIV/hepatitis C virus-coinfected patients has helped to reduce complications and improve overall treatment outcome (Rockstroh JK, Curr Opin Infect Dis 2006). However, several studies have shown the deleterious effect of HIV infection on the course of HCV-related liver disease and have emphasized the increased risk of death caused by liver disease among HIV/HCV coin-

fected persons with an accelerated course of progression to cirrhosis and end-stage liver disease (Benhamou Y, Hepatology 1999; Valleet-Pichard A, J Hepatol 2006). Pathogenesis of liver damage in patients with HIV and HCV coinfection is complex and multifactorial. How HCV causes liver injury is not fully understood. The pathology seems to be driven by chronic inflammation. Hepatic iron stores are frequently increased in hepatitis C, and the detrimental effects of excess iron, as a pro-inflammatory agent, are well documented. It is associated with increased morbidity and mortality of HCV disease and a poorer response to interferon treatment (Kaji K, Pathol Int. 1997). Elevated iron status is also associated with increased mortality in HIV infection (Drakesmith H, Nature Rev. 2008).
The aim of this study was to analyze the impact of HIV on iron hepatic accumulation in HCV infection patients, to investigate whether a high iron status may adversely influence the outcome of liver disease in HIV/HCV coinfection. A retrospective cohort of 81 patients with HIV/HCV co-infection and a past history of injection drug use, without known causes of iron overload, who were consecutively admitted between 2005-2008 for a liver biopsy, was included in this study. As a control group 81 HIV-negative patients with chronic hepatitis C and a past history of injection drug use, who were admitted for a liver biopsy during the same period, were included. Liver sections, stained with standard methods and with Perls' stain for iron grading were assessed by two independent observers (A.B.; G.L) according to Deugnier (Gastroenterology 1992). Iron deposits were assessed according to size, cellular and lobular locations in Rappaport's acinus, leading to three different scores: hepatocytic (HIS; range, 0-36), sinusoidal (SIS; range, 0-12) and portal iron scores (PIS; range, 0-12). The sum of these scores defined the total iron score (TIS; range, 0-60). The main result of this study was the observation of a different distribution of iron in the hepatocytic, sinusoidal and portal compartments in HIV/HCV coinfected patients compared with HIV-negative patients; while iron status in coinfected patients didn't correlate with activity (A) or fibrosis (F).

PO 007

Infection 2009; 37 (Suppl. II): 50

EVALUATION OF THE ANTI-HIV ACTIVITY OF NATALIZUMAB/TYSABRI, A MONOCLONAL ANTIBODY AGAINST INTEGRIN ALPHA 4

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Tysabri (Natalizumab, Biogen-Idec) is a humanized monoclonal antibody that belongs to a class of therapeutics known as alpha-4 integrin inhibitors has been approved for the treatment of multiple sclerosis and Crohn's disease. Tysabri binds to the cell surface receptors known as alpha-4-beta-1 (VLA-4) and alpha-4-beta-7. The receptors for the alpha4 family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium, and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) present on vascular endothelial cells of the gastrointestinal tract. The expression of alpha4beta7 integrin in CD4+Tcells has been recently associated with HIV entry and replication and it has been postulated that the alpha4beta7 integrin might serve as a co-receptor for HIV. It is then tempting to speculate that targeting the alpha4beta7 integrin with Natalizumab could provide an approach for the treatment of HIV-1 infection. We have then evaluated the effect of Natalizumab on HIV-1 replication in cell culture. Specifically, C8166 cells were pre and/or post-treated with different concentrations of Natalizumab (from100 ug/ml to 0.1 ug/ml) and then infected with a laboratory strain of HIV-1, namely HIV-P1, at a multiplicity of infection of 0.01. After 72 hrs the replication and the reduction of viral yield has been examined by measuring p24 viral antigen in the supernatant (by an ELISA assay). The results showed that the pretreatment of cells with 100 ug/ml of natalizumab reduced of about 90% the HIV yield. The post-treatment of C8166 cells at the same dosage resulted in an inhibition of about 70%. Since the experiments were performed in multiple cycles conditions, the antiviral activity of Natalizumab after the adsorption was, probably, due to an effect of the drugs on the adsorption of the neo-produced virus. Further experiments are in progress to characterize such preliminary findings. At the moment the data suggest that, in these experimental conditions, Natalizumab is able to inhibit HIV replication and that the expression of alpha 4 integrin might be associated with CD4-dependent or -indipendent binding (and entry) of HIV to the cells.

PO 008

Infection 2009; 37 (Suppl. II): 50

A UNIQUE ASSOCIATION OF RHINOPHARYNGEAL ACTINOMYCOSIS AND SQUAMOUS ADENOCARCINOMA DURING HIV INFECTION. DIAGNOSTIC AND TREATMENT CONCERNS

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Introduction: Solid malignancies, including those with atypical presentations, are increasing 12 y after the introduction of combined antiretroviral therapy (cART), and the differential diagnostic problems may be increased by the eventual concurrence of superinfections.
Methods-Results: An extremely infrequent episode of associated nasopharyngeal actinomycosis plus squamous adenocarcinoma occurred in a HIV-infected male patient (p) with a previous diagnosis of AIDS, treated with cART taken with insufficient adherence, so that a satisfactory immune system recovery (as expressed by a CD4+ count persistingly >400 cells/μL), was in contrast with a low-level persistance of detectable HIV viremia, and an enlarged genotypic resistance mutations. Interestingly, a number of local and specific risk factors for both infectious and neoplastic disorders were recognized by caregivers (tobacco smoke, long-term inhalatory substance abuse, in particular cocaine, and a half-professional mushroom-truffle search and evaluation also by systematic smelling). Although an appropriate and timely diagnostic workup carried out with repeated, combined computerized tomography, magnetic resonance imaging, and fiberoptic rhinoscopy with biopsy and histopathologic studies, the final diagnosis of a combined, dual infectious-neoplastic pathology occurred only after a demolitive surgical intervention and subsequent pathology studies. Despite a correct antimicrobial therapy, and an associated radiotherapy and cytotoxic chemotherapy schedule, a rapid dissemination of multiple secondary lesions to the brain rapidly led our p to death.
Conclusions: The imaging and histopathological diagnostic workup of dual illnesses of our HIV-infected p, and its therapeutic and outcome features, are presented and discussed on the ground of the available literature evidences. To the best of our knowledge, no cases of associated actinomycosis plus a local, underlying squamous cell adenocarcinoma of the same ear, nose, and throat district occurred until now in both HIV-infected and HIV-non-infected p, so that health care professionals should be alerted when facing p with rhinopharyngeal mass lesions.

PO 009

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RESOLUTION OF HIV-ASSOCIATED PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA WITH ART

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Primary central nervous system lymphoma (PCNSL) is the second most common intracranial mass lesion in adult patients with AIDS. PCNSL is characterized by a rapid progression and a high mortality rate, and is almost always associated with Epstein-Barr virus (EBV). We present a 34 year-old male with HIV-1 infection who presented with seizures in 2006 who was ultimately diagnosed with PCNSL. The patient had AIDS with a CD4 blood cell count of 48/mmc (2.2%) and HIV viral load of 12,100 cp/ml. He underwent CT scan of the brain which demonstrated a right occipital mass with significant T2 enhancement. He was started on empiric toxoplasmosis (Purimethamine/Sulfadiazine), and antiretroviral therapy (ART) was added 2 weeks later (boosted-Atazanvir, Tenofovir, and FTC). After three weeks of toxoplasmosis therapy, an MRI failed to show improvement of the mass and a lumbar puncture demonstrated an inflammatory pattern (glucose 54 mg/dl, 53 nucleated cells [100% lymphocytes], total protein 81mg/dL) EBV, cytomegalovirus, and JC virus PCR were negative, and CSF HIV-1 viral load was < 2700 cp/ml. A stereotactic biopsy was performed 8 weeks after his initial presentation, and pathology was consistent with an aggressive B-cell non-Hodgkin lymphoma (positive for CD20, bcl-2, MUM-1, and negative for CD3m, bcl-6, CD10 and CD68). The patient declined whole-brain radiotherapy, but agreed to continue on ART. He was closely followed as an outpatient and underwent serial MRIs, performed after 3, 5 and 10 months, which showed initial improvement and then a complete regression of the occipital lesion. His most recent MRI performed on May 2008 was negative, and he was maintained on ART. This case report describes a complete remission of PCNSL with isolated ART therapy. Since such cases are rare, we can only hypothesize on the reasons for his marked improvement. The absence of EBV in the CSF, while unexpected, may predict a less aggressive course in patients with PCNSL. Further studies are needed to evaluate the role of EBV viral load and ART regimen on outcome following HIV associated CNS lymphoma. Prompt institution of ART therapy is needed in HIV patients diagnosed with PCNSL.

PO 010

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UNCOMMON MALIGNANCIES IN HIV-PATIENTS DURING THE ERA OF THE HIGLHY ACTIVE ANTIRETROVIRAL THERAPY: A DESCRIPTION OF TWO CASES

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Large epidemiological and cohort studies clearly revealed that the risk of acquiring non-AIDS related malignancies is about two to three fold higher than in the general population, and the incidence of these tumors increased during the HAART era. We report on a case of Merkel cell carcinoma (MCC) in a male adult HIV patient, and a case of spinal subependymoma in a HIV-positive woman.
Case 1: A 66-years old patient presented on april 2008 with a painful left inguinal lymphoadenopathy. The patient, with a 25-years history of HIV infection, started HAART on 2002 with saquinavir, lamivudine and stavudine and he received also IL-2 from 2002 to 2006 in the context of an international trial. The biopsy of the inguinal mass documented massive growth of malignant cells inside the inguinal lymph nodes with the histological and immunohistochemical patterns of MCC carcinoma. At the time of diagnosis of the neoplasia the patient had HIV-RNA < 40 copies/mL and 479/mm3 T CD4 lymphocites. Six cycles of chemotherapy with carboplatin and etoposide with concurrent radiation therapy after complete excision of the tumoral mass were administered. Despite the lymphonodal involvement at presentation (MCC stage III), one year after the patient remained free of symptoms and a total body computed tomography scan and positron emission tomography did not show recurrence of the disease.
Case 2: A 44-years old woman was admitted to our department complaining burning pain radiating to the legs and footh with paresthesia lasting from five months. The patient was found to be HIV-positive in 1987 and her past history is remarkable for a chronic HCV-related hepatitis and a lumbar herpes zoster episode. She started HAART on 1999, and with the ongoing treatment (tipranavir/ritonavir + stavudine + tenofovir since 2005) her plasma HIV-RNA is below 40 copies/mL, and T CD4 cell count 424/mm3. The magnetic resonance imaging of the spine showed an intramedullary lesion of the thoracic tract with an enlargement of the ependimal channel along the first to the fourth thoracic vertebral body. The lesion appeared contrast-enhancing. Intraspinal thoracic subependymoma was diagnosed, and surgical resection of the mass was performed.
Conclusions: The HAART has dramatically reduced the incidence of AIDS-defining infectious and neoplastic diseases, but other malignancies are diagnosed in the HIV-positive patients with an increased incidence than in the general population. HIV positive individuals have a relative risk for MCC of 13.4, and, like HHV-8 virus for the Kaposi sarcoma a novel polyomavirus seems to be involved in the pathogenesis of MCC. There is not evidence that the incidence of brain tumors other than primary EBV-related cerebral lymphoma is increased in the HIV-infected population. Intraspinal subependymoma are very rare tumors and their symptoms could be easily misinterpreted with the symptoms due to HIV- and drug-related peripheral neuropathies.

PO 011

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OXALIPLATIN BASED CHEMOTHERAPY AND CONCOMITANT HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN METASTATIC COLORECTAL CANCER (M-CRC) HIV-POSITIVE PATIENTS (PTS): THE GICAT EXPERIENCE

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Background: This study was performed to evaluate retrospectively the efficacy and tolerance of FOLFOX4 regimen, with concomitant HAART, in M-CRC HIV-positive pts.
Methods: From February 2002 to June 2007, 24 consecutive M-CRC HIV-positive pts were treated, within the Gruppo Italiano Cooperativo AIDS e Tumori (GICAT). Before treatment, pts were staged by means of physical examinations, complete blood cell count (including CD4+), blood chemistry, HIV viral load, CEA and CT-Scan of thorax and abdomen. After every cycle of chemotherapy (CT) filgrastim (300µg/die sc, from day 5 to complete haematological recovery) were profilactically administered.
Results: An overall response rate of 50% was observed. There were 4.2% complete response (CR) and 45.8% partial response (PR). Toxicity was manageable and the most common severe toxicity was neutropenia (29.2%). No patient had opportunistic infection during chemotherapy.

The clinical characteristics of the patients and the results are reported in the table:

Sex M/F	19/5
Age median (range)	48 (29-63)
PS median	1 (0-3)
Primary tumor	
Colon	19 (79%)
Rectum	5 (21%)
Median CD4 cell count/μl*	380 (range 220-570)
Median HIV viral load, copies/ml*	8.200 (range 5.600-10.123)
Site of metastases	
Liver	14 (58.3%)
Lung	1 (4.2%)
Liver-Lung	5 (20.8%)
Others	4 (16.7%)
Prior CT (adjuvant)	2 (8.4%)
Prior RT (adjuvant)	1 (4.2%)
Total number of CT cycles	135
Median number of CT cycles per patient	4 (range 2-7)
Response to CT	
Complete + Partial remission	12 (50%)
Stable disease	5 (20.8%)
Progression disease	7 (29.2%)
Haematological toxicities (neutropenia)	
G1-G2	13 (54.2%)
G3-G4	7 (29.2%)
Gastrointestinal toxicities (diarrhoea)	
G1-G2	13 (54.2%)
G3-G4	3 (12.5%)

*At cancer diagnosis

Conclusions: These results suggest that FOLFOX4 regimen with concomitant HAART is feasible and active, while the HIV infection is not a limiting factor for its use. Moreover, the concomitant use of HAART does not seem to increase the toxicity of FOLFOX4 regimen.

PO 012

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EBV DNA LEVEL IN PLASMA AS DIAGNOSTIC AND PROGNOSTIC MARKER OF HIV-ASSOCIATED LYMPHOMAS

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Background. Epstein-Barr virus (EBV) is pathogenically linked to human immunodeficiency virus (HIV)-related lymphoma and is present in the tumor cells of about one half of Non Hodgkin lymphoma (NHL) and of nearly all Hodgkin lymphomas (HL). The goal of this study was to evaluate the potential of EBV DNA plasma level as a predictive, diagnostic, and prognostic marker of HIV-related lymphomas.
Patients and Methods. We studied 67 patients with HIV-related lymphoma (47 NHL and 19 HL) and 34 controls with HIV infection and other opportunistic pathologies. EBV DNA levels were determined by real-time polymerase chain reaction in plasma samples collected at time of diagnosis, during the 12 months before and the 12 months after diagnosis, during chemotherapy. In addition, lymphoma tissue samples collected by biopsy (22 NHL and 12 HL) were analysed 34 patients for small EBV encoded RNA (EBER) by in situ hybridization.
Results. In plasma samples collected at the time of diagnosis of lymphoma, EBV was identified in 22/47 (47%) NHL and in 16/19 (84%) of HL (median 1756, range 100-53,193 c/ml), and in 5/34 (15%) controls (median 100, range 100-1642 c/ml). The best cut-off diagnostic value was 1038 c/ml for NHL (sensitivity 43%, specificity 97%) and 600 c/ml for HL (sensitivity 79%, specificity 94%). When only cases with positive EBER were analysed (50% of LNH, and 83% of HL), the rate of EBV DNA detection was 100% in NHL and 60% in HL. In HL, EBV DNA levels were significantly higher in patients with bone marrow involvement than in those without (p=0.02), whereas, in NHL, levels were significantly lower in patients undergoing HAART compared to untreated patients (p=0.01). No different EBV DNA levels were observed as for tumor histotype, localization (nodal versus extranodal) or clinical stage, survival, and plasma levels of HIV RNA or CD4 and CD8 blood lymphocytes. In plasma samples collected before lymphoma diagnosis, EBV DNA levels were above the cut-off only in 2/17 patients (1 NHL and 1 HL), 90 and 60 days before diagnosis. In plasma samples collected during and/or at the end of chemotherapy, EBV DNA was cleared from plasma in 16/18 patients (10 NHL and 6 HL). A complete response to chemotherapy was observed in 13/16 patients who cleared EBV DNA from plasma and in none of the 2 who did not.
Conclusion. Plasma EBV DNA level seems to be a promising diagnostic marker of HL, and, to a lesser extent, of NHL. The low diagnostic sensitivity in NHL, however, reflects the association of these tumors with EBV in less than half of the cases. Plasma EBV DNA level does not seem to predict subsequent development of lymphomas, whereas it may be useful for monitoring response to chemotherapy. Finally, the association between HAART and reduced EBV replication in NHL supports the hypothesis that anti-HIV treatment may influence lymphomagenesis.

PO 013

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PARAGANGLIOMA IN PATIENT WITH HIV INFECTION

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We report a case of paraganglioma, a tumor arising from chromaffin cells in extra-adrenal paraganglia (para-aortic sympathetic chain) in patient with HIV infection.
A 47 years old man, HIV-HCV positive: diagnosis of infection with human immunodeficiency virus had been made 20 years earlier and he was treated with NRTI and NNRTI 10 years after the initial diagnosis. The CD4 count was more than 250/mm3 with viral load undetectable for along time. The patient had a story of pulmonary hypertension; hepatits B; Legionary diesease. He presented with arterial hypertension, heartbeat, sincopal episodis and glucose intollerance. The diagnosis of paraganglioma is made with documentation of catecholamine and metanephrine hypersecretion (measured in blood and urine) and with imaging. We used computerized tomography (CT), magnetic resonance imaging (MRI) and radionuclide molecular imaging with metaiodiobenzylguanidine (MIBG). 10-50% of paragangliomas are hereditary, but in this case genetic testing was negative. The treatment was the surgical resection with a clinical improvement. 4 weeks after surgery and now, 17 months after surgery) 24-h urinary fractionated catecholamines and metanephrine levels are nomal. Also the follow-up imaging (CT) is negative.

The occurrence of neuroendocrine tumor in the setting of HIV infection has not been well characterized and this is a rare reported case of paraganglioma in HIV patients.

PO 014

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MORTALITY IN HIV-1 INFECTED PATIENTS WITH OR WITHOUT CANCER IN COMPARISON TO THE ITALIAN GENERAL POPULATION

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Background: No data are available as for the mortality in HIV-1 infected patients with or without cancer in comparison to the general population.

We analysed mortality in HIV-1 infected subjects with or without malignancies and in the general population.

Methods: Patients with HIV infection followed at the Infectious Disease Department of IRCCS San Raffaele and with a documented date of HIV first-positive test were included. Standardized mortality ratio (SRM) was calculated using direct method, dividing the number of observed deaths by the number of expected deaths [calculated on the basis, of the last available, gender and age-specific rates for the italian general population (Year 2002, Istituto Superiore di Sanità)].
Ninety-five percent confidence intervals for SMRs were estimated according to Rothmann and Boice, 1979. Follow-up was calculated from the date of the first HIV-positive test to the last available visit or death or drop out dates. Malignancies were classified into AIDS defining malignancies (ADM) or non AIDS defining malignancies (NADM) according to 1993 CDC classification.

Results: Among 7167 patients recorded in IDD-HSR, 6506 patients met the inclusion criteria; median age, at the end of follow up, 43.2(37.4-48.3) years, 4974(76.5%) males, 379/4231(9%) HBV coinfected, 1835/4686 (39.2%) HCV coinfected, 1281 (19.7%) patients had an history of a CDC class C event. 11.3(5.68-17.18) years after HIV-infection, 4352(66.9%) subjects are alive, 1041 (16%) are dead, 1113(17.1%) were lost to follow up.

Table 1

CANCER STATUS	GENDER	CLASSES OF CURRENT AGE	NUMBER OF SUBJECTS	PERSON-YEARS	NUMBER OF DEATHS OBSERVED	NUMBER OF DEATHS EXPECTED	DEATH RATE PER 1,000 PERSON-YEARS	NATIONAL DEATH RATE(*)	SMR	95% CI (SMR) Lower	95% CI (SMR) Upper
Absent	Males	<40	1507	11089,2	299	9,96	26,96	0,90	***30,03***	26,726	33,640
		40-44	1073	13379,3	102	22,03	7,62	1,65	***4,63***	3,774	5,619
		45-49	934	13903	57	35,55	4,10	2,56	***1,60***	1,214	2,078
		50-54	435	6336,9	30	25,88	4,73	4,08	1,16	0,782	1,655
		55-59	215	2743,9	16	19,05	5,83	6,94	0,84	0,480	1,364
		60-64	147	1688,9	12	18,89	7,11	11,18	0,64	0,328	1,110
		65-69	93	1031,6	8	19,20	7,75	18,61	0,42	0,179	0,821
		>=70	51	554,8	4	31,48	7,21	56,74	0,13	0,034	0,325
		Total	4455	50727,6	528	506,45	10,41	9,98	1,04	0,956	1,135
	Females	<40	591	5356,7	132	1,91	24,64	0,36	***69,09***	57,809	81,937
		40-44	396	6174,2	15	5,56	2,43	0,90	***2,70***	1,508	4,448
		45-49	272	4644,4	7	6,67	1,51	1,44	1,05	0,420	2,162
		50-54	83	1239,7	5	2,86	4,03	2,30	1,75	0,564	4,086
		55-59	45	620,9	1	2,21	1,61	3,56	0,45	0,006	2,519
		60-64	26	280	3	1,50	10,71	5,34	2,01	0,403	5,860
		65-69	10	93,4	0	0,82	0,00	8,82	0,00	0,000	4,709
		>=70	14	146,7	2	4,77	13,63	32,50	0,42	0,047	1,515
		Total	1437	18556	165	175,83	8,89	9,48	0,94	0,801	1,093
Present	Males	<40	165	1074,1	134	0,96	124,76	0,90	***138,97***	116,434	164,590
		40-44	114	1336,2	62	2,20	46,40	1,65	***28,17***	21,599	36,118
		45-49	93	1215	38	3,11	31,28	2,56	***12,23***	8,655	16,791
		50-54	60	622,3	35	2,54	56,24	4,08	***13,77***	9,589	19,151
		55-59	30	393,6	17	2,73	43,19	6,94	***6,22***	3,623	9,963
		60-64	29	338,08	11	3,78	32,54	11,18	***2,91***	1,450	5,206
		65-69	15	181,17	3	3,37	16,56	18,61	0,89	0,179	2,600
		>=70	13	108,3	3	6,15	27,70	56,74	0,49	0,098	1,426
		Total	519	5268,75	303	52,60	57,51	9,98	***5,76***	5,130	6,447
	Females	<40	32	257,7	25	0,09	97,01	0,36	***272,01***	175,983	401,564
		40-44	16	249,6	6	0,22	24,04	0,90	***26,68***	9,743	58,075
		45-49	24	394,8	4	0,57	10,13	1,44	***7,05***	1,897	18,057
		50-54	11	120,3	5	0,28	41,56	2,30	***18,04***	5,815	42,109
		55-59	3	54,1	1	0,19	18,48	3,56	5,20	0,068	28,915
		60-64	3	33,47	1	0,18	29,88	5,34	5,59	0,073	31,118
		65-69	4	47,24	2	0,42	42,34	8,82	4,80	0,539	17,336
		>=70	2	11,15	1	0,36	89,69	32,50	2,76	0,036	15,355
		Total	95	1168,36	45	11,07	38,52	9,48	***4,06***	2,964	5,439

Table 2

CANCER STATUS	GENDER	CLASSES OF CURRENT AGE	NUMBER OF SUBJECTS	PERSON-YEARS	NUMBER OF DEATHS OBSERVED	NUMBER OF DEATHS EXPECTED	DEATH RATE PER 1,000 PERSON-YEARS	NATIONAL DEATH RATE(*)	SMR	95% CI (SMR) Lower	95% CI (SMR) Upper
Absent	Males	<40	797	3484,01	13	3,13	3,73	0,90	***4,16***	2,211	7,108
		40-44	397	2279,79	10	3,75	4,39	1,65	***2,66***	1,275	4,898
		45-49	263	1704,7	5	4,36	2,93	2,56	1,15	0,370	2,677
		50-54	111	676,85	6	2,76	8,86	4,08	2,17	0,792	4,724
		55-59	71	450,75	3	3,13	6,66	6,94	0,96	0,193	2,802
		60-64	62	367,47	1	4,11	2,72	11,18	0,24	0,003	1,354
		65-69	43	268,48	1	5,00	3,72	18,61	0,20	0,003	1,114
		>=70	22	138,07	1	7,83	7,24	56,74	***0,13***	0,002	0,710
		Total	1766	9370,12	40	93,55	4,27	9,98	***0,43***	0,305	0,582
	Females	<40	225	1185,72	6	0,42	5,06	0,36	***14,19***	5,181	30,883
		40-44	73	491,28	0	0,44	0,00	0,90	0,00	0,000	8,287
		45-49	40	233,39	0	0,34	0,00	1,44	0,00	0,000	10,941
		50-54	17	127,35	1	0,29	7,85	2,30	3,41	0,045	18,968
		55-59	10	72,58	0	0,26	0,00	3,56	0,00	0,000	14,209
		60-64	7	28,6	0	0,15	0,00	5,34	0,00	0,000	24,009
		65-69	6	38,99	0	0,34	0,00	8,82	0,00	0,000	10,670
		>=70	6	41,88	0	1,36	0,00	32,50	0,00	0,000	2,695
		Total	384	2219,79	7	21,03	3,15	9,48	***0,33***	0,133	0,686
Present	Males	<40	33	135,3	11	0,12	81,30	0,90	***90,56***	45,147	162,053
		40-44	27	115,14	6	0,19	52,11	1,65	***31,64***	11,554	68,871
		45-49	15	104,32	5	0,27	47,93	2,56	***18,75***	6,041	43,747
		50-54	12	45,63	1	0,19	21,92	4,08	5,37	0,070	29,852
		55-59	4	13,15	5	0,09	380,23	6,94	***54,78***	17,653	127,836
		60-64	10	58,63	3	0,66	51,17	11,18	4,58	0,920	13,369
		65-69	5	44,43	1	0,83	22,51	18,61	1,21	0,016	6,730
		>=70	6	32,16	1	1,82	31,09	56,74	0,55	0,007	3,049
		Total	112	548,76	33	5,48	60,14	9,98	***6,02***	4,146	8,459
	Females	<40	3	19,63	0	0,01	0,00	0,36	0,00	0,000	523,943
		40-44	2	18,72	1	0,02	53,42	0,90	59,29	0,775	329,887
		45-49	5	27,1	2	0,04	73,80	1,44	***51,37***	5,770	185,486
		50-54	3	22,36	1	0,05	44,72	2,30	19,42	0,254	108,029
		55-59	0	0	0	0,04	0,00	3,56	0,00	0,000	92,247
		60-64	1	11,18	0	0,08	0,00	5,34	0,00	0,000	47,783
		65-69	2	14,37	2	0,00	139,18	8,82	0,00	0,000	0,000
		>=70	0	0	0	0,00	0,00	32,50	0,00	0,000	0,000
		Total	16	113,36	6	1,07	52,93	9,48	***5,59***	2,040	12,158

Overall 614/6506 (9.4%) subjects developed cancer [ADM: 429(6.6%); NADM: 185(2.8%)].
Overall SMR was higher in HIV-1 infected patients [Males: SMR= 1.64, 95%CI :1.53-1.76 ; Females SMR = 1.19 , 95% CI: 1.04-1.37] than the general population.
Sex and age-adjusted SMR according to the presence/absence of cancer are shown in Table 1.
An excess of mortality was observed in HIV-i1 nfected subjects with cancer [Males: SMR= 5.76, 95%CI: 5.1-6.4; Females: SMR=4.06, 95%CI: 3-5.4] with a dramatic SMR elevation for subjects younger than 40 years [Males: SMR= 138.97, 95%CI: 116.4-164.6; Females: SMR=272, 95%CI: 176-401.6].
In the post HAART era (HIV-1 infection >1997, Table 2) neoplastic HIV-1 infected subjects continued to present an higher SMR than the general population [Males: SMR= 6.02, 95%CI: 4.1-8.5; Females: SMR=5.59, 95%CI: 2-12.1].
Conclusions: HIV-1 infected patients with cancer showed a 6 fold for males and 4 fold for females excess of mortality in comparison to HIV-1 infected patients without cancer or to the general population. In the post-HAART era mortality decreased even in patients with cancer but it remained significantly higher than the Italian population.

PO 015

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UNILATERAL MOYAMOYA SYNDROME IN A PATIENT WITH HIV INFECTION

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Background: Moyamoya disease (MD) is a rare idiopathic neurological disorder, first described in Japan in the 1960's, due to occlusion of the circle of Willis with development of collateral network at the base of the brain. Defined cases show bilateral involvement, while cases with unilateral involvement are defined as probable cases. "Moyamoya syndrome" (MS), a radiographic picture resembling MD, is associated with several systemic diseases. Only two cases of bilateral moyamoya syndrome in adults and a single case in a child have been associated with HIV infection. These patients presented either comorbidities or advanced AIDS condition.

We describe a case of unilateral MS in a patient with well-controlled HIV infection.
Case description: a 65 years old HIV-infected male presented recurrent episodes of paresthesia, hypostenia and hemiparesis of the left body site. After the first episode, a brain MR study showed acute ischemic lesions in the right thalamus and ipsilateral occipital lobe. Further episodes of worsening of left hemiparesis and dysartria occurred in the next month. Follow-up brain MR study showed new ischemic lesions in the right cerebral lobe, with ischemic stroke in the territory of right posterior cerebral artery (PCA), and development of collateral vessels with a pattern consistent with MS.
Conclusion: Association between MS and HIV/AIDS has rarely been described. Differently by the other cases described in the literature, our patient showed unilateral involvement; moreover, his HIV disease was well-controlled and there was no evidence of co-morbidities. More research is needed to assess the exact role of HIV infection in the pathogenesis of this syndrome. Due to the advances in the treatment of HIV and the long-term survival in these patients, neurovascular complications, including MS, could become more frequent in the future.

PO 016

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DEPRESSION, ANXIETY AND COGNITIVE IMPAIRMENT IN ELDERLY PATIENTS RECEIVING HAART: PREVALENCE AND RISK FACTORS

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Background: Depression, anxiety and cognitive impairment are commonly seen in HIV-positive patients. However, data on prevalence and risk factors for these conditions in subjects aged more than 50 years are incomplete. We examined frequency and determinants of depression, anxiety and cognitive impairment in patients aged >50 years.
Methods: Cross-sectional study of 169 HAART treated HIV-infected patients aged >50 years. Patients were administered the IPAT Depression Scale Questionnaire (CDQ), IPAT Anxiety Scale Questionnaire (ASQ), the and a battery of 17 standardized neuropsychological tests (NPT) as part of psychiatric, medical, and laboratory assessment.
Results: Patients characteristics: age 56,8 yrs (mean, range 50-85), male gender 82.8%, CD4 count 555/cmm (mean, SD ±347), subjects with HIV RNA <50 cp/mL 70.7%, patients with previous AIDS events 43.8%, current HAART schemes: EFV-based 32,5%, PI-based 63.3%, and NVP-based 4.1% patients. Overall, scores consistent with anxiety (ASQ score>6) and depression (CDQ score>5) were observed in 66,9% and in 54,4% of patients, respectively. Cognitive impairment (<1SD from the normative mean on ≥2 age and gender adjusted NPT, or <2SD from the mean on ≥1 adjusted NPT) was present in 46,8% patients. Cognitive performance was not influenced by anxiety and depression scores. Similarly, age, sex, risk factors, CDC stage, plasma HIV RNA, duration of HAART exposure were not related to anxiety and depression scores. Patients aged >60 years had greater impairment at NPT than patients aged 50-60 years (mean NPT-Z4 score: -2,0 vs -0,7; p=0.002). Moreover, patients with ASQ scores consistent with anxiety had CD4 counts lower than patients reporting no anxiety (mean CD4 count/cmm 447 vs. 598; p=0.026). Finally, EFV treated patients were more likely to show summary scores consistent with absence of both depression (CDQ<5: 41,8% vs 60,5%; p=0.022) and anxiety (ASQ<6: 54,5% vs 72,8%; p=0.018) than PI treated subjects.
Conclusions: Depression and anxiety were reported in nearly two third of patients aged >50years. Anxiety was associated with low CD4 cell count. Cognitive impairment was present in almost fifty percent of patients aged >50 years. Cognitive decline increased with increasing age. By contrast, anxiety and depression did not influence cognitive performance. Anxiety and depression were less common in EFV-treated patients, suggesting a prescription bias. Physicians must be aware of the high prevalence psychiatric and cognitive disturbances in HIV patients aged >50 years.

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DIFFERENT HIV TROPISM IN THREE DISTINCT DISTRICTS: PLASMA, PBMC AND CEREBRO SPINAL FLUID

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Objectives: HIV-1 variants can be classified into those that exclusively use CCR5 (R5), CXCR4 (X4) or both coreceptors (R5X4 or dual-tropic viruses) to enter cells. R5 viruses are characteristic of the asymptomatic stage of infection and are selectively transmitted between individuals. However, coreceptor switch from R5 to R5X4 or X4 viruses occurs in around 50% of infected individuals and has been associated with accelerated CD4 T-cell decline and disease progression. Moreover, HIV circulating in blood and cerebrospinal fluid (CSF) showed evidence of homing to different cellular coreceptors.
Methods: the relationship between CD4, HIV-RNA and different tropism in different districts was evaluated. Paired of plasma, PBMC and CSF virus, sampled from 10 HIV-infected people were analyzed. Six patients were naive for HAART, four were on treatment.
Results: the median age was 43, 8 of them were men, homosexual behaviour was the main risk factor (60%), the median value of HIV-RNA was 67.424 cp/mL and of CD4 was 316/mmc. R5-tropic virus predominated in both plasma (70%) and CSF (80%). Four of 10 people had concordant R5-coreceptor tropism in plasma, PBMC and CSF. Four people harbouring dual-tropic HIV in PBMC isolates, two of them had only R5-tropic virus in CSF and the other two had R5-tropic viruses in CSF and in plasma. Two of 10 people with R5-tropic virus in plasma and PBMC had X4-tropic viruses in CSF.
Discussion: the presence of X4 virus in CSF or in PBMC in patients with R5 virus in plasma can justify the virological failure of Maraviroc treatment and could correlate with higher risk to develop a neurologic disease. Many authors suggest that evolution of different coreceptor tropism in blood and CSF most likely reflects more efficient viral replication in abundant target CSF cells, such as macrophages and microglial cells. In conclusion the discordance of viral phenotype in plasma and CSF is frequent and needs to be considered in the context of emergent treatment with CCR5 antagonists.

PO 018

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AN EX-ADJUVANTIBUS TREATMENT IN A HIV+ PATIENT WITH NEUROLOGICAL LESIONS

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Introduction: The neurocognitive deficits in the immunocompromised population are often associated with opportunistic infections due to immunosuppression.
A neurological involvement may occur in this kind of population and the differential diagnosis should raise viral and not-viral agents or neoplasms.

We describe a case of neurological lesions associated with a wide wound of the head treated with *ex-adjuvantibus* chemotherapy in a HIV positive patient.
Case report: A 36-year-old man was admitted at our Division for fever and disturbance of consciousness. He discovered HIV infection in 2008 but stopped by himself antiretroviral treatment. So CD4 count was very low (6 cell/mmc) and plasmatic HIVRNA was equal to 29000 copies/ml. Before the appearance of the fever the patient referred a wide wound of the head not treated.
On the basis of clinical findings first of all it was necessary to exclude an encephalitis or an opportunistic infection. Cerebrospinal fluid examination not was possible to performed and serum analysis was negative for an active opportunistic agent. The patient underwent magnetic resonance (MR) imaging and MR images showed signal intensity abnormalities, with prominent involvement of the mesencephalic and diencephalic area, hyperintense lesions in the thalamic region and anterior frontal lobe. Brain MRI revealed abnormal T2 and FLAIR high intensities in the lateral ventricle.
Clinical signs and symptoms, laboratory data, MRI findings supported the hypothesis of a possible infection of the skin head related to the previous wound (*S. aureus*? *Nocardia spp*?) and so the patient was treated with ex-adjuvantibus chemotherapy associated with corticosteroids.
Progressively the clinical and neurological status improved.
Conclusions: Sometimes when neurological involvement is present in HIV population it is difficult to make a specific diagnosis and therapy is made on the basis of clinical findings. In our case clinical report was important to support an ethiological hypothesis and treatment *ex adjuvantibus* improved the neurological condition of our patient.

PO 019

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NEUROCOGNITIVE IMPAIREMENT IN HIV-INFECTED NAÏVE PATIENTS WITH ADVANCED DISEASE: THE ROLE OF GENETIC POLYMORPHISMS, VIRAL CHANGES AND INTRATHECAL IMMUNE ACTIVATION

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Background. HIV penetrates the central nervous system (CNS) early during primary infection, leading to HIV-associated neurocognitive disorders (HANDs), that are sustained by a double mechanism: the persistent HIV replication in CNS and HIV-related CNS immune activation. We correlated the change in CNS viral replication and intrathecal immune activation in naïve HIV-infected patients (pts) with advanced disease with or without HANDs after combination antiretroviral therapy (cART) introduction. Moreover, we sought for possible association between specific genetic polymorphisms of immune activation markers and increased risk of HANDs.
Methods. In naïve HIV pts with CD4<200/µl starting cART with ZDV/3TC and LPV/r, neurocognitive tests were performed. HIV RNA, pro-inflammatory cytokines (IL-6, IL-10, INF-γ, TNF-α, TGF-β1, TGF-β2) and chemokines (MIP-1α, MIP-1β, MCP-1) were measured on plasma and cerebrospinal fluid (CSF) samples at baseline (T0) and after 3 months (T3) by enzyme-linked immunosorbent assay.
Single nucleotide polymorphisms (SNPs) in genes of TNF-α (-308 G/A), TGF-β1 (+10 T/C and +25 C/G), IL-10 (-1082 A/G, -819 T/C and -592 A/C), IL-6 (-174 G/C) and INF-γ (+874 T/A) were assessed by SSP-PCR methodology.
Results. At T0 HANDs was diagnosed in 6/18 pts (5/6 with asymptomatic neurocognitive impairment, 1/6 with mild neurocognitive disorder). There were no significant differences in CSF HIV RNA levels between pts with normal and impaired tests at T0 (3.69 vs. 3.15 $\log_{10}$ copies/ml). Conversely, when cytokine and chemokine expression (measured on 8 pts) was compared between the two groups, higher median CSF IL-6 (2.3 vs. 0.55 pg/ml) was found in pts with HANDs. CSF and plasma HIV RNA levels decreased significantly in all of the pts over 3 months. However, a significant discrepancy in HIV RNA Δ levels in plasma and CSF was found in all of the pts between T0 and T3 (1.5 vs. 0.0 $\log_{10}$ copies/ml, respectively), indicating a slower HIV RNA decrease in CSF than in plasma. Despite the significant drop in HIV RNA in both compartments, we did not observe a significant change in cytokine and chemokine expression from T0 to T3.
In pts with HANDs there was a 12.5% higher frequency of IL-10-1082A allele, that is known to be associated with Alzheimer disease.
Conclusions. Different decrease rate of HIV RNA between plasmatic and liquoral compartment support the hypothesis of the compartmentalization of HIV replication in advanced disease. Impairment of neurocognitive function did not seem to be primarily associated with CSF HIV RNA levels. Conversely, we found an association between pro-inflammatory cytokines levels and the development of cognitive disorders. Moreover, albeit HIV RNA control in CSF, cytokine and chemokine CSF expression was not modified by cART. Both findings suggest a major role of pro-inflammatory cytokines in the pathogenesis of HANDs in advanced HIV pts, which in turn could be favoured by a specific genetic background.

PO 020

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NAC REDUCES APOPTOSIS AND TELOMERES SHORTENING SUBSEQUENT TO HIV-1 EXPOSURE IN AN ASTROCYTOMA CELL LINE

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Oxidative stress and the alteration of the homeostasis induced by HIV-1 infection, have shown to contribute in the mechanisms underlying apoptotic cell death occurring in AIDS-dementia complex. HIV-1 infected cells produce free radicals, involved in the apoptosis of astroglia and neurons. Recent data show that oxidative stress is responsible also of accelerates telomere shortening of human fibroblast in vitro. Our study was focused on the relationship between HIV-1/oxidative stress/astrocytic damage. U373 human astrocytoma cells were directly exposed to X4-using strain HIV-1IIIB, for several days and treated (where requested) with different doses of N-acetylcysteine (NAC), compound essential for the synthesis of glutathione (GSH), a cellular antioxidant. Apoptosis was analyzed by FACS analysis, and telomere length, by Quantitative-FISH (Q-FISH). Intracellular GSH and GSSG were determined by High-Performance Liquid Chromatography (HPLC). In the cellular samples in which we observed a reduction of telomere shortening TRAP assay was used to analyze the activity of telomerase. Statistical analysis performed using ANOVA

followed by Student-Newman-Keuls unless specified. Incubation of U373 with HIV-1IIIB led to significant induction of cellular apoptosis (1day: 17%; 3day: 32%; 5day: 70%; 10 day: 54%; 15 day: 76%). Apoptosis was reduced of 48% in the presence of 1mM NAC at day 5 after virus exposure ($p<0.001$). Moreover, NAC improved the reduced glutathione/oxidized glutathione ratio (GSH/GSSG), a sensitive indicator of oxidative stress, that decreased strongly after HIV-1IIIB exposure in U373. Analysis of telomere length showed, in HIV-1 exposed U373, a statistically significant telomere shortening (1day: 18%; 3day: 11%; 5day: 55%), that was completely resumed in U373 NAC-treated. At the same treatment time-points, TRAP assay not show a decrease of telomerase activity in HIV-exposed U373.
Our results support the role of HIV-1-mediated oxidative stress in astrocytic death, and the importance of antioxidant compounds in preventing these cellular damages. Moreover, indicate that the telomere structure, target for oxidative damage, could be the key sensor of cell apoptosis induced by oxidative stress after HIV infection.

PO 021

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RHODOCOCCUS EQUI INFECTION IN HIV INFECTED PATIENTS: CASE SERIES IN A REFERRAL HOSPITAL OVER THE LAST 18 YEARS

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Introduction: *Rhodococcus equi* (*R. equi*) is a Gram-positive, coryneform bacterium that sometimes affects humans presenting mostly as cavitary pneumonia. Immunocompromised patients are more susceptible to *R. equi* infection.[1] In 1986 the first case of lung abscess due to *R. equi* in a patient with acquired immune deficiency syndrome was described.[2]
Case series: We present ten cases of *R. equi* infection in HIV positive patients admitted to our Institute for Infectious Diseases from 1991 to June 2008; distribution by year is shown in the table. Seven were men; the mean age of the patients was 34.9 years (range 27 – 41). Risk factors for HIV infection included injecting drug use (6 patients), sexual transmission (3 patients), unknown risk (1 patient). Mean CD4+ lymphocytes count was 48 cells/cmm (median 37.5, range 1-117). CDC classification was C3 and B3 for 7 and 3 patients, respectively. No patients were on antiretroviral treatment. All patients complained with fever and cough; three had a weight loss, and one patient referred chest pain. The site of *R. equi* infection was the lung for 9 patients; the other one had a primary bloodstream infection. The radiological findings were focal consolidations, including lung cavitations in 6 patients, and bilateral pulmonary involvement in 4 patients. In 3 cases, pleural effusion was also evidenced. *R. equi* was isolated from blood culture, sputum, and both specimens in 8, 5, and 3 patients, respectively. All isolated strains were sensitive to aminoglycosides, fluorquinolones, macrolides, rifampin, and glycopeptides. Resistance to penicillin was evidenced for all strains; nine strains were resistant to piperacillin and oxacillin. All patients received combined antibiotic treatment for four weeks or more, with at least two drugs, including fluorquinolones, macrolides, carbapenems, and glycopeptides. Seven of ten patients recovered from *R. equi* infection. Three out of them experienced one or more relapses in a period of time between three and fifteen months after discharge. Among the 5 patients who received highly active antiretroviral therapy (HAART) at the time of diagnosis of *R. equi* infection, none experienced relapses of this disease. Three patients died. In two cases death was related to *R. equi* infection.
Conclusion: HIV patients account for approximately two-thirds of cases of R.equi in humans, with an higher mortality than non HIV infected patients (54,5% vs 20%).[3] In our case series, attributable mortality for *R. equi* infection was lower than that reported in the literature, likely due to the early instauration of HAART with an effective immune restoration.
Indeed, *R. equi* infection should be suspected in HIV infected patients with low CD4 cell counts in the presence of cavitary pneumonia. A prompt diagnosis, combined antimicrobial treatment and early initiation of antiretroviral treatment seem to be effective for the eradication of the infection and for avoiding relapses and improving the outcome.

Table: Patients' characteristics.

Pt	Age	Gender	Risk factor	CD4 (cells/mm^3)	Staging CDC	Primary site of Infection	Year of diagnosis	Outcome
1	38	F	SEX	30	C3	lung	1991	exitus
2	28	M	IDU	18	C3	lung	1993	relapses/ recovery
3	27	F	IDU	13	C3	lung	1996	exitus
4	33	M	IDU	1	C3	lung	1996	recovery
5	36	M	IDU	23	C3	lung	1996	relapses/ exitus
6	36	F	IDU	110	C3	lung	1999	recovery
7	38	M	IDU	117	B3	blood-stream	2000	recovery
8	41	M	N.A.	45	C3	lung	2001	recovery
9	41	M	SEX	53	B3	lung	2002	recovery
10	34	M	SEX	72	B3	lung	2005	recovery

Legend
Pt : patient IDU: intravenous drug user, SEX: sexual transmission, N.A.: not available, M: male, F: female

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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY MAY RELAPSE FOLLOWING YEARS OF REMISSION: REPORT OF THREE CASES

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Background: Progressive multifocal leukoencephalopathy (PML) is a deadly demyelinating disease caused by reactivation of JC virus (JCV), occurring in HIV-infected and other immunosuppressed patients. There is no specific treatment for PML and the only benefit is the reduction of immune suppression. In patient with HIV infection, highly active antiretroviral therapy (HAART) can halt disease progression in approximately half of the cases, with stabilization of clinical picture and magnetic resonance (MRI) lesions and clearance of JCV-DNA from cerebrospinal fluid (CSF), indicating a switch from active to inactive disease. We here describe three cases of PML relapse in patients with HIV infection receiving HAART.

Case report: We observed three cases of PML relapse out of 102 patients who developed PML between 1996 and 2008. They occurred in the 6% of 53 patients undergoing PML remission and followed-up for a median of 5 months (3-68(IQR)).Relapse occurred 1.5, 3 and 9 years after remission of the first event and was fatal in two patients. In all the three case remission was defined by stabilization of the clinical picture and inactivity of MRI lesions. In two cases JCV was cleared from CSF, whereas lumbar puncture was not performed in the third patient at the time of clinical stabilization. Diagnosis of PML relapse was confirmed by JCV DNA detection in CSF in two cases and was presumptive, based on typical clinical symptoms and MRI findings in the third case. Although all the three patients were on "chronic" HAART, the immunovirological context was different: one patient was on stable virological failure; the second patient experienced a partial immune reconstitution and HIV-RNA level (VL) decrease following treatment failure and switch to a new regimen; the third patient was on stable HAART with optimal immunovirological status (CD4 above 500 and suppressed VL). In one patient we sequenced the JCV non coding transcriptional control region (NCCR) from CSF samples obtained both at onset of the first episode and at relapse, which showed two distinct rearrangement profiles.
Conclusion: Given the relatively low frequency of PML, dual occurrence in the same patient seems to be not fortuitous. It is hypothesised that, in PML, "neuropathogenic" JCV variants are selected from sites of persistent benign infection with "non-neuropathogenic" virus. It is possible that, in relapse, non-neuropathogenic variants are reactivated in the presence of patient predisposition and favorable immunovirological conditions. Alternatively, neuropathogenic variants may have survived in sites of persistent infection following the first PML episode and been more readily reactivated at the time of relapse. In any event, reactivated virus must then evolve further into a new neuropathogenic variant, as observed in one of our patient. From a practical point of view, accurate clinical and MRI monitoring of PML survivors is essential to early recognize possible disease relapses.

PO 023

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RHODOCOCCUS EQUI PNEUMONIA AS MANIFESTATION OF COMBINATION ART (CART)-INDUCED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

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Introduction. Before the introduction of cART, *Rhodococcus equi* pneumonia was a rare opportunistic infection associated with high mortality. This complication has virtually disappeared in patients on cART. We here describe two cases of *R. equi* pneumonia, one of which associated with central nervous system (CNS) involvement, in association with cART-induced immune reconstitution.
Case 1. The first case is a 48-year-old woman who initiated cART in October 2001. After one month CD4+ cells were 118/µL and HIV-1 RNA (VL) 190 c/mL. Five months later (March 2002) the patient presented with fever and cough and a pulmonary nodule; *R. equi* was cultured from blood and expectorate. CD4 cells were 123/µL and VL undetectable. The patient received vancomicin, imipenem, ceftriaxone and cyprofloxacin for two months, followed by cyprofloxacin and chlaritromycin for four additional months, and several courses of oral prednisone as treatment of a thrombocytopenia. In May 2002 she had generalized seizures; brain MRI showed multiple contrast-enhancing white matter, vasculitis-like lesions and an extracranial abscess, diagnosed to be caused by *R. equi* and surgically removed. In January 2003 the patient was admitted for loss of consciousness; MRI showed two new nodular contrast-enhancing lesions sourronded by edema, with the previously described white matter lesions no longer enhancing. The nodular lesions worsened with anti-toxoplasmic therapy but improved with anti-rhodococcal therapy. At last follow-up (December 2008) CD4+ cells were 690/µl and VL undetectable; brain MRI showed resolution of the nodular lesions and persistence of leukoencephalopathy. The patient, however, is left with severe cognitive and motor impairment.
Case 2. The second case is a 45 year-old woman who started cART in December 2004. One month later CD4+ cells were 106/µl and VL undetectable. Two months later, the patient self-suspended cART. In May 2005 she presented with fever, cough and dyspnea; *R. equi* pneumonia was diagnosed based on the presence of pulmonary nodules and *R. equi* cultured from expectorate. The patient started rifampin, levofloxacin, azythromicin and cART. Six weeks later the lung nodule was enlarged with involvement of the scissural pleura. CD4+ cells were 60/µl and VL undetectable. Antibiotic therapy was continued until reduction of the pulmonary opacities and clinical remission. At follow-up, the patient took cART inconstantly, with CD4+ always below 200/µl. Nevertheless, she did not experience any other manifestation.
Conclusions. *R. equi* infection is an additional cause of IRIS. *R equi* pneumonia was disclosed by cART in the first case, and paradoxically worsened by cART in the second, although treatment, initiated five months earlier and subsequently discontinued might have played a role in disclosing the infection. While *R. equi* infection responded well to antibiotic treatment and cART, CNS involvement resulted in severe persistent neurological deficit.

PO 024

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IMMUNE-RECONSTITUTION SYNDROME RELATED TO ATYPICAL MYCOBACTERIAL INFECTION IN LATE-PRESENTING HIV PATIENTS

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Background: In the Western world, 10% to 30% of HIV-infected individuals are reported to present late for care. Day to months after the start of HAART, restoration of immunity resulted in immune-reconstitution inflammatory syndrome (IRIS), a paradoxical inflammatory response to preexisting or coexisting diseases. Signs of IRIS can include high fever, worsening respiratory status, increase in size and inflammation of involved lymph nodes or new lymphadenopathy, and radiologic worsening of pulmonary parenchymal infiltrations. This new clinical manifestation can resemble a worsening of clinical or laboratory parameters despite a good virologic and immunologic responses. We present two patients with AIDS and IRIS in association with atypical mycobacterium infection.
Case 1: A 43-year-old woman was admitted to our Clinic with a history of fever, non-productive cough, fatigue for 1 month. After three negative acid-fast bacilli (AFB) smears and PCR for M. tuberculosis, a contrast-enhanced chest and abdomen CT revealed hepatomegaly and two upper right lobe nodules (4 mm) and mediastinal and hilar lymphadenopathy. Laboratory tests revealed leukopenia and anemia. The HIV test was positive, CD4 count 26 cells/mm3 (6%), VL 125633 copies/ml. She was started on FTC, TDF and EFV. ETB, RFB and AZM were started 15 days later because the sputum and bone marrow culture were positive for Mycobacterium avium-intracellulare (MAI). Prednisone was started for the persistence of fever. She presented 12 weeks after initiation of ART with worsening of lung symptoms. A contrast-enhanced abdominal and chest CT revealed a large upper right lobe soft-tissue mass with other minor several nodular densities and enlargement of several lymph nodes. Multiple sputum cultures revealed persistence of MAI.

Case 2: A 55-year-old man was admitted with a history of fever, non-productive cough, sweating, nausea for 6 months. A contrast-enhanced abdominal and chest CT revealed several thoracic and abdominal lymph nodes. Laboratory tests revealed anemia. The HIV test was positive, CD4 count 71 cells/mm3(8%), VL 375512 copies/ml. He was started on ETB, RFB and CAM because the needle aspiration of the mediastinal lymph nodes revealed AFB. After 20 days he started FTC, TDF and EFV. For the persistence of fever he was initiated on prednisone and 8 weeks after initiation of ART he was admitted on hospital. A contrast-enhanced abdominal and chest CT revealed an lower right lobe nodule (15 mm) and enlargement of mediastinal lymph nodes (60 x 30 mm).
Conclusion: nearly 30% of patients with MAI developed IRIS upon ART start. MAI immune-reconstitution disease occurs mainly in late-presenting HIV patients within 8 to 12 weeks of ART initiation, after improvement of HIV parameters.

PO 025

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ANALYSIS OF THE JC VIRUS (JCV) NON CODING TRANSCRIPTIONAL CONTROL REGION (NCCR) IN PATIENTS WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) SUPPORTS INTRATHECAL VIRUS EVOLUTION

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Background. JC virus (JCV) causes progressive multifocal leukoencephalopathy (PML), a fatal demyelinating brain disease resulting from infection of oligodendrocytes. The JCV non coding transcriptional control region (NCCR) might play a role in neuropathogenesis, because it contains specific binding sites for cell proteins and also drives the transcription of JCV early genes. A NCCR "archetype" form is present in urine of healthy people, whereas "rearranged" sequences, characterized by multiple mutations, insertions and/or deletions, are found in the brain and cerebrospinal fluid (CSF) of patients with PML.
Objective. To investigate the type and dynamics of NCCR sequences in different body compartments and at different time points during PML, to gain information as for the route of JCV entry into the central nervous system (CNS) and its evolution during the disease.
Patients and Methods. The JCV NCCR region was amplified and directly sequenced from CSF, plasma and urine samples drawn from 29 PML patients, 21 of whom with HIV-related PML. Sequences were obtained from either paired samples (triplets or pairs of CSF, plasma and/or urine, n=16) or sequential samples (both or either CSF, plasma and/or urine, n=21). The NCCR region was amplified and directly sequenced.
Results: Highly rearranged NCCR sequences were present in all CSF and plasma samples, whereas sequences from paired urine were either archetype-like or only mildly rearranged. CSF and plasma paired sequences were nearly identical in 8/11 (73%) patients, whereas different rearrangement profiles were observed in 3 cases. The analysis of NCCR in 13 sequential CSF and 4 sequential plasma samples showed nearly identical rearrangement profiles in 5/5 cases with samples drawn <4 weeks apart, but substantially different rerrangement patterns in 10/12 taken >4 weeks apart. Of note, one of the remaining two patients maintained identical NCCR sequences over a period of 64 weeks, and both showed an abnormally prolonged, but progressive, course of disease.
Conclusions: PML was associated with NCCR rearrangements in CSF and plasma, but not in urine, indicating that the kidney is unlikely the site of selection of PML-associated rearrangements. These findings are consistent with the hypothesis by which rearranged virus is selected in peripheral sites, gains access to the CNS through the blood, and evolves further in the CNS.

PO 026

Infection 2009; 37 (Suppl. II): 59

THE SAFETY AND EFFICACY OF TENOFOVIR DF (TDF) IN COMBINATION WITH LAMIVUDINE (3TC) AND EFAVIRENZ (EFV) IN ANTIRETROVIRAL-NAÏVE PATIENTS THROUGH SEVEN YEARS

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Background: Study 903 is a Phase III trial with a 3 year, double-blind (DB) phase comparing TDF to d4T in combination with 3TC and EFV. In the study, TDF was associated with durable efficacy, better lipid profiles and less lipodystrophy. Study 903E is the ongoing open-label (OL) extension evaluating up to 10 year safety and efficacy of a once-daily TDF+3TC+EFV regimen.
Methods: All patients in Argentina, Brazil, and the Dominican Republic who completed the double-blind phase were eligible to roll over to Study 903E and receive a once-daily regimen of open-label TDF+3TC+EFV.
Results: 86 patients (62% male, 70% white, mean age 33 yrs) originally randomized to TDF continued treatment in the OL extension. At DB baseline (BL), mean HIV RNA=4.9 log10 c/mL and mean CD4 count=299 cells/mm3. At year 7, 81% (M=F) had HIV RNA <400 c/mL and 80% (M=F) had HIV RNA<50 c/mL; mean CD4 cell increase from BL=459 cells/mm3. One patient discontinued study due to adverse event (elevated amylase/lipase) and 4 due to virologic failure. No patient developed K65R mutation. No patient discontinued due to renal abnormalities or adverse events. No patient developed Fanconi syndrome. The median GFR, calculated both by the CG and MDRD equations, did not significantly change from baseline (CG: 116 mL/min at baseline vs. 120 mL/min at year 7; MDRD: 112 mL/min/1.73 m2 at both baseline and year 7) There was an overall mean decrease of 1.5% from baseline in BMD at the lumbar spine and 2.6% at the hip (both $P < 0.001$). Decreases from baseline in spine and hip BMD occurred during the first 24–48 weeks with little or no progression in BMD loss through year 7. No patient sustained pathologic fractures. Median limb fat was 6.7 kg at year 2 and increased to 8.0 kg at year 7.
Conclusions: Through 7 years of therapy, the once-daily regimen of TDF+3TC+EFV demonstrated sustained, durable antiretroviral efficacy with continued immunologic recovery in antiretroviral-naïve patients and was not associated with limb fat loss or progressive bone loss, nor was it associated with declines in estimated GFR.

PO 027

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HIGHLY ACTIVE ANTIRETROVIRAL TREATMENT (HAART) IN LATE PRESENTERS: THE EARLIER THE BETTER?

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Background: With the aim of understanding whether HAART should be started immediately or delayed in HIV late presenters (LP), we performed a multivariate analysis of factors associated with survival among LP observed in 7 infectious disease centers in the Liguria region (Italy) between January 2001 and December 2006.
Methods: Information about <18 years-old patients with a new diagnosis of HIV infection was prospectively collected. LP were defined as patients with a diagnosis of HIV infection within 3 months before the AIDS event. Follow-up was until last visit or death within 31 December 2007. The chi square test was used to assess differences in the frequency of categorical variables between LP and non-LP. Survival was estimated by the Kaplan Meier curves. In the LP group, a Cox model was applied to the data in order to evaluate the impact of baseline covariates on survival. Time to initiating treatment was included in the Cox analysis as a time dependent covariate.
Results: Out of 689 newly diagnosed patients there were 150 (18%) LP. There was a higher chance for LP to be males (74%; OR 1.35 95% CI 0.89-2.06), foreigners (32%; OR 1.61-95% CI 1.07-2.41), heterosexuals (55%; OR 0.91 95% CI 0.63-1.32) and older than 40 years (56%; OR 1.44 -95% CI 0.98-2.11). AIDS-defining conditions were *Pneumocistys jirovecii* pneumonia in 41 cases (37%), *Candida* or *Cryptococcus* infections in 22 (20%), mycobacterial infections in 21 (15%), tumors in 7 (5%), *Toxoplasma* encephalitis in 17 (13%) and other in 42 (32%). The overall survival rates at 12, 24 and 72 months were 85%, 80% and 75% respectively. With a mean follow-up of 34.8 months, multivariate analysis showed that factors significantly associated with survival were time to HAART (OR 0.251, 95% CI 0.10 to 0.62, p = 0.003), CD4+ count at baseline (OR 0.22, 95% CI 0.90 to 0.546 p=0.001), and age (OR 1.04, 95%CI 1.00 to 1.07 p= 0.034).
Conclusions: In our cohort, 20% of newly diagnosed patients presented with an AIDS-defining condition. Despite limitations due to the fact that these data were not stemming from a randomized clinical trial and that starting treatment was an event occurring after the baseline group allocation and therefore dependent upon clinical evolution, our data suggest that early HAART might be beneficial in LP.

PO 028

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EVALUATION OF LOPINAVIR/RITONAVIR VERSUS EFAVIRENZ- BASED ANTIRETROVIRAL REGIMENS: RESULTS FROM A RETROSPECTIVE LONGITUDINAL ANALYSIS OF 68 ADVANCED NAÏVE HIV INFECTED PATIENTS

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Introduction: The introduction of highly active antiretroviral therapy (HAART) in developed countries has achieved a good control of HIV infection. Despite this, a delayed HIV diagnosis makes it necessary to start antiretroviral treatment in individuals with severe impairment of their immunological function. The best antiretroviral regimen (ARV) and the best timing for starting ARV in patients with advanced infection have not been yet established. On the basis of existing efficacy data, NNRTI-based or PI-based HAART are strongly recommended as first therapeutic choice.
Little is known about the comparison of LPV/r or EFV containing regimen in patients with advanced HIV infection.
Objective: The primary objective of this study was to compare both virological and immunological response to ARV containing either efavirenz (EFV) or lopinavir/ritonavir (LPV/r) in patients with advanced HIV infection. The secondary objective was to evaluate the metabolic effects of different therapeutic regimes.
Methods: A retrospective longitudinal analysis of 68 HIV infected advanced naïve patients was conducted between 1998-2003. Virological and immunological response to the therapy were evaluated at 24-48 weeks with a total follow up of 5years.
Results: The study population consisted of 68 advanced HIV infected patients (31% F, 67% M; median age 40,5 years): 23 subjects were CDC C3. The sample was homogenous for age, gender and HIV-RNA.
HIV/HBV co-infection was found in 3 subjects; HIV/HCV co-infection was present in 6 subjects.
21 patients started ARV with EFV, 47 patients were on LPV/r containing regimens. The backbone was not considered. In the EFV group, median CD4 cell count was 112 cell/mmc (±13 DS), in LPV/r group it was 86 cells/mmc (±7 DS).
Considering LPV/r group,16% developed osteopenia and 4% had osteoporosis. 28% of the subjects developed lipid metabolism abnormalities and started lipid-lowering therapy, compared with only 2% in EFV group.
After 24 weeks of treatment, both EFV- and LPV/r treated subjects achieved undetectable viral load; the mean increase in CD4 cell count was 68 cells/mm^3 in the EFV group and 113 cells/mm^3 in the LPV/r group.
After 26 months, 30 individuals discontinued LPV/r due to gastrointestinal toxicity and abnormalities in lipid metabolism: 5 switched to ABC/3TC/AZT (trizivir), 20 to ATV/r and 5 to EFV.
Only 2 patients discontinued EFV after 32 months of therapy because of neuropsychiatric disorders and started therapy with trizivir and TDF.
After 5 years all patients were undetectable and showed a good immunological response.
Conclusion: Although at the enrollment the EFV group had an higher CD4 nadir, the achieved outcome was similar in both groups. The first regimen of therapy have to include drugs with high genetic barrier to permit simplification to EFV or other regimens.

PO 029

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SUBSTITUTIONS/DISCONTINUATIONS OF ANTIRETROVIRAL THERAPY IN A COHORT OF PATIENTS TREATED WITH TENOFOVIR-BASED FIRST HAART

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Introduction: Recent findings suggest that, despite the virological and immunological outcomes improved over time, the frequency of treatment change after initiation of antiretroviral therapy did not decrease over time. Thus, HAART durability remains essential to achieve long-term success in the management of HIV-infection. Over the past few years, several new drugs with improved efficacy, tolerability, and more-convenient administration in terms of the number of pills, frequency of intake, and diet restrictions have become available. In light of these improvements, we aimed this study to evaluate rates and reasons for antiretroviral therapy substitution/discontinuation of initial cART regimens TDF-based.
Methods: This analysis was carried out using the GNOMO (Genotypic Networking organization Multicentric Observation) Cohort database, and included all patients who received first-line TDF-based HAART. Primary end-point was substitution or discontinuation of at least one ARV component of the regimen. Kaplan-Meier survival analyses of regimen durability were performed. Cox proportional hazard models evaluated the role of regimen composition as predictor of regimen durability.
Results: From 2003 to 2008, 637 patients started TDF-based HAART (53% NNRTI, 40% PI/b, 4% single-PI) and contributed with 927 person-years. A total of 270 (42.4%) patients substituted/discontinued at least one ARV component for the following reasons: simplification 22.9%, virological failure 8%, CNS side-effects 7.8%, gastrointestinal toxicity 7.4%, rash 6.3%, patient's choice 6.3%, renal toxicity 1.1%. Overall 1-year probability of ARV substitution/discontinuation was 24.8% (95%CI 21.5-28.6) with a median time to event of 10.6 months (IQR, 6.9-25.8). Considering specific reasons for ARV substitution/discontinuation median months to event occurrence were 7.8 for toxicity, 10.7 for virological failure, 12.9 for patient's decision, 20.7 for simplification. Using EFV+TDF-based regimens as reference, LPV/r+TDF (HR 1.42; 95%CI 1.06-1.94), and NVP+TDF-containing HAART (HR 2.29; 95% CI 1.06-4.97) showed an increased risk of study event. ATV/RTV+TDF-based regimens had a lower, although not significant, risk (HR 0.70; 95%CI 0.30-1.61). Neither sociodemographic- nor disease-related variables impacted treatment durability. Use of didanosine+TDF was associated with a significantly higher risk of ARV discontinuation/substitution (HR 3.05; 95%CI 3.05-0.77).
Conclusions: In recent years among first-line TDF-containing HAART, substitution or discontinuation of at least one ARV component is a relatively common event and principally due to simplification strategy. TDF-based regimens with more convenient dosing frequency performed better in terms of treatment durability.

PO 030

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LONG-TERM TOLERABILITY, SAFETY AND EFFICACY OF NNRTI-BASED THERAPY REGIMENS IN NAIVE PATIENTS WITH HIV INFECTION

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Background: Large randomized, controlled trials and cohort studies of treatment-naïve patients have demonstrated potent viral suppression in efavirenz (EFV) or nevirapine (NVP)-treated patients. EFV-based regimens also had comparable activities to NVP and atazanavir-based regimens. Objective of this study was to compare NVP- and EFV-based regimens in term of viro-immunological response, tolerability, efficacy and safety in chronic HIV-infected patients HAART-naïve.
Methods: A prospective observational cohort study was conducted on antiretroviral-naïve HIV-infected patients.
Demographic, viro-immunological and biochemical data were collected at baseline and every 3 months. Statistical analysis was performed using SPSS software for Windows 13.0. A descriptive analysis of virological, immunological and biochemical measurements at baseline were performed using non parametric tests. A survival analysis using Kaplan –Meier was performed to estimate the probability of virological success (HIV-RNA < 50 cp/mL) after receiving EFV or NVP-treatment.
Results: Two hundred and six HIV-infected patients starting a NNRTIs-based regimen were consecutively enrolled from January 2000 to December 2007. Of them, the 68% (140) was on EFV, the 32% (66) on NVP.
At baseline, no differences between groups were found in age, sex, CDC stage, CD4 cells count at nadir, HCV or HBV co-infection mean CD4 cells count (357 vs 284/mmc in NVP and EFV group respectively, p= 0.1), mean viral load (4.8 vs 5.1 log cp/mL in NVP and EFV group respectively, p= 0.2). The mean duration of HIV-infection was longer in patients on NVP than those on EFV (9.6 vs 4.6 ys, p=0.01).
At day 30, CD4 cells count was similar in both groups. Conversely, 90% of patients in NVP-group had HIV-RNA still >50 cp/mL vs 75% in EFV-group. At day 60, HIV-RNA was ≤50 cp/mL in 85% of patients in EFV-group vs 60% in NVP-group. None of patients had a liver toxicity grade 2 or higher.
At day 100 on treatment, the proportion of patients with HIV-RNA≤50 cp/mL was similar in both groups (94% vs 88% in EFV and NVP group respectively, p=0.056).
After a follow-up period of 3 years, the mean CD4 cells count increase was 194 cells/mmc in NVP group and 272cells/mmc in EFV group (p=0.5). None patients discontinued HAART because of central nervous system or hepatic toxicities. No significant increase in total cholesterol and triglycerides levels was documented in the 2 groups.
Conclusions: EFV-based regimens demonstrated a better profile than NVP in term of rapid viral clearance in treatment-naïve patients. After 3 months on treatment, NVP and EFV show a similar profile in term of virological and immunological potency. No difference were found in term of toxicities between the 2 NNRTI-based regimens in the short and long-term. Further studies were necessary to evaluate the possible use of NVP in simplification regimens rather than in treatment-naïve patients.

PO 031

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THE 48-WEEK EFFICACY AND SAFETY OF SWITCHING TO FIXED-DOSE EFAVIRENZ/EMTRICITABINE/ TENOFOVIR DF IN HIV-1-INFECTED PATIENTS RECEIVING HAART

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Background: Study 934 is a 144-week randomized, multicentre, open-label trial comparing the safety and efficacy of emtricitabine/tenofovir DF (TVD) versus lamivudine/zidovudine (CBV) both in combination with efavirenz (EFV) in treatment-naïve patients (pts).
Methods: After completing 144 weeks, patients in both arms were given the option to switch CBV+EFV or TVD+EFV to the fixed-dose combination EFV/emtricitabine/tenofovir DF (ATR) once daily taken on an empty stomach, preferably at bedtime.
Results: 286 pts (160 switched from TVD; 126 from CBV) rolled over into the extension (12% female, 65% white, mean age 40 yrs, mean CD4 535 cells/mm^3) and received ATR. At time of switch, 94% in TVD arm and 97% in CBV arm had HIV RNA<50 copies/mL. 12 pts discontinued study prior 48 week (post-switch): 1 pt died from cardiac arrest due to cardiac dysfunction assessed as unrelated to study drug; 1 pt experienced virologic failure; 2 pts discontinued due to AEs (MAI, anal CA); 8 pts discontinued for other reasons. No pt experienced renal AEs.

Results	TVD+EFV to ATR	CBV+EFV to ATR
HIV RNA <50 at Wk 48 post-switch (M=F, M=E)	94%, 96%	90%, 96%
Est. GFRa by CG (mL/min)	115, -2	120, -10
Est. GFRa by MDRD (mL/min/1.73 m^2)	98, -1	106, -9
Fasting Total Cholesterola (mg/dL)	189, +6	199, -9
Fasting LDL-Ca (mg/dL)	114, 0	118, -6
Fasting Triglyceridesa (mg/dL)	120, -3	128, -21
Median Total Limb Fat (kg) at time of switch & at Wk 48	8.0, 8.1	5.5, 5.7

[a]median at time of switch, median change at Wk 48

Conclusions: Switching TVD or CBV + EFV to a single tablet once-daily regimen of efavirenz/ emtricitabine/tenofovir DF was well-tolerated and resulted in maintenance of virologic suppression through 48 wks. Renal function remained stable through 48 weeks post-switch. Decreases in fasting triglycerides and fasting cholesterol were seen 48 weeks after switching from CBV+EFV to ATR. In pts on CBV+EFV for 3 years, switching to ATR did not significantly improve limb fat after 48 wks.

PO 032

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PATIENT REPORTED OUTCOMES AFTER SIMPLIFICATION TO A SINGLE TABLET REGIMEN OF EFAVIRENZ (EFV)/ EMTRICITABINE (FTC)/TENOFOVIR DF (TDF)

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Objective: To assess patient (pt) reported outcomes in AI266073, a 48-week, prospective, randomized, open-label, multi-center study.
Methods: Pts on stable antiretroviral therapy (ART) with HIV-1 RNA <200 c/mL for ≥ 3 months were randomized (2:1) to EFV/FTC/TDF (single tablet regimen) or to remain on their baseline regimen (SBR) and were stratified by prior PI- or NNRTI-based therapy. In addition to efficacy/safety, the following were collected from both study arms: adherence by visual analog scale, quality of life by SF-36(v2) survey, a 20-item self-reported HIV Symptoms Index, and the Perceived Ease of the Regimen for Condition questionnaire. In the EFV/FTC/TDF arm only, a protocol specific single-item Preference of Medication (POM) questionnaire was collected.
Results: 300 treated pts (EFV/FTC/TDF 203, SBR 97) were evaluated (prior PI/NNRTI 53%/47%); Through 48 weeks, 89% vs. 88% in the EFV/FTC/TDF vs. SBR arms, respectively, maintained HIV-1 RNA <200 c/mL by TLOVR (ITT; NC=F). Adherence in both arms at baseline and all visits was ≥ 96%. Baseline SF-36 scores were similar to the general non-HIV infected population. There were no marked changes in adherence and SF-36 scores for either arm during the study. HIV Symptoms Index results demonstrated improvements in the proportion of pts randomized to EFV/FTC/TDF who experienced diarrhea or loose bowel movements (prior PI stratum: 52% at baseline; 32% at Week 48 [p = 0.002]); bloating, pain, or gas in the stomach (p=0.002); changes in the way their body looked (p=0.002); and problems having sex (p=0.032). There was a transient worsening of dizziness or lightheadedness symptoms (observed at Week 4 only) in pts switched to EFV/FTC/TDF (p <0.02), primarily in pts who switched from a PI-based regimen. Significantly more pts who received EFV/FTC/TDF considered it an easier regimen to take than their previous regimen (p < 0.001) at all study visits. By POM, pts randomized to EFV/FTC/TDF preferred this treatment over their previous regimen (p <0.001) at all post-baseline visits; 85% reported at Week 48 that EFV/FTC/TDF was "much better" than their previous regimen.
Conclusion: Simplification to EFV/FTC/TDF from a variety of ART maintained high levels of virologic suppression, adherence and quality of life through 48 weeks. Pts switched to EFV/FTC/TDF reported improvements in many HIV-related symptoms, found the new regimen easier to follow and preferred EFV/FTC/TDF over their previous ART regimen. Among patients randomized to EFV/FTC/TDF 91% indicated a preference for the single tablet regimen compared to prior therapy, and 97% found RFV/FTC/TDF easy to take.

PO 033

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SIMPLIFICATION OF THERAPY (ART) WITH EFAVIRENZ/ EMTRICITABINE/TENOFOVIR DF SINGLE TABLET REGIMEN VS. CONTINUED ART IN SUPPRESSED, HIV-INFECTED PATIENTS

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Background: AI266073 is a 48 week, randomized, open-label, multicenter study with the primary objective of evaluating non-inferiority of simplification of ART to efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF) vs. continuation of the same baseline regimen (SBR) unmodified.
Methods: Patients on stable ART with HIV-RNA (VL) <200 copies/mL for ≥3 months were stratified by NNRTI- or PI-based ART, and randomized (2:1) to switch to EFV/FTC/TDF or continue SBR. The primary endpoint was maintenance of VL <200 copies/mL at 48 weeks by time to loss of virologic response algorithm (TLOVR) (intent-to-treat, missing = failure [ITT, M=F], Δ=15%); efficacy was also assessed by VL <50 copies/mL (TLOVR; ITT, M=F), pure virologic response (non-responders defined as 2 consecutive VL ≥50 copies/mL or one VL ≥50 copies/mL followed by study discontinuation; PVR - by Kaplan Meier); and by last observation carried forward (LOCF) analysis where early discontinuations for an adverse event (AE) were considered failures.
Results: 300 treated patients (EFV/FTC/TDF 203, SBR 97) were evaluated (prior PI/NNRTI 53%/47%). Treatment arms were well balanced: 88% males, 29% blacks, mean age 43 years, median baseline CD4 516 cells/mm^3, 96% had VL <50 copies/mL.

VL Endpoint (copies/mL)	EFV/FTC/ TDF	SBR	Difference EFV/FTC/ TDF – SBR (95% CI)
<200 by TLOVR	89%	88%	1.1% (-6.7%, 8.8%)
<50 by TLOVR	87%	85%	2.6% (-5.9%, 11.1%)
<50 by PVR	95%	86%	8.9% (-7.7%, 25.6%)
<50 by LOCF	94%	97%	-3.3% (-8.3%, 2.7%)

At 48 weeks, EFV/FTC/TDF was found to be non-inferior to SBR. Similar virologic responses were also observed between arms when analyzed by PI and NNRTI strata and prior or no prior use of TDF. Overall discontinuation rates for EFV/FTC/TDF vs. SBR were 11% vs. 12% (AE 5% vs. 1%; withdrawal of consent 2% vs. 7%). In the EFV/FTC/TDF arm, 1 patient discontinued for virologic failure. Overall, more nervous system symptoms (NSS) were reported for EFV/FTC/TDF vs. SBR (dizziness 11% vs. 1%, abnormal dreams 7% vs. 0%); these occurred early, were generally transient, mild, and more common with prior PI-based ART. At 48 weeks, estimated GFR (MDRD) was unchanged from baseline in both arms (median <1 mL/min/1.73m^2; p=0.870); a greater decline in fasting triglycerides was observed at 48 weeks with EFV/FTC/TDF vs. SBR (median -20 vs. -3 mg/dL; p=.035) which was more pronounced in prior PI patients.
Conclusions: High and comparable rates of virologic suppression were maintained with EFV/FTC/TDF vs. SBR, regardless of type of prior ART. Simplification to EFV/FTC/TDF was well tolerated with low rates of discontinuations observed in both treatment arms. Renal function remained stable through 48 weeks, including patients maive to TDF at baseline. The grade and frequency of AEs reported for patients that switched to EFV/FTC/TDF was consistent with previous studies.

PO 034

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ISS-NIA ITALIAN COHORT: NEW ANTI-HIV INHIBITORS IN PATIENTS EXPERIENCED TO IP, NRTI, NNRTI

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Background: Management of HIV infection can now rely on new classes of antiretroviral drugs (CCR5 antagonists, integrase inhibitors, fusion inhibitors) which represent innovative options compared to the three main drug classes targeting HIV protease or reverse transcriptase (PI, NRTI, NNRTI).
Although there is evidence that these new antiretroviral drugs can be effective and relatively safe in patients resistant to the other anti-HIV drugs who have limited treatment options, available data have only been collected for a short period of time and within controlled trials. Thus, collecting long-term safety and efficacy information as well as patient-reported outcomes in a setting of clinical practice is a necessary step to better define the profile of these drugs.
Objectives: The rationale for this study is based on the necessity to follow over a long period of time the effects of first-use of new drug-classes in HIV infected people, exploring from a multidimensional point of view the profile of these drugs. In order to follow this objective, clinical, immunological and virological parameters, along with patients-reported outcomes and pharmacoeconomic data, will be collected, and pharmacokinetic analyses conducted.
Design: ISS-NIA is an Italian open cohort of HIV-infected patients with triple-class (PI, NRTI, NNRTI) experience, starting a new-class based regimen (CCR5 antagonists, Integrase inhibitors, Fusion inihibitors). Outcome measures of the study include survival, virological and immunological response, adverse events, resistance, health-related quality of life measures, cost-efficacy, and pharmacokinetics.
Results: As of March 3, 2009, 140 patients were enrolled (male: 72.9%, sexual transmission: 70.7%, HBV+: 9.3%, HCV+: 30%, median age: 46) . Most of them had symptomatic HIV disease (CDC group B 34.3%, group C 42.9%). Patients had a very long past history of antiretroviral treatment (median: 12.0 years) and of HAART (10 median years), with most of them (77%) carrying multiresistant (NRTI, NNRTI and IP) HIV when starting the new drugs. Raltegravir was used in 89% of the cases, alone (60.7%) or associated to enfuvirtide (13.6%), maraviroc (11.4%) or both (3.6%). Maraviroc was used less commonly (overall: 24.3%), mostly in combination with raltegravir and/or enfuvirtide (15.0%). Among the other drugs, the most commonly used were darunavir (59%), tenofovir (46%), emtricitabine (40%), lamivudine (30%) and etravirine (20%). Use of enfuvirtide was relatively uncommon (16%). Only in 13% of cases the new inhibitor was the only active drug in the regimen. Preliminary follow up

data at three months indicate a median increase of about 70 CD4 cells/mm^3, accompanied by a 2.5 log median decrease in HIV-RNA (<50 copies: 75%).
Future perspectives: ISS-NIA cohort represents an opportunity to evaluate for a long period the real impact of the new drugs on several aspects of HIV+ people's life. Enrollment is open to new patients and new centres wishing to join this cohort.

PO 035

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EVALUATION OF SAFETY, EFFICACY AND ADHERENCE OF ATRIPLA TREATMENT IN 74 PATIENTS SWITCHING FROM TRUVADA AND SUSTIVA THERAPY

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74 out-patients, afferent to our department and previously treated with Truvada and Sustiva, switched to Atripla. For 30 patients Truvada and Sustiva was first-line therapy (Group I), 31 patients had previously assumed 1 PI (Group II), 13 patients, at switch, were multi-experienced (≥ 2 PI) (Group III). After switching to Atripla the median of follow-up was 5 months (range 3-9). All patients, included in the study, had HIV-RNA undetectable at baseline (<50 UI/ml). Before and after Atripla-switch, CD4, HIV-RNA, total cholesterol, triglycerides, AST e ALT were evaluated. To check adherence to Atripla therapy a questionnaire was administered before and after switch.

Table 1

	Group I baseline	**Group I atripla**	**Group II baseline**	**Group II atripla**	**Group III baseline**	**Group III** atripla
Got median (IQR 25,75)	30 (16,62)	29 (24,41)	26 (21,31)	28 (23,37)	26 (24,53)	27 (23,37)
Gpt median (IQR 25,75)	36 (25,75))	31 (21,46)	26 (18,42)	37 (23,48)	25 (20,34	29 (21,43)
Col. totale median (IQR25,75)	196 (127,214)	182 (161,228)	177 (154,227)	195 (170,230)	189 (175,222)	214 (170,234)
Triglyc. median (IQR 25,75)	91 (60,124)	120 (67,189)	140 (90,207)	135 (92,196)	143 (109,289	207 (89,280)
CD4 cell/mm^3 median (IQR 25,75)	618 (505,858)	723 (562,917)	540 (402,758)	658 (502,966)	558 (396,728)	592 (492,669)

Results and conclusions: None of the patients discontinued Atripla therapy. All patients maintained virological suppression. We did not found statistically significant differences among values of transaminases, total cholesterol, tryglicerides before and after Atripla switch. Renal function maintained stable after switch. CD4 cells increased in all groups, but this increase was not statistically significant. Adverse events were mainly related to Efavirenz both before switching (10%) and after switching to Atripla (12%). Adherence at baseline was high and maintained high in all groups.
All patients indicated a preference for the single tablet regimen with respect to prior therapy, with a higher percentage (94%) of patients from Group II and III compared to Group I (82%).

PO 036

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HIV TROPISM AND USE OF MARAVIROC IN CLINICAL PRACTICE

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The CCR5 antagonists are a new class of antiretroviral drugs used for the treatment of patients with infected with R5-tropic virus. Data from clinical trials showed the potent virologic and immunologic activity of Maraviroc, the only approved CCR5 antagonist. Because of the unique mechanism of action of maraviroc, a coreceptor tropism assay for CCR5 tropic virus is necessary not only at screening, but also for monitoring during treatment. In our center 29 viremic experienced patients were screened by Trofile assay (Monogram Biosciences, South San Francisco, California, USA). We collected data concerning HIV-RNA load and number of T CD4+ lymphocytes at the day of the test, T CD4+ nadir level; ARV therapy, CDC stage, adherence and HIV tropism. Mean HIV-RNA level was 168,183 copies/ml. Mean T CD4+ lymphocytes count was 262 cells/mm^3. Mean T CD4+ nadir was 121 cells/mm^3. R5 virus were present in the 42% of patients; D/M virus were found in 29% of patients and X4-positive samples were 4%. 25% of the patients did not received a tropism result because of low viral load or technical problems. The median CD4 count in R5 positive patients were 357 cells/mmc (146-619) and were signficantly higher than D/M positive patients (18 cells/mmc; 8-219) (p=0.003). No differences were found in term of viral load (p=0.6). 30% of patients infected with R5 viruses received maraviroc treatment. The time between testing HIV tropism and starting of maraviroc treatment was about 2 months. Our data from a single HIV care center underline the need to develop easier and more rapid determination of HIV tropism in order to facilitate a more appropriate use in clinical practice of CCR5 antagonists. The identification and development of genotypic tests which assess both drug resistance and HIV tropism should be strongly encouraged.

PO 037

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EARLY ACCESS TO DARUNAVIR ASSOCIATED WITH RITONAVIR IN HIV+, HEAVILY PRE-TREATED PATIENTS, WITH LIMITED THERAPEUTIC OPTIONS. FINAL RESULTS OF THE ITALIAN CENTRES TAKING PART IN THE INTERNATIONAL TMC114-C226 (TIGRE) STUDY

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Objective: To assess the efficacy and safety of darunavir/ritonavir (600/100mg b.i.d. oral) in adult, HIV+patients previously treated with ≥2 different protease inhibitor regimens, with limited therapeutic options.
Materials and methods: International early access program (79 Italian centres).
349 patients who reached week 48 at study closure (24July2007).
Assessments: efficacy: virologic and immunologic response; safety: adverse events.
Results: 22.5%women, age 44.8±7.9 years (mean ±DS), CDC class C=43.5%, viral load 4.4±1.0 Log10 copies/ml, CD4 197±163cell/µl. Infection duration 14.9±4.4 years. Previous antiretrovirals: median 4 (range 2-21). Most used concomitant treatments: NNRTI+FI 43.2%, NRTI 38.3%.
Virologic response week 24 N=633; week 48 N=349.

Virologic	Overall	initial HIV load <100.000 cp/ml	initial HIV load response >100.000 cp/ml
Complete (VL<50cp/ml)			
Week 24	62.0%	67.3%	47.0%
Week 48	61.3%	66.7%	45.5%
Relapse			
Week 24	10.0%	11.7%	4.9%
Week 48	16.9%	18.0%	13.6%
No response			
Week 24	28.0%	21.0%	48.1%
Week 48	21.8%	15.3%	40.9%

Virological response: Median time to virologic suppression (HIV-1 RNA <50copies/ml): 105days.
During first 12 weeks of treatment baseline viral load is the most important predictive factor for virological response(HR 0.51). BL CD4 coun t shows predictivity on virologic response only starting from week 12 (HR 2.37) because of the strong effect of viral load which overlook other factors.
Immunological response: Mean±SD CD4+ increase: week 24 +88±106cell/ml, week 48 +118±127 cell/ml.
Safety: 657adverse events (100 adverse reactions) were reported in 32.3%patients.
Thirty-six (4.8%) patients discontinued treatment because of AEs. Nineteen events only (observed on 15 patients) were judged at least possibly related to treatment by physicians: liver enzymes increased(4), nausea(2), vomiting(1), diarrhea(3), abdominal distension(1), rash(2), dermatitis(1), extrasystoles(1), tachycardia(1), dizziness(1), fatigue(1), fat redistribution(1).
Eleven patients died for reasons not related to study treatment (3 of them for HIV disease progression).
The most common ADRs were: hypertriglyceridemia (17, severe 7), diarrhea (10, severe 1).
Conclusions: Darunavir/ritonavir efficacy in HIV+ patients with limited therapeutic options at W48 is strongly related with BL viral load until week 12; after this timepoint BL CD4 count arise as other predictive factor of virologic response. Overall, 61.3% patients achieved undetectable VL at W48 (66.7% of patients with BL VL <100.000 cp/ml). Virologic response has been mantained over 48 weeks (62.0% at W24).
Thirty-six patients discontinued treatment because of AEs: only nineteen events (observed on 15 patients) were judged at least possibly related to Darunavir/ritonavir.

PO 038

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ANTIRETROVIRAL ACTIVITY OF RALTEGRAVIR IN EXPERIENCED PATIENTS

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Background: Raltegravir is the first HIV-1 integrase inhibitor approved by the US Food and Drug Administration for use in antiretroviral treatment of experienced patients.
Methods: In this study we evaluated the antiretroviral activity of raltegravir in combination with optimised background therapy in a cohort of 52 failed antiretroviral patients enrolled in four clinical centres in Genoa, Liguria, Italy. In failing patients we performed a sequencing assay for detection of integrase inhibitor resistance by using the TruGene sequencing system.
Results: Among the 33/52 (63.5%) patients enrolled, 14/52 (26.9%) and 5/52 (9.6%) had triple, double or single class drug resistance respectively. Forty-eight/52 (92.3%) and 27/52 (51.9%) reached 3 or 6 months of treatment respectively. The mean HIV-1 RNA level shifted from 4.8 log 10 cp/ml at baseline to 3.6 at month 3 and 4.4 at month 6. Suppression of HIV-RNA to a level below 50 cp/ml was achieved in 38/48 (79.2%), and in 20/27 (74%) patients at month 3 and 6 respectively. The mean CD4+ cells increased from 265 cells/mmc at baseline to 320 at month 3 and 300 at month 6. In all the patients with undetectable virus at month 6, it had been undetectable also at month 3. Conversely all failing patients at month 6 had failed also at month 3.
Integrase gene sequencing in virological patients failure showed the presence of pathways Q148H and N155H with additional mutations in 2/7 and in 3/7 respectively; in 2/7 any integrase resistance associated mutation was found.

Conclusions: In patients, with limited therapeutic options, such as those included in our study, raltegravir in combination with optimised background showed a considerable antiretroviral activity. Typical genetic pathways of raltegravir resistance mutations were found in failing patients.

PO 039

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EDUCATIONAL AUDIOVISUAL AIDS TO SUPPORT THE DELIVERY OF INFORMATION REGARDING HAART ADHERENCE: THE SUPPORT HIV STUDY

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Background: The use of audiovisual aids as means to address information lack is a relatively new notion, although a substantial body of literature supports the efficacy of video in influencing patient knowledge and attitudes. Regarding adherence to antiretrovirals (ARVs), modest disease knowledge among HIV-infected patients, impossibility of symptom-guided drug intake, and high complexity of treatment-adherence-resistance relationship underscore the need for materials that effectively convey complicated information. Partial, unclear and insufficient knowledge is frequently the reason for patients not to engage in efficient health behaviors.
Objective: Aim of this part of the SupportHIV study was to develop audiovisual aids intended to promote better awareness of the importance of maintaining adherence to ARV regimens among HIV-infected persons.
Methods: To identify potential barriers to adherence and potentially effective strategies to promote correct medication intake, a focus group with HIV-specialists and HIV-infected patients was held. The participants agreed on developing a video for the patient and a set of illustrated cards for the physician in order to explain the fundamentals regarding HAART, adherence, and HIV resistance. For the video a draft script was produced by the study authors in conjunction with an experienced screenwriter and for the cards a professional graphic designer was hired.
Results: In the 10-minutes video, technical and scientific information are explained by a narrator who guides the auditor in a friendly emotional manner. Basic drug-taking concepts and practical advice on how to improve adherence are presented by showing every-day life situations. A composer created a rap music expressly for the adherence video by using specifically agreed wordings.
The set of illustrated cards included 10 double-face images and was structured as follows: three cards address general information on HIV infection; three cards focus on HAART; three cards deal with adherence-resistance relationship. The last card summarizes "10 good tips" for HAART adherence. Each card opens with a prompt and direct question, that synthesizes possible worries of the patient. Answers to the questions emerge essentially through graphical illustrations, which give straight visual information. On the rear of each card a picture tries to show the inner feelings which might accompany the question on the card.
Conclusions: Effective physician-patient communication and patient empowerment are key elements to enhance health motivation and improve self-efficacy among HIV-infected persons. Specific patient populations, such as recently HIV-diagnosed, HAART non-adherent, illiterates, and immigrants, might benefit more clearly from this educational audiovisual aids. The "next step" in the evaluation of the materials is a randomized clinical trial comparing antiretroviral adherence among self-reported non-adherent patients who are given or not given the tools.

PO 040

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EVALUATION OF CCR5 EXPRESSION BY FLOW CYTOMETRY IN PATIENTS WHO UNDERWENT TREATMENT WITH OPTIMAL BACKGROUND THERAPY (OBT) PLUS THE CCR5 INHIBITOR MARAVIROC (MVC)

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CCR5 inhibitors have recently joined the therapeutic armamentarium against HIV-1 and are currently the only class of antiretroviral drugs that target a cellular molecule. CCR5 is indeed the major co-receptor for entry of HIV-1 in CD4+ T lymphocytes and monocytes/macrophages. Nevertheless, it should be underlined that expression of CCR5 is not restricted to the latter cells, because CCR5 is present also on the surface of CD8+ T lymphocytes, as well as on peripheral γ, δ T lymphocytes. Although clinical trials evaluating safety/efficacy of three different small-molecule CCR5 inhibitors (aplaviroc, maraviroc and vicriviroc) have taken place in the past years, at present only MVC, orally bioavailable, has been approved by the american and european regulatory agencies.
We sought to investigate expression of CCR5 by means of flow cytometry and three different monoclonal antibodies (mAb) against human CCR5: 2D7 is known to recognize domain A of the extracellular loop 2 (ECL2) of CCR5, 45531 binds domain B of ECL2 and 45502 is claimed to bind the N-terminal domain of CCR5. Frozen samples of peripheral blood mononuclear cells (PBMC) from five experienced individuals who added MVC to their OBT were used in this *ex vivo* study. Two time points were evaluated: prior to initiation of MVC (T0) and after approximately 4-6 months of treatment (T1).
In four out of five individuals an increase (about 4%) of the percentage of CD4+ lymphocytes was documented in T1 as compared to T0. The percentage of CD4+CCR5+ lymphocytes was <2% in all patients and did not change substantially. This subpopulation, poorly represented in peripheral blood, is particularly enriched in mucosal gut. Expression of total CCR5+ lymphocytes was consistently higher when staining was carried out with 2D7 as compared to the other two mAbs. Decrease of CCR5 expression as determined by 2D7 staining was observed in three out of five patients in T1 as compared to T0, and was particularly pronounced in one subject. Of note, the latter was the only one in which an increase of the percentage of CD4 did not occur.
MVC is believed to be devoid of agonist activity, thus it should not induce intracellular signalling or CCR5 internalization, although very limited *ex vivo* data exist. Due to the limited number of sequential samples and subjects evaluated it is difficult to ascertain whether the observed inhibition of CCR5 expression in total lymphocytes of 3/5 subjects could be directly linked to the prolonged *in vivo* use of MVC. Patients undegoing placebo treatment would be precious to include in this study. It should be stressed that MVC *in vivo* will certainly encounter many CCR5+ cells which are not the targets of HIV-1 entry, especially in peripheral blood where CD8+ and γ, δ lymphocytes are numerically well represented. Thus, the antiviral effect of MVC, as inhibitor of HIV-1 entry in appropriate CD4+ target cells, can be blunted by its binding to CD4 negative CCR5+ cells.

PO 041

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USE OF PI UNBOOSTED IN ANTIRETROVIRAL TREATMENT

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Introduction: In 2009, it is possible to use many drug combinations against HIV.infection. The last edition of Guidelines of Antiretroviral Agents in HIV-1 infected adults and adolescents consider use of PI boosted with ritonavir or use of efavirenz as preferred regimen for HIV treatment, particularly in PI-experienced patients. However, these guidelines consider use of atazanavir or fosamprenavir unboosted like alternative therapy.
Material and methods: In our Infectious Diseases Unit, we observe 430 patients with HIV-infection. 386 of these patients are on antiretroviral treatment. We analyzed 39 patients on treatment with PI unboosted for six months or over, 22 with atazanavir 400 mg/die unboosted and 17 with fosamprenavir 1400 mg twice daily unboosted. These patients aren't on treatment with ritonavir for different reasons: 15 patients on treatment with atazanavir are coinfected with hepatitis C, 4 patients revealed intolerance to ritonavir, 3 patients have increase of lipid serum. All patients on treatment with fosamprenavir are coinfected with hepatitis virus, 16 with hepatitis C and one is HBsAg positive with HBV-DNA positive.
Three patients are on treatment with co-formulation abacavir+lamivudine plus atazanavir and 19 are on treatment with co-formulation tenofovir+emtricitabine plus atazanavir, while 5 patients are on treatment with co-formulation abacavir+lamivudine plus fosamprenavir, 11 with co-formulation tenofovir+emtricitabine plus fosamprenavir and one with lamivudine plus fosamprenavir for renal failure and contemporary treatment with Peg-interferon and ribavirin.
We prescribe these treatment based on anamnesis and clinical conditions.
Results: We evaluated CD4+ count and HIV viral load of these patients after six months or over of these treatment.
In cohort of subjects on treatment with atazanavir, we observed 20 patients with undectable HIV viremia (90,9%) and two with HIV viremia under 350 copies/ml. Median of CD4 was 439/mmc (135/mmc-1053/mmc) and only three patients have a CD4 count under 200/mmc.
The median of CD4 of patients on treatment with fosamprenavir was 239, and 13 patients had a HIV viral load under 50 copies/ml (76,5%). Two patients had a HIV viremia over 100,000 copies/ml, probably for a bad adherence to therapy.
Conclusions: For different reasons, in a moderate percentage of HIV positive patients, it's necessary to use a regimen with PI unboosted. Our cohort of patients on treatment with atazanavir or fosamprenavir unboosted have a good immunovirological condition, despite the major part of patients on treatment with atazanavir takes emtricitabine+tenofovir. In fact, DHHS Guidelines advised the use of this association for adverse pharmacokinetic interactions.
In our opinion, a regimen with atazanavir or fosamprenavir unboosted can be a good and effective alternative therapy in patients with hepatitis coinfection or intolerance to ritonavir or high level of lipid serum.

PO 042

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EFFICACY AND SAFETY OF AN ANTIRETROVIRAL REGIMEN CONTAINING RALTEGRAVIR IN HIV-1 TREATMENT EXPERIENCED PATIENTS

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Objective: to evaluate the efficacy of an antiretroviral therapy containing raltegravir in association of an optimized background therapy (OBT) in HIV-positive patients with multiple drug failures and multiple drug resistances.
Methods: We have recruited HIV-positive patients naïve to raltegravir, with multiple therapeutic failures with evidence of resistance at least 3-class of antiretroviral drugs or impossibility to take a drug class for side effects and/or interactions; the pharmacologic resistance was evidenced by genotypic resistance test and analyzed by Stanford database. The OBT was chosen on the basis of genotypic resistance test (GRT) evaluating the best options for each patient. At the failure of regimen containing raltegravir, a specific GRT for integrase was performed. Primary end-point was the proportin of patient with viral load undetectable at week 48.
Results: overall 30 patients were recruited from infectious diseases unit of Genoa and Florence. Baseline characteristics were as follows: median age was 43,3 years; 21 pts were male; median exposure to HAART was over 13 years; 19 pts (63%) had been exposed to enfuvirtide;16 out of 30 pts were assigned to class C, median viral load at baseline was of 28,725 copies/ml; median CD4 count at baseline was of 152 cells/ml. On the basis of GRT 3 OBT regimens contained 2 active drugs apart of raltegravir, 10 regimens contained 1 active drug while in 17 pts raltegravir was the only active drug. OBT included etravirine for 16 pts (43,3%), darunavir for 12 pts (40%) and enfuvirtide for 5 pts (16,7%). After 4 weeks 14 pts (47%) presented a suppressed viral load. After 12 months 14/19 (74%) presented a undetectable viral load. Median CD4 cell count increased from baseline up to the end of follow up by 108 cells/mmc. None of the patients had adverse events leading to discontinuation of the regimen. During the follow-up five patients failed the raltegravir-based regimen and developed a specific mutation profile: 2 patients develop a 148Q mutation; 3 patients developed 155H. Of note, all patients failed had a high mutation score on boosted protease inhibitor.
Conclusions: in our cohort raltegravir permitted a rapid decrease in viral load and an important immunologic restoration, so that this drug seems to be an important option for patients with multiple therapeutic failures. Anyway the lack of a high genetic barrier permits the development of drug resistance, even if there is a limited experience.

PO 043

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VIRO-IMMMUNOLOGICAL PARAMETERS OF A PROLONGED AND SAFE ANTIRETOVIRAL TREATMENT INTERRUPTION

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Aim of the study was to determine predictors of the duration of antiretroviral treatment interruption
(TI) in patients infected with HIV. A pilot prospective, open-label, multicenter trial comprised 62 HIV-seropositive subjects who decided voluntarily to interrupt therapy after two or more years of successful HAART. The primary end-point was the time to patients being free of therapy before reaching a CD4+ cell count <350/ml.
Several immunological and virological parameters were analyzed. Particularly, HIV-RNA residual viremia (limit detection 1 copy/ml), proviral HIV-DNA, HIV neutralizing antibody titre (NtAb-HIV), tropism of HIV isolates, were evaluated at TI and at restart of therapy.
Fifteen of 62 patients remained in TI for more than 180 days. Patients restarting therapy after less than 180 days had higher HIV-DNA levels (p=0.05), were treated more frequently with NNRTI-drugs (p=0.02), had a shorter period of HAART (p=0.046), and lower CD4+ cell counts after day 14 of TI (p=0.04).
Relatively to HIV tropism, at Kaplan-Meyer analysis, after adjusting for baseline CD4 cell count, patients with R5X4 strain had a significantly shorter time period of TI than patients with R5 variant (160 +/- 127 vs 533 +/- 418 days, p=0.02). Moreover, all four patients still on TI after a mean of 942 days had a R5 strain. In absence of treatment a switch from R5X4 to R5 tropism was observed in the 60% of patients, whereas the inverse switch from R5 to R5X4 tropism was detected in 5% of patients, only. Nine patients with the switch in the tropism from R5X4 to R5 HIV strain remain in treatment interruption for 175 days compared to 118 days of patients who maintained a R5X4 strain.
An increase in NtAb-HIV after TI was detected in 5 out of 23 patients analyzed. These patients had the longer period of TI compared to patients with constant or reduced NtAb-HIV.
At multivariate regression analysis, a baseline provirale HIV-DNA level of <323 cp/106 PBMCs and a CD4 cell count at day 14 of GTI of >564 cells/ml were independently associated to a reduced risk of restarting therapy (p=0.041 and p=0.012, respectively).
Finally, a virological and immunological score associated with TI of more than 180 days was defined.
A score based on viro-immunological parameters can identify patients with a prolonged period free safely of treatment. The CD4+ cell counts at nadir, at baseline and at week 2 of TI, the baseline HIV-DNA values, the presence of HIV R5 variant and an increase of NtAb-HIV were all parameters correlated with a prolonged a safe TI.
In conclusion, although several studies showed that continuous use of ART is superior to its episodic use, selected patients could benefit from long periods free o therapy without risk of developing AIDS or major clinical complications.

PO 044

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PREDICTIVE CRITERIA OF SUSTAINED VIROLOGICAL RESPONSE (MORE THAN 60 MONTHS) TO NEVIRAPINE BASED ANTIRETROVIRAL TREATMENT

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Nevirapine (NVP) is the first non-nucleoside reverse transcriptase inhibitors (NNRTI) used for the treatment of HIV infection. NVP is generally well tolerated, showed a favourable metabolic profile and therefore used in simplification strategies; otherwise, low genetic barrier and early adverse events, as hypersensitive reaction and hepatic toxicity, are the main limitations. Nevertheless, a considerable number of patients obtained a durable virological success for a long time. Aim of this study is to identify predictive criteria of long term NVP virological response (more than 60 months) in a cohort of NNRTIs naive subjects followed at two different Unit of Infectious Diseases in Catania between January 1998 and November 2008.
Clinical records of 137 HIV positive subjects treated with regimens including NVP plus two nucleoside reverse transcriptase inhibitors (NRTIs) were reviewed retrospectively for age, sex, route of HIV transmission, clinical stage (CDC stage, CD4+ lymphocyte cell count, HIV RNA viremia), HCV co-infection, therapeutic regimens, length of treatment, side effects, hepatic (ALT, GGT) and metabolic (total cholesterol, triglycerides and glucose) blood values and reasons for treatment failure.
Of 137 subjects, 100 (73%) stopped NVP after a median of 13.3 months (RIQ 1.78-32.1); of 37 subjects (27%) still on treatment (95.9 months, RIQ 76.1-110), 9 were excluded from analysis because treated for less than 60 months. Finally, 128 patients were included into the study. 66.4% males; 50% heterosexuals, 27% MSMs, 18% IVDUs; 67% CDC A, 10% CDC B, 23% CDC C; 20% anti HCV+; 75% ARV experienced. 28 of them (22%) were still on treatment.
Main reason leading to NVP discontinuation were virological failure (32.8%) after a median of 16.2 months (RIQ 8.1-37.9), toxicity (21.9%) (1 month, RIQ 0.8-5), patient's choice (21.1%) (17.6 months, RIQ 2.8-39). Hypersensitivity was the more frequent adverse reason leading to interruption (p<0.009).
39 (30.5%) subjects were treated for more than 60 months (long term responder or LTR), 89 (69.5%) stopped NVP before 60 months (long term not responder or LTNR). When characteristics of subjects into the two groups were compared, LTRs were older (41.2 years (RIQ 36-49.6) vs 36.6 (RIQ 32.1-42.7) (p=0.012), with a baseline lower median HIV RNA viral load (2.6 log10 vs 3.7 log10 (p=0.01) and showed a trend to be ARV naïve (35% vs 20%), anti HCV negative (10% vs 25%) and to have baseline higher CD4+ cell count (400 lymphocyte/µl (RIQ 264-548) vs 341 lymphocyte/µl (206-487).
In conclusion patients older, with lower HIV RNA viral load at baseline have better probability to maintain a sustained virological response with a NVP based treatment over 60 months. Higher CD4 cell count at baseline, anti HCV negative and to be ARV naïve could be related to a sustained response. Although some limitations, NVP should be considered for this specific groups of patients an economic, safe and efficacious treatment for very long time.

PO 045

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ALBUMIN IMPAIRS CD36 OVEREXPRESSION AND CELL DEATH OF THP-1 MONOCYTES INDUCED BY SAQUINAVIR

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Background: CD36 is a member of the scavenger B receptor family which is overexpressed on the cell surface of monocytes in the presence of many targets such as apoptotic cells or oxidized lipoproteins. HIV protease inhibitors (PIs), including saquinavir (SQV), increase the expression of CD36 suggesting that monocytes could transform in foam cells even in the absence of hyperlipidemia. Moreover some cells toxicities have been described for SQV. This raised the question whether the overexpression of CD36 could represent a marker of cell death due to the toxic effects of SQV rather than of hyperlipidemia. Here, the dose- and time-dependent effects of SQV on the CD36 expression and the cell death of THP-1 cells is reported. Moreover, since *in vivo* SQV is for 98 % bound to plasma proteins, the effect of human serum albumin (HSA) has been investigated.
Methods: Human THP-1 cells ($5x10^5$ per plate) were cultured in complete RPMI and treated with different concentrations of SQV (NIH AIDS Research Reagent Program) at 37°C and 5% CO_2, in the absence and presence of HSA (Sigma-Aldrich). Cells were stained with CD14-FITC and CD36-PE (BD Pharmingen). The expression of CD36 as MIF was quantified by flow cytometry (FACSCalibur, BD). Cell death was analyzed by human Annexin V-FITC Kit (BD).
Results: CD36 expression is dose and time dependent: The CD36 expression increases in THP-1 cells incubated for 12 ($p<.05$) and 18 ($p<.005$) hours with 20 and 30 ng/mL of SQV. The highest effect ($p<.001$) was observed at 24 hours (MIF 18.0 ± 2.5). No effect was observed at 10 ng/mL SQV, and after 6 hours of incubation (MIF 4.9 ± 0.8 and MIF 5.0 ± 1.1) compared to control cells (MIF 5.0 ± 0.9).
SQV toxicity is dose and time dependent: In the Annexin-V experiments, after the incubation for 24 hours, a significant increase of necrotic cells (*i.e.*, double positive stained) was observed with SQV at concentrations higher than 6 ng/mL (21.56 ± 2.9% of double positive cells; p=.0347). When THP-1 cells were incubated at 30 ng/mL SQV for different periods, only 4% of cells was double positive (4.29 ± 1.01%; p=.0058) after 12 hours incubation while after 24 hours, almost all the cells were double positive (96.79 ± 2.0%; $p<.0001$).
HSA impairs SQV toxicity and CD36 expression: The overexpression of CD36 and necrosis of THP-1 cells by 30 ng/mL SQV was abolished by adding HSA (20, 40, and 80 mg/mL) for 24 hours in a dose related manner.
Conclusions: In THP-1 cells, the CD36 overexpression is related to the SQV toxic effects and is reversed by HSA. Therefore, the bioavailability of drugs should be considered when addressing their effects in *in vitro* models.

PO 046

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PHARMACOKINETICS OF RALTEGRAVIR IN THE CLINICAL SETTING

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Background: Raltegravir (RGV) is a novel antiretroviral targeting HIV integrase that has been proven to be effective and well-tolerated. Main metabolism pathway seems to be through glucuridation by UGT1A1. In clinical trials, RGV plasmatic concentrations showed very wide inter- and intra-patient variability. Aim of this study was to evaluate the determinants of RGV levels in the clinical setting.
Methods: Repeated blood samples from patients treated with raltegravir were withdrawn at each follow up visit after steady state was reached. After centrifugation, plasma was extracted, frozen (-20°C) and stocked; plasmatic MVC concentrations were measured by a validated HPLC. Trough concentrations were considered between 10 and 14 hours from drug intake and geometric mean of all available samples was calculated. Demographic and laboratory data were analysed with SPSS 14.0 and were expressed as median values (IQR).
Results: Seventy-two patients were included in the analysis. 67.5% were men with median age of 46.5 (42.8 – 55.5) years and BMI of 22.9 (21.7 – 26.3) Kg/m^2. 224 samples were withdrawn at a median time of 12 (11.8 - 13) hours; 2.7 (1 - 4) trough concentrations were measured for each patient. Co-administered drugs were etravirine (45.6%), maraviroc (46.8%), darunavir (17.7%), atazanavir [as 200 mg bid (29.1%)], enfuvirtide (8.9%), other PIs (1%), NRTIs (9%), other NNRTIs (5%). Most used regimen was RGV/ETV/MVC (40.5%). Geometric mean of RGV was 194 (98-389) ng/ml. Significantly higher concentrations were found in the ETV/MVC group [257 (172-611) ng/ml] as compared to all other regimens [148 (88-237) ng/ml, p=0.01] and to the ATV group [154 (68.7-222) ng/ml, p=0.018]. 97.8% of samples were above the in vitro IC95 for wild type virus (15 ng/ml). No correlation was found between PK levels and gender, age, and BMI. Median bilirubin levels were 0.8 (0.42 – 1.2) mg/dl; a significant correlation was found between the latter and RGV plasma concentrations at each pharmacokinetics evaluation ($p<0.01$, Pearson's).
Conclusion: RGV trough concentrations showed a high variability but adequate levels in almost all the patients. The highest RGV plasma exposure was observed in the group of patients co-administered with ETV/MVC and not in ATV 200 mg bid intakers, as expected from previous drug drug interaction studies. Moreover, a significant correlation between levels of bilirubin and plasma RGV, sharing the same metabolic pathway, was found. Further clinical investigation including pharmacogenetics evaluation is warranted.

PO 047

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PLASMA LEVELS OF VCAM-1 AND ICAM-1 IN 103 HIV-POSITIVE PATIENTS VERSUS 54 HIV-NEGATIVE CONTROLS: ASSOCIATION WITH HIV INFECTION AND CONCOMITANT ANTIRETROVIRAL THERAPY

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Objectives. Increased risk of cardiovascular diseases has been associated in HIV-negative population with elevated circulating levels of adhesion molecules released by the vascular endothelium. Aim of our study is to evaluate plasma levels of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in 103 HIV-infected patients versus 54 HIV-negative healthy individuals.
Patients and methods. Epidemiological, clinical and laboratory parameters of enrolled subjects were evaluated and plasma levels of VCAM-1 and ICAM-1 were assessed by enzyme-linked immunosorbent assay. Patients were divided into the following 3 groups: HIV-positive patients naive to antiretroviral therapy (group A), HIV-positive patients on continuous antiretroviral therapy (group B), and HIV-negative controls (group C).
Results. 103 HIV-infected patients were enrolled (51 in group A and 52 in group B), in association with 54 HIV-negative persons (group C). In group A, males were 47, median age was 39 years (range, 32-56), mean duration of HIV infection was 62 months, mean CD4 lymphocyte count was 639 cells/mm3, mean HIV viral load was 31,000 copies/mL. In group B, males were 33, median age was 47 years (range, 31-66), mean duration of HIV infection was 158 months, mean CD4 lymphocyte count was 735 cells/mm3, HIV RNA was undetectable in 32 subjects. Concomitant antiretroviral therapy included a protease inhibitor (PI) in 21 subjects, and a non-nucleoside reverse transcriptase inhibitor (NNRTI) in 20 patients; median duration of therapy was 139 months. In group C, males were 39, median age was 31 years (range, 19-57), and mean 10-year risk of coronary events was 4.22%. Mean value + SD of VCAM-1 was 593.3 + 162.4 ng/mL in group A, 337.1 + 125.7 in group B, and 148.4 + 81.7 ng/mL in group C: plasma levels were significantly lower in group B and in group C than in group A ($p<0.001$). Mean value + SD of ICAM-1 was 145.6 + 46.5 in group A, 114.1 + 38.9 in group C, and 142.4 + 39.6 in group C: plasma levels did not differ significantly in the 3 considered groups. By a multivariate analysis, higher values of VCAM-1 in groups A and B were associated with higher HIV viral load and lower CD4 lymphocyte count.
Discussion. In our study, plasma levels of VCAM-1 were significantly higher in HIV-positive patients naive to antiretroviral treatment than in HIV-positive experienced patients and in HIV-negative controls, and were associated with higher plasma HIV RNA and lower CD4 cell count. On the contrary, plasma levels of ICAM-1 did not show significant association with HIV infection, current therapy, and virological or immunological parameters.

PO 048

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PATIENTS REPORTED OUTCOMES EVALUATION IN A RANDOMIZED, CONTROLLED STUDY OF IMMEDIATE VERSUS DELAYED LIPOFILLING SURGERY ON HIV-POSITIVE PEOPLE WITH FACIAL LIPOATROPHY

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Background: Facial lipoatrophy (FLA) is one of the most distressing and stigmatizing expression of the antiretroviral-associated lipodystrophy syndrome. It may deeply affect the patient's life quality, rendering them more exposed in being identified as HIV-positive, thus leading to a decreased self-esteem and social withdrawal. Despite the improved knowledge on FLA etiology and risk factors, successful medical treatments for the management of this side effect are still troublesome. Recently, surgical interventions for FLA have been increasingly considered as they appear to be a remedy in giving patients an immediate psychological relief. Up to day, moreover, the effects of lipofilling surgery on patients reported outcomes (PROs) as health related quality of life (HRQoL), anxiety and psychological consequences of body changes are poorly understood and need to be studied.
Design and method: The study was a randomized, controlled, and open-label study of immediate versus delayed surgical intervention with filling components for the correction of severe HIV-associated FLA. A wide number of PROs instruments were used in this study. To measure HRQoL, the EuroQoL 5 domains (EQ-5D) and the Istituto Superiore di Sanità Quality of Life (ISSQoL) self-administered instruments were adopted. To evaluate the relationships between the lipodystrophy syndrome and the quality of life the ABCD (Assessment of Body Change and Distress) self-administrated questionnaire was used. To measure the person's anxiety perception the Zung self-rating anxiety scale (SAS) was used.
Objective: The study was aimed at evaluating the efficacy of the lipofilling surgery in the treatment of HIV-related FLA, in terms of both FLA severity grade (assessed by physicians) and PROs [changes in FLA severity grade as determined by the patient, HRQoL measures, relationships between the lipodystrophy syndrome and the quality of life, and patient's anxiety perception]
Results: Compared to patients randomized to the delayed treatment, patients assigned to the immediate treatment group had significantly lower physician-rated (0.0 versus –3.0; $p<0.0001$) and patient-rated (0.1 versus -1.8; $p<0.0001$) FLA severity scores. However, no significant differences between the immediate and delayed treatment groups were observed in terms of PROs. In particular, our study was not able to show any significant gain in HRQoL (EQ-5D and (ISSQoL), in social aspects, in relational-psychological consequences of body changes (ABCD), as well as in anxiety related concerns (SAS). Adverse events were mild and resolved after a mean of 4 days.
Conclusion: Reconstructive therapy with facial fillers was effective, safe and lead to significant improvements in FLA severity . No significant improvement in patients reported evaluations were observed. However, in spite of wide number of the PROs measures used in this study, the lack at present of a specific lipoatrophy instruments evaluating correctly the full impact of lipoatrophy on psychosocial and HRQoL dimensions in HIV-infected people does not allow definitive conclusions.

PO 049

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UNBOOSTED ATAZANAVIR IN PATIENTS WITH SEVERE LIVER DISEASE: A CLINICAL EXPERIENCE

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Background: highly-active antiretroviral therapy (HAART) can be contraindicated in HIV-positive patients with severe liver disease, especially if containing boosted protease inhibitors (PIs). Atazanavir (ATV) is currently one of the most used PIs and its role in this subset of patients is still controversial. Even if its unboosted formulation is not yet licensed in Europe, it could be an interesting option by decreasing the risk of hepatotoxicity. We describe the outcomes using unboosted ATV, in association with nucleoside reverse transcriptase inhibitors (NRTIs), in a small group of HIV-positive patients with advanced liver disease, followed up in our Clinic.
Methods: twelve HIV-positive patients, 10 males and 2 females, switched to an unboosted-ATV-containing regimen. Ten of them were HIV/HCV co-infected (genotype 1 in 6/10, genotype 3 in 3/10, genotype 4 in 1/10); no one was HBsAg positive but 3/10 had HBcAb. Two patients were affected by cryptogenetic liver disease (as defined by Maida et al, JAIDS 2006) with portal hypertension and history of upper gastrointestinal bleeding. All patients had been assessed for clinical, histological, radiological/ultrasound and elastographic features.
The median length of HIV infection was 16.4 years; median nadir CD4+ count was 242/mm^3. Previous therapeutic regimens included boosted atazanavir in 5/12, other boosted PIs in 4/12 and unboosted PIs in 3/12 (NFV). All patients were switched to once-daily (OD) 400 mg unboosted ATV plus the following backbone therapies: emtricitabine (FTC) 200 mg once-daily + tenofovir (TDF) 300 mg OD in 10/12, lamivudine (3TC) 150 mg twice-a-day (BD) + zidovudine (AZT) 300 mg BD in 1/12 and 3TC 300 mg OD + abacavir (ABC) 600 mg OD in 1/12.
Results: eleven out of twelve patients are currently still on treatment, with a median duration 11 months; at last follow up the mean CD4 count is 408 cells/mm3 and HIV viral load is in all of them undetectable. No significant elevation in transaminases or bilirubin levels have been noted during the follow up, with mean total bilirubin of 2.48 mg/dL and mean ALT and AST levels of 73 IU/L and 87 IU/L, respectively.
One patient has recently interrupted the therapy for the presence of fever, hypertransaminasemia and hyperbilirubinaemia and he is currently being clinically monitored.
Conclusions: in our experience the use of unboosted ATV in HIV patients with advanced liver disease seems to be safe, with minimal liver toxicity. Furthermore, such regimens show to have anti-HIV efficacy and durability, as demonstrated by the complete and durable viral suppression.

PO 050

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THE EFFECT OF HIV-1 IN DECREASING MITOCHONDRIAL DNA IN PERIPHERAL BLOOD MONONUCLEAR CELLS OVERCOMES THE TOXIC EFFECT OF ANTIRETROVIRAL THERAPY (ART)

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Background: Both HIV-1 infection and antiretroviral therapy (ART), especially nucleoside reverse transcriptase inhibitors (nRTIs), are associated with mitochondrial (mt) DNA depletion in peripheral blood mononuclear cells (PBMC). The objective was to evaluate the effect of different ART regimens compared to ART discontinuation on mtDNA level in PBMC.
Methods: We evaluated 29 patients divided into three groups: combination ART (cART, n=10, including 5 virologically suppressed patients switching to a simplified regimen and 5 failing patients switching to a different regimen), 3TC monotherapy (n=10) and therapy interruption (TI, n=9). Patients from 3TC and TI groups were selected from 58 patients enrolled in a pilot study (E184V) comparing 3TC monotherapy versus TI following cART failure. At baseline (BL), patients from the cART group were already on cART and switched to the new regimen, 3TC patients interrupted cART and continued 3TC monotherapy, and TI patients withdrew ART. MtDNA, CD4 counts and plasma HIV-1 RNA level (VL) were measured at BL and after 24 (W24) and 48 weeks (W48) - under new regimen or interruption. MtDNA was measured by real-time polymerase chain reaction with primers amplifying CCR2 (nuclear) and cytB sequences, following PBMC separation optimized for platelet depletion and DNA extraction. All group comparisons were calculated by Kruskall-Wallis and Mann-Whitney tests.
Results: At BL, the TI, 3TC and cART groups had similar values of mtDNA (median 711, 707, 780 c/cell), CD4 (621, 585 and 612 cells/μL) and VL (3.50, 3.87 and 2.73 log c/mL). The distribution of individual nRTIs in previous cART regimen was similar in the three groups. At W24 no significant change of mtDNA was observed compared to BL in any group (median 386, 624, 692 c/cell; p=n.s.). At W48 mtDNA was significantly decreased in TI (median 487 c/cell; p=.027) but not in 3TC (513 c/cell; p=.064) and in cART patients (791 c/cell). At W48 CD4 cell counts were decreased in TI (median 464/μL, p=.004) and in 3TC (460/μL, p=.048) but not in cART patients (610/μL); and VL increased in TI (median 4.87 c/mL, p=.004) and 3TC (4.37 c/mL, p=.004) but not in cART patients (1.69 c/mL). In the TI and 3TC groups the decrease in mtDNA at W24 and W48 was associated with higher mtDNA BL level (W24: p=.0002 and p=.028; W48: p=.002 and p<.0001) and correlated with higher BL CD4% in the 3TC group (W24: p=.073; W48: p=.004).
Conclusions: The observation of decreased mtDNA in TI patients, in association with increased VL, but not in treated patients, indicates that the direct influence of HIV-1 may be superior to the toxic effect of antiviral drugs on PBMC mtDNA depletion.

PO 051

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SWITCHING FROM LPV/R OR NNRTI-CONTAINING REGIMEN TO ATV/R-BASED ARV: EFFECT ON INSULIN SENSITIVITY AND IMPAIRED GLUCOSE TOLERANCE

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Background: HIV-infected subjects are at major risk of developing disorders of glucose metabolism comparing with HIV seronegative: although the pathogenesis of glucose abnormalities during HIV infection is believed to be multifactorial, the induction of insulin resistance (IR) is a direct effect of treatment with protease inhibitors (PI) such as LPV/r. ATV-containing regimens do not significantly affect insulin sensitivity, leading to an improvement of PI-induced IR among HIV-infected adults.
Aim of the study was to analize the effect of switching from a LPV/r-based regimen to ATV/r-based regimen on insulin sensitivity in HIV infected adults.
Design: A retrospective study was conducted among 184 HIV-infected outpatients attending an urban clinic in Rome between 2002 and 2008. Patients were evaluated for age, staging of HIV infection, HCV co-infection, glucidic and lipid metabolism at the enrollment and after switching from a LPV/r-based regimen to ATV/r-based regimen. To assess insulin sensitivity and impaired glucose tolerance (IGT) respectively HOMA index and serological glucose determination were used.
Results: A total of 184 HIV infected patients (109 M, 75 F; median age 37years) were enrolled in the study. All the subjects were in ARV therapy (median time on ARV 1.6 years). At the enrollment, the median CD4+ cell count was 312 cell/mmc (nadir 154 cell/mmc); HIV-RNA was undetectable in the totality of the subjects. 15% had HCV/HIV co-infection. Medium BMI and HOMA index were 23.5 and 2.1, respectively. 103 patients had LPV/r-based ARV, 81 NNRTI-based regimen (60 EFV, 21 NVP). After a 32-months therapy, a total of 74 patients were switched to ATV/r (32 from LPV/r-based regimen, 42 from NNRTI-based regimen). Before changing therapy, IR was observed in 11%-14%-19% of subjects respectively in the 1st, in the 2nd and in the 3rd year of LPV/r-based regimen, compared with 2%-3%-3% of NNRTI- based regimen. Alike, the exposure to LPV/r was associated with an higher rate of IGT than NNRTI-therapy (7% and 1% of the subjects, respectively).
Switching to ATV/r led to a significant reduction in glucose metabolism abnormalities both in LPV/r and NNRTI-containing groups. A significant proportion of subjects showed an improved insulin sensitivity after therapy change: 48% in the 1st year, 79% in the 2nd (medium HOMA-IR before switching 3.3, after switching 2.3). Similarly, medium BMI determination decreased from 24.3 to 23.7. No differences were observed in terms of immunological and virological efficacy between LPV/r and ATV/r-treated patients.
Conclusions: The use of LPV/r as a component of ARV is associated with higher glucose abnormalities comparing with ATV/r or NNRTI-based regimens. The length of exposure to LPV/r is a major determinant of insulin resistance and impaired glucose tolerance. Switching from LPV/r -based ARV to ATV/r -based ARV contribute to improve glucose metabolism nearly in half of patients.

PO 052

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TREATMENT OPTIONS FOR FACIAL HIV-RELATED LIPOATROPHY: INTRADERMAL INJECTIONS OF POLY-L-LACTIC-ACID AND POLYACRYLAMIDE HYDROGEL

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Background: The fact that there is no clinically proven therapy for lipodystrophy, such as the slowness, and in some cases apparent absence of clinical recovery from lipoatrophy, makes the need for cosmetic surgical interventions for patients with this problem essential. Surgical fillers, which may be either permanent or biodegradable, are the mainstay of cosmetic management.
Objective: This prospective, open-label, twin-arm study of treatment options for facial HIV-related lipoatrophy was conducted at the National Institute of Infectious Diseases " L. Spallanzani" Rome, Italy. The aim of this study was to evaluate tolerability, safety and effectiveness of interventions with two different fillers (Poly-L-Lactic-acid PML, Scupltra® and Polyacrylamide hydrogel PAIG, Aquamid ®) in deep subcutaneous application for facial soft-tissue augmentation.
Methods: Severity of facial lipoatrophy was estimated by surgeon before the treatment and 6 months after the treatment competition using a scale of 4 grades (Facial lipoatrophy severity scale). The specific facial morphologic features of the patients were carefully analyzed before the injection of fillers, and standardised colour digital photographs were taken before and after each injection session to visually assess the benefit of the procedure. At each treatment 1 to 3 vials of PLA or 1 to 4 vials of PAIG was injected. After seven days from the surgical application of the fillers, patients were photographed and visited. Ulterior control visits had been scheduled at months 6 and 12 after the end of the treatment. The occurrence of adverse events or complications was recorded at each control visit. A patient's subjective perception of improvement of facial lipoatrophy and personal satisfaction with treatment result was estimated by a self-administrated questionnaire of personal satisfaction completed by patient at control visit 6 month after treatment termination.
Results: From September 2005 to September 2008, 298 adult HIV-infected patients were evaluated and 151 patients with moderate or sever lipoatrophy were treated with PLA (n= 64: 52 males, 12 females) or PAIG (n= 87: 78 males, 9 females). 143 of them (n=60 PLA; n=82 PAIG) completed 12 months follow-up . The maximum aesthetic result (lipoatrofy grade 0) was archived by 52 patients (63.4%) from PAIG group and 48 patients (80%) from PLA group. Self reported patient satisfaction (scale 0-5) after treatment with PAIG, or PLA was 4.5(± 0.6) and 4.2 (± 0.6) respectively. Pain (scale 0-10) related to the injection was reported in all patients. A mean level of measured pain was 4 (± 1.7) for PLA group and 5 (± 2) for PAIG group. No serious complications and adverse effects were observed during the treatment and follow-up.
Conclusions: Favourable results, in means of maximum aesthetic gains, efficacy, tolerability and safety with the use of PAIG and PLA fillers for the reconstruction of facial lipoatrophy were demonstrated in this study. However, further observations, including long-term follow-up and cost-effectiveness evaluation are warranted to clarify the outcome and benefits of these treatments.

PO 053

Infection 2009; 37 (Suppl. II): 73

HIV-ASSOCIATED PML: AN IMMUNE-MEDIATED DEREGULATION DISEASE?

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The immune reconstitution inflammatory syndrome (IRIS) is defined as a paradoxical worsening or onset of systemic clinical signs and symptoms and occurs in HIV-infected patients receiving HAART, particularly in those with profound immune suppression. Recently it has been reported that some patients may develop additional or novel neurological manifestations described as neurologic IRIS (Neuro-IRIS). IRIS has been reported wit association with JCV infection.
Methods: Four HIV-infected patients, all men, median age of the 37 years. Risk factor for acquisition of HIV included IV drug abuse (n=1), men having sex with men (n=2) and heterosexual transmission (n= 1). The mean CD4+ T-cell count before ART initiation was 68 cells/mm3. The median CD4+ T-cell count before ART initiation was 28 cells/ mm3 with a range from 4 to 160 cells/mm3. CSF examination and neuroimaging studies including MRI were performed in all patients. Two patients were naive and in the remaining two patients ART was optimized.
Results: All patients presented with new onset neurological signs and symptoms. Three patients developed neurologic alterations whitin m 4 - 6 weeks after the initiation of the ART, the remaining patients developed neurological disabilities two months later. The clinical presentation was an acute encephalopathy, requiring admission to the hospital. In addition to confusion, signs also included generalized seizure, asymmetric weakness in their legs and visus disorders. CSF examination revealed normal profile in 2 patients and a mild lymphocitic pleocytosis combined with an elevation in protein in the remaining patients. JCV PCR was positive in in all but one patients. In the JCV PCR negative patient JCV was demonstrated by brain biopsy.
MRI revealed diffuse increased signal in the white matter on T2-weghted and fluid attenuated inversion recovery images.
Conclusion: ART and subsequent immune reconstitution is changing the features of the HIV associated-diseases. PML is one of the manifestation of the spectrum of neuroIRIS and clinician must be alert to the differential diagnosis.

PO 054

Infection 2009; 37 (Suppl. II): 73

IMPAIRED ADIPOKINE PROFILE IN HIV POSITIVE PATIENTS: THE ROLE OF BACKBONE

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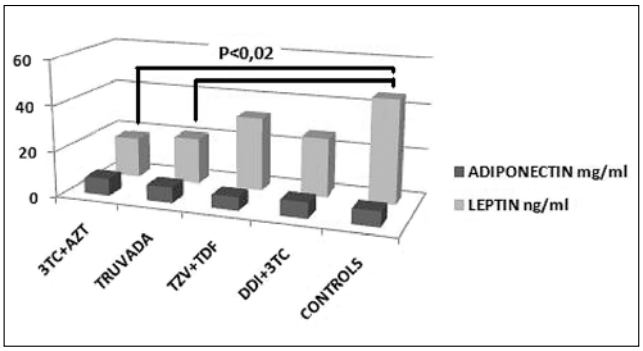
Background: Adipose tissue secretes of a range of proteins called adipokines. Dysregulation of adipokines is implicated in the etiology of metabolic syndrome, but the relation between adiponectin, leptin and antiretroviral therapy has been poorly studied and subject to controversy. The aim of study was to investigate the relation between adipokine levels and different backbones exposure in HIV+ subjects with similar metabolic and anthropometric parameters and without metabolic syndrome.
Methods: The study population consisted of 56 subjects. 32 patients of 46 HIV+ were on a first line antiretroviral therapy (14 patients with TDF/FTC, 9 patients with 3TC/AZT, 8 patients with ddI/3TC), 15



patients were on a simplified therapy with Trizivir+TDF. Ten age-matched HIV- patients with metabolic syndrome served as controls. Patients were studied for CD4+, HIV-RNA, metabolic and anthropometric parametres. Serum leptin and adiponectin was measured using commercially available kits.
Results: Anthropometric, clinical and laboratory features of the 46 HIV+ subjects were similar in all groups. Cardiovascular risk of HIV+ patients, evaluated by the Framingham model, was not higher than the risk of the general population.
Data showed that plasma adiponectin levels were similar in groups of HIV+ patients and in HIV- controls with the metabolic syndrome. Leptin levels of patients on TDF/FTC and on 3TC/AZT were significantly lower than leptin levels of controls (p<0,02). Plasma leptin levels were similar in HIV- controls and in ddI/3TC and trizivir+TDF groups (Fig 1). An important finding is that adiponectin and leptin levels were altered in patients with a cardiovascular risk similar to the risk of the general population of the same sex and age.
Conclusions: Our data show that all backbones analyzed impair the adipokine profiles in HIV positive patients without metabolic syndrome and in the absence of impaired glycemic and lipidic parameters. TDF/FTC and 3TC/AZT impair the adipokine profiles less than Trizivir+TDF or ddI/3TC.

PO 055

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ANTIRETROVIRAL THERAPY AND LIPODYSTROPHY AS PREDICTORS OF SUB-CLINICAL ATHEROSCLEROSIS

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Background and Objective: Although anti-retroviral therapy (ART) has prolonged survival in human immunodeficiency virus (HIV)-infected persons, an increase in cardiovascular disease (CVD) has been observed. A frequent complication of ART is the development of lipodystrophy (LD) that may be associated with CVD. We assessed the contribution of chronic HIV infection, ART use and LD to the presence and extent of sub-clinical atherosclerosis as evaluated by coronary artery calcium (CAC) imaging.
Methods: Observational cross-sectional study of 372 HIV-infected patients receiving ART who attended a cardiometabolic clinic (mean age 48.21±8.07; 73.92% men). All patients underwent CAC surveil-

lance with computed tomography and the Agatston score was used to quantitate CAC. Presence of CAC was defined as a score above 10. Multivariable logistic regression was used to evaluate associations between HIV clinical factors, ART and LD with the presence of CAC.
Findings: CAC was found in 134 patients (36.02%) with an average CAC score of 50 (range 10; 1243). Lipoatrophy alone (OR 4.29, 95% CI: 1.11; 16.55), fat accumulation alone (OR 9.51, 95% CI: 1.83; 49.25) and mixed lipodystrophy phenotypes (OR 4.20, 95% CI: 1.08; 16.26) were strongly associated with presence and extent of CAC after adjustment for sex (OR 2.95, 95% CI: 1.25; 6.96), age (OR 1.11 per year, 95% CI: 1.06; 1.16) and cumulative exposure to ART (OR 1.20 per year, 95% CI: 1.05; 1.38).
Conclusion: CAC was prevalent among long-term ART users. The association between CAC and LD underscores the potential CV risk inherent with ART and the need to undertake routine cardiovascular surveillance in patients treated with these drugs.

PO 056

Infection 2009; 37 (Suppl. II): 74

SELF-REPORTED ADHERENCE IS CORRELATED TO HEALTH-RELATED QUALITY OF LIFE AND TOLERABILITY MORE THAN TO REGIMEN CONVENIENCE IN HIV-INFECTED PEOPLE TAKING CART

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Objective: To evaluate whether self-report tolerability or convenience of the cART regimen were correlated to self-reported adherence (SelfAdher).
Methods: Prospective, cohort (Ad-UCSC), monocenter study. A short questionnaire on adherence (0 to 100 scale), satisfaction with therapy, trust in antiretrovirals efficacy, Physical (PhysH) and Mental (MentH)Health, and self-reported symptoms was administered to any outpatient taking HAART at the Infectious Diseases Department, Catholic University, Rome, Italy. Patients are required to fill the questionnaire at any clinic visit. Regimen was defined according to drug classes, number of daily doses, and symmetry (if pills are equally distributed into daily doses or not). A composite measure for defining viro-immunological failure was used (failure if, at the moment of the survey, CD4<200 or CD4 decreasing respect to a 1-year previous value or HIV RNA>50 c/ml). A symptom score was built summing self-reported scores (from 0 –at all -to 4 – very much-) for each of 19 listed symptoms
Results: At Oct 2008, 620 patients filled the questionnaire. 33.5% were females, mean age 46 yrs (SD 8.6), IDU 20%, median of years since knowing to be HIV-infected: 12 (SD 6); median log HIV RNA 1.7 c/ml (IQR 1.7-1.7), median CD4 567/mm3 (IQR 412-760). 56% were taking PI, 30% NNRTI, and 12% only NRTI; <10% were previously naive to antiretrovirals. Mean SelfAdher was 79.2 (SD 18.3); 19.5% reported adherence≤60. 15.8% reported having missed at least one dose in the previous week. People with SelfAdher score <60 had lower CD4 cell count (p at Mann-Whitney test =0.018) compared to people reporting SelfAdher>60. SelfAdher was lower in people with a viro-immunological failure (mean, SD 81+17) than in in people not failed (77+21; p 0.05).
SelfAdher was higher in people taking NNRTI (85.7; SD 18.0) compared to those taking PI (76.9; SD18.9; p<0.0001), taking a once-a-day regimen (82.9; SD 16.2) compared to those not (78.2; SD 19.3; p=0.01), and in those taking a symmetric regimen (82.6; SD 17.0) than those taking an asymmetric one (75.3; SD 19.3). SelfAdher was significantly correlated to symptom score (p<0.001), satisfaction with therapy (p<0.001), PhysH (p<0.001) and MentH (p<0.001). At multivariable analysis on the subsample of people taking PI or NNRTI, symptom score (B –0.24 95% CI –0.44; -0.04; p=0.02) but not symmetry or once daily regimen were significantly correlated to SelfAdher even when adjusted for viroimmunological failure (B –3.79 95% CI –7.62; 0.03; p=0.05) and PhysH (B 0.27 95% CI 0.16; 0.38; p<0.001).
Conclusions: Self-reported adherence was found to be significantly correlated to health-related quality of life and tolerability and not to characteristics of regimen convenience. However, the cross-sectional analysis does not allow assessing the correlation direction between variables.

PO 057

Infection 2009; 37 (Suppl. II): 74

DETERMINANTS OF SELF-REPORTED SYMPTOMS IN HIV-INFECTED PEOPLE TAKING CART

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Objective: To evaluate determinants of self-report symptoms in patients taking cART regimens.
Methods: Prospective, cohort (Ad-UCSC), monocenter study. A short questionnaire on adherence (0 to 100 scale), satisfaction with therapy, belief in antiretrovirals efficacy, Physical (PhysH) and Mental (MentH)Health, and self-reported symptoms was administered to any outpatient taking cART at the Infectious Diseases Department, Catholic University, Rome, Italy. Patients are required to fill the questionnaire at any clinic visit. A Symptom Score was built summing self-reported scores (from 0 –at all -to 4 – very much-) for each of 19 listed symptoms. Possible scores ranged from 0 to 76. Regimen was defined according to drug classes and number of daily doses.
Results: At Oct 2008, 620 patients filled the questionnaire. 33.5% were females, mean age 46 yrs (SD 8.6), IDU 20%, median of knowing to be HIV-infected 12 yrs (SD 6); median log HIV RNA 1.7 c/ml (IQR 1.7-1.7), median CD4 567/mm3 (IQR 412-760). 56% were taking PI, 30% NNRTI, and 12% only NRTI; <10% were previously naive to antiretrovirals.
Mean Symptom score was 13.4 (SD 9.8); 39 (6%) had a Symptom score >30. 95.2% reported at least 1 symptom and 283 (44.9%) at least 1 symptom as "much" or "very much". More frequent reported symptoms were fatigue (75%), abdominal bloating (58%), insomnia (52%), anxiety (51%), and myalgias (51%). More frequent reported serious symptoms ("much" or "very much") were fatigue (14%), abdominal bloating (13%), lipoaccumule (10%), insomnia (9%), and anxiety (9%).
Females self-reported an higher Symptom Score (16.3 ±12.2 vs 12.2 ± 9.0 for males; p<0.0001). Mean of Symptom Score was 15.1 (SD 10.6) in people taking PI, 10.6 (SD 9.4) in those taking NNRTI, 14.2 (SD 9.1) in those taking both PI and NNRTI and 13.0 (SD 9.8) in those taking only NRTI (p at ANOVA <0.001). At multivariable analysis with a linear regression model, gender (B for being male -4.6; 95% CI -6.74; -2.37; p<0.0001), age (B 0.15; 95% CI 0.03; -0.15; p=0.012), time since the first HIV test (B 0.18; 95% CI 0.03; 0.36; p=0.05), PhysH (B -0.20; 95% CI -0.27; -0.14; p<0.0001), MentH (B -0.09; 95% CI -0.15; -0.03; p=0.003), and belief in therapy efficacy (B -0.89; 95% CI -1.63 -0.15; p=0.02) were correlated to Symptom Score.
Conclusions: Symptoms were still highly prevalent in HIV people taking cART. Females self-reported significantly higher symptoms while belief in the antiretroviral efficacy was inversely correlated to symptoms. Symptom score was significantly correlated also to health-related quality of life and time since the first HIV+ test. Differences in Symptom Score observed according to drug classes disappeared in the multivariable model. The assessment of symptoms through a unexpensive and easy self-report approach may give important information to physicians in charge of HIV people.

PO 058

Infection 2009; 37 (Suppl. II): 75

MAY HIGH COSTS OF HIV/AIDS ANTIRETROVIRAL DRUGS INFLUENCE THE PHYSICIAN CAPACITY ATTITUDE OF PRESCRIBING THE CORRECT ARV FOR PATIENTS? RESULTS OF AN ITALIAN AWARENESS CAMPAIGN ('HIV: TODAY THE GAME IS EASIER')

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Background: The approval of new effective drugs for treating HIV/AIDS (starting from enfuvirtide, new PIs and, the last year, drugs of the new classes) potentially allows most physicians to design and prescribe new regimens that can effectively reduce patients' viral load below the limit of detectability and, in most situation, make patients' gain CD4 and potentially improve health status. But costs of these regimens are very high. Often patients and physicians denounce the difficulty of having access to new drugs, mainly 'caused by local hospital management and budgets that impose limits to physicians.
Methods: Nadir Onlus Foundation launches a 3 months (Oct '08-Dec'08) Italian awareness campaign through its website www.nadironlus.org consisting in a video and an anonymous web survey directed to HIV/AIDS patients including 30 items on demographic, social, clinical (therapy prescribed and drug toxicities), lifestyle characteristics, focusing on access to drugs, diagnostics and prevention technological tools (i.e. vaccinations) as well as satisfaction of assistance and global information received on HIV/AIDS disease.
Results: 175 web communities were contacted, 2036 people saw the video, 367 patients answered the survey and data analysis is divided according to the Nielsen macro region division: N-West (38,8%), N-East (21,6%), Centre (28,9%), South (10,7%). Video vision: mean age: 35-44 years (70%), 55% men, 40% through a player in a website, 60% directly on You-tube. Virilised external websites: 31%. 255 people are included in a dedicated Facebook group. Web survey responders: mean age: 41,2 years, 79,5% men, 76,2% high level of education (41,8% secondary school, 34,4% university), mean diagnosis year: 1998-99. High percentage of patients don't know the existence of high cost drugs (28,6%), don't have a correct standard of care routine follow-up (28,2%), don't know the existence of resistance testing (10%), ABC hypersensitivity testing (61,1%), CCR5 tropism testing (75,7%). High percentage of patients was never offered a hepatitis A/B vaccination (42%), pneumococcal (87,2%) or influenza (38,9%). 67,6% of patients was never offered to enter in a clinical trial with a new drug. 22% denounce overall discontent on general information received on HIV/AIDS treatment. 15% had to migrate not having access to new compounds.
Conclusions: Data stratified according to therapy prescribed, geography, age of diagnosis denounce high lack of modern standard of care assistance to Italian HIV/AIDS patients, especially concerning adequate follow-up and tailoring of correct HAART. In particular, high costs of new drugs and, consequently, pressure of hospital managers concerning the budget control may be the cause. We suggest an urgent action of the Health Ministry to the Italian regional Health authorities.

PO 059

Infection 2009; 37 (Suppl. II): 75

EFFICIENCY OF SURGICAL INTERVENTION FOR THERAPY-INDUCED FACIAL LIPOATROPHY IN HIV-INFECTED PATIENTS

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Objectives: Facial lipoatrophy is a significant problem related to antiretroviral therapy for people living with HIV. The only intervention currently available is the surgical correction with facial fillers. Objective of this study was to evaluate efficacy and efficiency of injection of two kind of fillers: poly-L-lactid acid *(Sculptra)* and polyacrylamide hydrogel *(Aquamid / Aquamid Rec)*.
Methods: Cost-effectiveness analysis (CEA) was performed on the results of a randomized controlled clinical trial comparing a surgical correction of lipoatrophy *versus* the usual clinical care without intervention, on 134 patients (67 per arm) over six-month follow-up. Efficacy was evaluated with data collected by surgery with the facial lipoatrophy scale (possible score 1=mild lipoatrophy, to 5=most severe lipodystrophy) and by patients with HOPS (HIV Outpatient Study) severity scale (possible score 0= none to 3= severe).
Direct costs (costs of surgeon, fillers, surgical instruments) were evaluated from the service supplier's perspective in Italy and analysed according to prices and tariffs applied in 2008. Data from 132 patients (66 per arm)* were collected at baseline and at 0-6 time points.
Results: Lipofilling intervention resulted in a lipoatrophy improvement, with a mean±SD change in facial lipoatrophy scale of -2.93±0.9 according to physicians evaluation and with a mean±SD change of 1.8±0.8 according to the patients. To implement this surgical procedure, service supplier should sustain an overall mean cost of 2128.04 € per patient, corresponding to an incremental cost-effectiveness ratio of 709.34 € per unit of improved facial lipoatrophy, if we consider efficacy evaluated by physicians; taking into account efficacy estimated by patients, the incremental cost-effectiveness ratio is 1182.24
Conclusions: According to preliminary results, lipofilling intervention for lipoatrophy in HIV patients is cost-effective: to obtain a decrease of one grade of lipoatrophy, a cost of 739.31 or 1182.24 € is expected to be sustained. Information obtained with this study, can be helpful to make appropriate decisions for the provision of optimal health care for these patients.
(*) Baseline values of 132 patients were substantially unchanged in comparison with baseline values of 134 patients.

PO 060

Infection 2009; 37 (Suppl. II): 76

RANTES DERIVATIVES AS MUCOSAL ANTI-HIV MICROBICIDES

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In the urge to attain efficacious AIDS preventive measures, topical anti-HIV microbicides represent a more realistic alternative and complementary option to an AIDS vaccine. Failure of clinical trials with broad-spectrum non-specific compounds highlighted the need for the development of highly active, target-specific microbicides. Among microbicide targets, CCR5 (the main HIV coreceptor) is of major interest, considering the large number of CD4+ T lymphocytes, usually activated, present at the level of the vaginal, rectal and foreskin epithelium. Aside of its physiological role as a chemokine, RANTES, a ligand of CCR5, is the most potent natural HIV inhibitor. RANTES has therefore been recognized as a lead anti-HIV molecule and worldwide efforts are being pursued to engineer RANTES derivatives with high anti-HIV potency [1]. We developed small peptides deriving from the N-loop/β1-strand region of RANTES, which act as potent HIV inhibitors and CCR5 antagonists [1]. Moreover, we produced CCR5 antagonist full-length RANTES mutants retaining potent anti-HIV activity [1]. These platforms are now being expanded by engineering: A) peptide multimers to increase avidity towards CCR5; and B) conceptually novel full-length RANTES mutants. CCR5 antagonism by these inhibitors is crucial to avoid pro-inflammatory activity (or even provide anti-inflammatory properties) to prevent possible side effects due to mucosal inflammation and long-term enhancement of HIV transmission. Our RANTES derivatives are being developed in the context of international collaboration/funding schemes aimed at obtaining both conventional as well as live microbicides. The live microbicide concept is based on the engineering of commensal bacteria belonging to the human microbiota, in order to achieve in vivo and in situ production of anti-HIV agents.

PO 064

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REGULATION OF HIV-1 LATENCY AND EXPRESSION BY THE BALANCE BETWEEN STAT5 AND C-TERMINALLY TRUNCATED STAT5 (STAT5Δ)

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Human immunodeficiency virus 1 (HIV-1) persists in infected individuals even in the presence of highly active anti-retroviral therapy (HAART). The issue of HIV-1 latency establishment and its reactivation is still open.
Signal transducers and activator of transcription (STAT) proteins, namely STAT1 and STAT5Δ, are frequently constitutively activated in the PBMC of most of HIV-1$^+$ individuals HIV-1. STAT5D is also the predominant isoform of STAT5 detected in HIV chronically infected promonocytic cell line (U1). U1 cells are characterized by a constitutive state of viral latency and inducibily by PMA or several cytokine. We have recently reported that STAT5Δ can act as inhibitor of HIV-1 transcription in GM-CSF-stimulated U1 cells and IL-2 stimulated PBMC of HIV$^+$ individuals due to its binding to target DNA sequence in the provirus LTR causing an impaired recruitment of RNA Pol II *(A. Crotti et al., Blood, 2007)*. GM-CSF also triggered the late activation of an ERK/AP-1 dependent pathway inducing HIV-1 expression in U1 cells. Selective inhibition of this pathway turned off, while inhibitors of STAT5 enhanced, viral expression in GM-CSF stimulated U1 cells. We also demonstrated that STAT5D can compete with STAT5 full length in activating LTR driven transcription, acting as a dominant negative. Therefore, It is interesting to better define the balance between STAT5D and full length in regulating productive vs latent viral expression, further investigating if any other host factors can be involved.

PO 065

Infection 2009; 37 (Suppl. II): 77

CPA-7, A NOVEL STAT INHIBITOR REGULATING HIV EXPRESSION IN CHRONICALLY HIV-INFECTED U1 CELLS

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Signal transducers and activator of transcription (STAT) proteins, namely STAT1 and STAT5, are frequently constitutively activated in the PBMC of most of HIV-1$^+$ individuals. We previously described that STAT5 is frequently detected as a C-terminally truncated isoform (STAT5Δ) both in infected individuals and in the chronically HIV-1 infected promonocytic cell line U1 that is characterized by a constitutive state of viral latency and inducibility of virus expression by PMA or other cytokines. STAT5Δ, like STAT5, binds to target sequences in the HIV-1 LTR but, unlike STAT5, inhibits rather than induces viral transcription in GM-CSF-stimulated U1 cells and IL-2 stimulated PBMC of HIV$^+$ individuals *(A. Crotti et al., Blood, 2007)*. GM-CSF also triggers the late activation of an ERK/AP-1-dependent pathway inducing HIV-1 expression in U1 cells. Selective inhibition of this pathway turned off, while inhibitors of STAT5 enhanced, viral expression in GM-CSF stimulated U1 cells. We are currently investigating a new platinum-based compound, termed CPA-7, reported to interfere with STAT3 activation in several solid tumor cell lines by inducing apoptosis *(J. Turkson , H. Kay et al., Mol Cancer Ther, 2004)*. CPA-7 increased HIV-1 exxpression in GM-CSF stimulated U1 cells and, surprisingly enough, also in unstimulated cells. Selective inhibition of the ERK/AP1 pathway did not alter CPA-7-mediated increased viral expression. In contrast, blocking the activation of JAK2/3 pathway led to a reduced HIV expression in U1 cells that were preincubated with CPA-7 and then stimulated with GM-CSF. These results suggest that CPA-7 may induce both STAT5-dependent and independent effects on HIV expression in U1 cells that deserve further investigations.

PO 066

Infection 2009; 37 (Suppl. II): 77

CD3ζ DOWN-MODULATION MAY EXPLAIN Vγ9Vδ2 T LYMPHOCYTES ANERGY IN HIV-INFECTED PATIENTS

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T Cell Receptor (TCR) is a multisubunit complex in which the invariant subunit CD3ζ is a 16 KDa transmembrane protein indispensable for coupling antigen recognition by TCR to diverse signal transduction pathways. Approximately 3-6% of human peripheral blood lymphocytes express the gamma delta TCR and the majority of these cells express the Vδ2 TCR variable segment associated with the Vγ9 segment, and recognize phosphorylated non-peptidic metabolites from microbial or self origin. These compounds trigger Vγ9Vδ2 T cells without antigen presentation. In vitro stimulated V Vγ9Vδ2 T cells with antigens are able to produce IFN-γ and TNF-α and exert a powerful cytotoxic activity against infected cells as HIV-infected cells. However, during HIV infection a marked decrease of Vγ9Vδ2 T cells was observed and the remaining cells are unable to respond to their non-peptidic ligands. Aim of the present work was to study the mechanisms of Vγ9Vδ2 T cell anergy observed in HIV+ patients. To this aim, CD3ζ expression and IFN- γ production by Vγ9Vδ2 T cells from HIV+ and HIV- subjects were analyzed. We show that Vγ9Vδ2 T cells from HIV-infected patients expressed lower level of CD3ζ compared with healthy donors. A direct correlation between CD3ζ expression and IFN- γ production capability by Vγ9Vδ2 T cell was found. However, PKC activation by PMA is able to restore CD3ζ expression and IFN-γ production. Our findings may contribute to clarify the molecular mechanisms of Vγ9Vδ2 T cell anergy found in HIV+ patients and have implication in the design of effective immune-based therapies.

PO 067

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CASCADE EFFECT OF IL-15, IL-17 AND IL-22 IN HIV INFECTION

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Background: Recently described T helper 17 (Th17) cells seem to play an important role in host defence against pathogens; they are characterized by the production of IL17 and IL22. Two cytokines are described to induce the development of Th17 cells: IL6 and TGF-beta-two.
Controversial data are emerging about the production and the homeostasis of Th17 in HIV infection. Recently it has been suggested that IL15 triggers the production of IL17 from PBMCs of healthy donors and patients with autoimmune disorders. Moreover in HIV+ patients the effect of plasma viremia on the production of IL17 has been argued.
Our aim was to investigate the production of IL17 and IL22 by CD4 T cells from HIV negative donors and HIV+ patients triggered by IL15.
Methods: Heparinised blood was collected by 5 healthy donors, 5 HIV+ long term non progressors (LTNP) (mean CD4 T 728,6 cells/µl; RNA 5341 cp/ml) , 5 HIV+ with sustained response to HAART (RP) (mean CD4 T 696.4 cells/µl; RNA <50 cp/ml) and 5 HIV+ with viremia >50 cp/ml under HAART (VP) (mean CD4 T 384.6 cells/µl; RNA 2305 cp/ml). PBMC were obtained by density gradient centrifugation and CD4+ cells isolated by magnetic positive selection. CD4 T cells (2x106/ml) were cultured in 24 well plate for 72 hr in presence and absence of PMA (1nM) and IL15 (10 and 50 ng/ml). Donors CD4 T cells were cultured with IL15 (100 ng) alone and in presence of anti-IL15 mAb (3 µg). IL17 and IL22 concentrations were quantified in culture supernatants by standard ELISA.
Results: We observed that IL15 induces IL17 secretion from CD4 T cells of HIV+ patients.
IL17 concentrations in supernatant cultures from CD4 T cells stimulated with IL15 were significantly lower in VP and in LTNP patients respect to healthy donors; any significative difference was observed between RP and healthy donors. In presence of anti-IL15 mAb we observed the reduction of IL17 concentrations induced by IL15.
Moreover IL 22 concentrations were also increased by the presence of IL15 in the cell cultures in all patients. All groups responded to PMA in IL17 and IL22 production.
Conclusions: IL15 is able to stimulate CD4+ T cells from HIV+ patients to secrete IL17 an IL22 confirming the role of IL15 in Th17 induction.
CD4 T cells from patients with detectable plasma viremia are less responsive, than healthy donors and RP, to IL15 stimulation in producing IL17: this data suggest either a lower frequency of CD4 Th17 cells in this patients or an impairment of their functions.

PO 068

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PROGNOSTIC EVALUATION OF NK CELL IMBALANCES BEFORE CD4-GUIDED TREATMENT INTERRUPTIONS ASSOCIATED TO THE DURATION OF ANTIRETROVIRAL TREATMENT INTERRUPTION

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The introduction of HAART has positive effects in the management of HIV-1+ patients with immune reconstitution and viremic control. Long-term metabolic side effects may represent a relevant burden when the treatment is maintained along the time. For these reasons, CD4-guided treatment interruption (TI) has been evaluated to address this point in patients with sustained successful control of viremia and immune reconstitution. TI results in a wide spectrum of time off-HAART in different patients. Here we studied whether differences in innate immune responses, in particular NK cells, may be associated to patterns of longer (LT) or a shorter (ST) treatment interruption period.
Clinical cohort parameters were analysed on a group of 8 LT and 8 ST patients. Cryopreserved PBMC collected before TI were stored at -140°C until used. Cytofluorimetric analysis was performed to determine NK cell phenotype and specific function by γ-IFN production. Phenotypic analysis of NK cells was performed on PBMC by four-colour cytofluorimetry using mAbs specific for activating and inhibitory NK receptors. In addition intracellular γ-IFN production was evaluated after challenge with NK-sensitive target cells and/or with anti-Natural Cytotoxicity Receptors (NCR) mAbs.
LT and ST patients had significant differences in HAART-free time post-TI (27,5±11,51 /4,6±1,94 months, respectively) with comparable median CD4+ T cell count nadir (327±60,27/µl and 334±135,7/µl respectively). At TI, median CD4+ T cell counts were 568,5±373,35 and 733,5±190/µl, while CD8+ T cell proportions were 38,5±10,38% and 45,5±6,50% for patients with LT and ST respectively.
In all patients persistent NK cell activation is evident despite immunoreconstitution and control of HIV replication. More importantly, persistent deficiency of NCR expression was observed in this group of patients under long-term successful HAART. With regard to the expression of some triggering surface NK cell receptors, relevant differences were observed in those patients who develop an LT course on TI vs. ST patients. Lower expression of NCRs on NK cells was evident. While this does not translate in different γ-IFN production in redirected functional assays, total γ-IFN production was impaired in LT.
NK cell phenotype and function may represent an additional parameter useful for the prognostic identification of patients who may undergo safe prolonged treatment interruption. Additional studies to evaluate larger patient cohorts and to the underlying mechanisms are warranted.

PO 069

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ANALYSIS OF HIV-SPECIFIC CELLULAR IMMUNE RESPONSE IN LONG-TERM NONPROGRESSORS, CHRONICALLY INFECTED PATIENTS UNDER ANTIRETROVIRAL THERAPY AND PATIENTS CONTROLLING VIRAL REPLICATION IN ABSENCE OF ANTIRETROVIRAL THERAPY

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The development of an efficacious HIV vaccine, that is absolutely needed due to the worldwide spreading of the infection, requests informations about the immune correlates that allow a successful control of the HIV-1 infection. Features of T-cell response are of particular interest, because cell-mediated immunity has been shown to play a key role in controlling HIV infection. The aim of our study was to elucidate the characteristics of Tat and Nef-specific T-cell responses associated with HIV-infection control, by analyzing and comparing T-cells immunity towards these two viral antigens in 5 patients cohorts with different clinical evolution of their HIV infections. T-cell response was analyzed in Elispot assay, to investigate its breadth, magnitude and specificity at the single peptide level. Our studies indicate that T-cell response to Tat is an important component of the antiviral immunity, characterizing seropositive individuals who are able to naturally control HIV replication: in these patients, Tat-specific cellular response is more frequent, higher and wider than in other cohorts, recognizing selected epitopes of the viral protein. T-cell response to Nef is not only frequent in HIV-infected patients from any cohorts, but is also largely dependent to the level of viral load, that correlates with its magnitude. Even if the presence of a Nef-specific response in HIV positive individuals does not guarantee the control of the viral replication, recognition of a higher number of distinct epitopes correlates with the natural control of the HIV replication.
Further investigations with a polychromatic flow cytometry approach, combining the simultaneous detection of phenotypic markers (CD3, CD4, CD8), functional markers (INF-γ, IL-2, CD-154 and MIP-1β) and a marker of T-cells maturation (CD45RA) are in progress; these studies are aimed to evaluate the functional phenotypes of HIV-specific T-cell subsets.

PO 070

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ANALYSES OF NUMBERS AND FUNCTION OF T REGULATORY CELLS FROM PERIPHERAL BLOOD MONONUCLEAR CELLS OF HIV LONG-TERM NONPROGRESSORS AND PROGRESSORS

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T regulatory cells are an important subpopulation of lymphocytes that are involved in immunosuppression and affect immune responses against infectious agents. They are mainly defined by high levels of expression of the alpha chain of the IL-2 receptor (CD25) and presence of the transcription factor FOXP3. Additionally, they show constitutive expression of OX40 molecule, that when cross linked with OX40L inhibits their suppressive function. In our study we enrolled HIV infected patients, naive to ART with progressive infection and long-term non progressors (LTNP) whose infection did not progress clinically for more than 8 years and whose CD4 T cell counts were always above 500 cells/μL. Our preliminary results show that the number of T regulatory cells among peripheral blood lymphocytes and mRNA expression of FOXP3 are not significantly different between LTNP and progressors. Although proliferation of T cells in response to PHA stimulation was higher in LTNP patients, the measure of T regulatory cells activity by using OX40L did not reveal significant differences between the two groups. Also, no significant differences in expression of CXCR4 were present in T regulatory cells of the 2 groups. Significantly ($p<0.05$) higher levels of IL-10 were detected in supernatants of PBMC cultures of progressors compared to LTNP, while IFN-γ was higher in LTNP's although not at significant level. Statistical analyses of correlation between T regulatory cells and viral load did not show significant association in any of the studied groups. In conclusion, our preliminary data show that there are not significant differences between peripheral blood natural T regulatory cells of progressors and LTNP. Additionally, lack of difference in expression of CXCR4 on T regulatory cells between the studied groups implies also that there might not be any differences in infection rate of the Tregs from LTNP and progressors. Although significant differences in expression markers of T regulatory cells were previously reported in lymphoid tissues of LTNP and progressors there is lack of such evidence in peripheral blood. From our preliminary study it seems that T regulatory cells do not predict or reflect disease progression or long-term non progression. IL-10 production is significantly different between studied groups and this cytokine is also produced by regulatory T cells that develop during adaptive antigen responses that will be the focus of our further investigations.

PO 071

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HIV-1 INFECTED LONG-TERM NON PROGRESSORS IN COMPARISON TO PROGRESSORS SHOW HIGH IL-15 EXPRESSION IN MONOCYTES AND CLOSELY REGULATED SYSTEM OF EXPRESSION OF GENES FOR IL15/IL15RALPHA CHAIN

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Background: Homeostatic imbalance of T cells is a key feature of HIV-1 infection and results in functional defects in various lymphoid organs. However, a minority of HIV-1 infected patients, called long-term non progressors (LTNP), are able to maintain a stable CD4 T cell count and their infection does not progress for many years. We sought to investigate if one of the T cell homeostatic factor, interleukin-15 and its receptor, can be differentialy expressed in monocytes of patients with different rates of progression to AIDS.
Methods: Studied groups consisted of HIV infected LTNP and HIV progressorss. Expression of IL-15 and IL15R as assessed by means of flowcytometry, was investigated in blood CD14+ monocytes and in these cells after overnight stimulation of peripheral blood mononuclear cells with IFN-gamma. Gene expression analyses for IL15 and alpha chain of IL15R were performed by use of double dye RT-PCR method and adjusted for house keeping gene expression analyses. Statistical analyses were performed by Kruskal-Wallis test and Dunn's multiple comparison test.
Results: Our data show that LTNP have a significantly ($p<0.05$) higher percentage of CD14+IL-15+ monocytes than patients with disease progression who never received antiretroviral therapy. We have also observed higher expression of IL15R on monocytes of LTNP patients than in progressors but the difference was not significant and the stimulation with IFN-gamma did not cause its further upregulation. In contrast to IL15R, intracellular expression of IL15 was found to be highly upregulated by IFN-gamma stimulation and only at significant ($p<0.05$) levels in monocytes of LTNP patients. In progressors such an effect was almost completely absent. Moreover, gene expression for IL15 and IL15R alpha chain in PBMC and stimulated PBMC showed high correlation ($p<0.05$ and $p<0.005$ respectively) only LTNP. Analyses of activation markers, CD38 and PD-1 on CD4 and CD8 T cells showed that progressors are at higher level of immunoactivation than LTNP and IFN-γ stimulation did not cause enhanced expression in any group.
Conclusions: We show that despite lower state of immune activation or due to this reason, monocytes of HIV LTNP in comparison to progressors show higher levels of IL-15 expression in monocytes. The expression of this cytokine in monocytes of LTNP but not progressors can be further enhanced by addition of IFN-γ. We also show that in contrast to progressors, IL15 and IL15R alpha chain genes expression are possibly expleining the differences at protein levels. Given the anti-apoptic and pro-activating properties of IL-15 toward CD8 T cells, the increased levels of this cytokine in LTNP patients may explain the presence of highly functional HIV-specific CD8 T cells in these patients, able to control HIV replication and preserve CD4+ T cells and indicate a target for therapeutic interventions.

PO 072

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IFN MAY PREVENT VIRAL REBOUND AFTER HAART INTERRUPTION IN HIV PATIENTS: POSSIBLE INVOLVEMENT OF PLASMACYTOID DENDRITIC CELL ACTIVATION

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Background: Early clinical trials showed that IFN treatment was able to delay AIDS progression and prolong survival. More recently, it has been shown that IFN may favourably affect the efficacy of HAART. Plasmacytoid dendritic cells (pDC) may play an important role in the control of HIV replication, and these cells are activated by IFN. The aim of this study was to evaluate the efficacy of Peg-IFN in the control of HIV viral rebound in patients who interrupted HAART and to explore a possible involvement of pDC in this immunomodulatory effect.
Methods: A subgroup of 6 HIV-HCV coinfected patients (Group A), among 26 HIV- HCV patients who started IFN treatment for liver disease, were treated with Peg-IFN α2b at a dose of 1.5 µg/kg, subcutaneously concomitantly with the HAART discontinuation. As controls HIV-1 monoinfected patients who interrupted HAART for any reasons were considered (Group B). The activation state of plasmacytoid dendritic cells (pDC) was evaluated by flow cytometry before and after 7, 28 and 56 days of treatment.
Results: Five of the 6 patients who started IFN concomitantly with the HAART discontinuation (Group A) showed complete control of viral rebound for at least 4 weeks, with a delayed resumption of viral replication with respect to the control group (Group B).
In the patients who controlled HIV rebound, baseline expression of CD80 and CD86 on pDC was up-regulated at day 7 from treatment start, and remained stable throughout the follow-up; in the unique patient who did not control HIV rebound, the baseline expression of CD80 and CD86 on pDC was higher, and was not further increased after IFN administration.
Conclusions: Although the small number of enrolled patients does not allow to reach a firm conclusion, our data strongly suggest that IFN administration in concomitance of HAART discontinuation may boost innate immunity mechanisms potentially involved in the control of HIV replication. Activation of pDCs may play a role this context, as one of the mechanisms involved in the IFN-driven control of viral rebound.
IFN administration in concomitance of HAART discontinuation may be considered a promising approach to minimize some of the detrimental effects of therapy discontinuation. If feasible and maintainable for long enough periods of time, this approach should be able to substantially prolong the effectiveness of antiretroviral agents also during limited therapy interruptions, hence minimizing toxicity, enhancing patient survival and reducing antiretroviral drug costs.

PO 073

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MAGNIFYING GLASS ONTO THE IMMUNOLOGIC STATUS OF A COHORT OF UNTREATED HIV+ PATIENTS

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Objective: 1) to analyze percentages and numbers of different T and B cells populations thought to be involved in lymphocytes homeostasis or in fighting the HIV infection together with markers and predic-

tors of disease progression; 2) to compare the above variables between untreated HIV-infected patients and a group of antiretroviral treated patients (ART) with full virological ART response.
Methods: 40 antiretroviral-untreated HIV-infected individuals, 4 Elite Controllers (patients with a follow-up longer than 10 years who spontaneously control HIV replication to undetectable levels in the absence of therapy) and 20 ART experienced HIV-infected subjects were recruited. Lastly, 34 age-matched healthy controls (HC) were enrolled. Predictors for disease progression (CD38 and HLA-DR), naïve, memory, effector CD8+ T cells, CD127-CD8+ T lymphocytes (proposed to be effector-like T cells in HIV- individuals), regulatory T cells (TREGS), apoptosis prone annexinV+ T cells and, finally, different populations of B cells (CD21+/-CD27+/-) were investigated in a cross-sectional study. Moreover, main markers (numbers and percentages of CD4 cells and plasma viremia) were longitudinally followed for more than 2 years (but also retrospectively recovered from our data base) in all HIV-patients.
Results: 1) Many significant immunologic abnormalities were found in untreated HIV-patients compared to HC. Among them, higher percentages and numbers of activated CD8+ T-cells ($p<0.01$ for both DR and CD38) and of CD8+CD127- T lymphocytes ($p<0.01$) or of annexinV+ CD8+ ($p<0.01$) were recognized. By contrast, lower percentages of naïve (CD45RA+CCR7+, $p<0.01$) but higher values of terminal differentiated effector memory (TDEM, CD45RA-CCR7+, $p<0.05$) CD8+ T cells were detected.
2) When ART -treated patients were analyzed we found that significant higher percentages of activated and CD127- CD8+ T cells compared to HC were still present although a virological control and normal numbers of CD4+ T cells (but not of percentages) were established in these patients. However, levels of naïve, TDEM and CD8+annexin+ T cells were similar to those in HC. Interestingly, as far as the B-cell compartment is concerned, the CD21-CD27+, CD21-CD27-, and CD21+CD27- lymphocytes, whose proportions were altered in untreated patients compared to HC ($p<0.01$), did not differ significantly in ART treated individuals compared to HC.
Conclusions: Herein we show that several multiple immunologic abnormalities of both T and B cell compartments are present in the ART-naïve HIV-population. Some of these defects were apparently corrected by effective ART. The study of multiple immunologic parameters in combination allowed us to derive useful information on the immune status. Further longitudinal studies should clarify and weight the value of different immunologic determinations as predictors of disease progression, markers of immunological response to treatment or to therapeutic T/B vaccinations.

PO 074

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NEUTRALIZATION IMMUNITY LINKED TO THE PROGRESSION TO HIV-1 DESEASE IN A WELL CHARACTERISED COHORT OF LONG TERM NON PROGRESSORS

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The World Health Organization extimated that approximately 33 million of people were HIV-1 infected in 2008. Even if preventive measures and antiretroviral therapy are a priority, introduction of an active immunoprophylaxis will be a chance to change this epidemic. For this reason an important goal is to identify immunological correlates of control and prevention of the infection.
Some individuals, defined as Long Term Non Progressors (LTNP), present a course of HIV-1 disease characterized by absence of symptoms for at least 10 years from the sero-conversion. The emergence of symptoms thereafter defines the group of Late Progressors (LP). In our study we took advantage of a very well characterized cohort of LTNP and LP followed during approximately 12 years: two LTNP remained asymptomatic for more than 21 years with CD4+ T cells counts above 500/µl, whereas four patients progressed after 11-19 years, their CD4+ T cell counts dropped and were in need of antiretroviral therapy. Virus isolates were obtained from the culture of the PBMC of the individuals when still asymptomatic. Five to seven sera for each individual were tested against isolates of the cohort and three virus isolates of unrelated patients in a classical PBMC-based neutralization assay to study the autologous and the cross neutralizing capacity.
Sera from two LP showed an absence or low neutralizing activity towards their own viral isolates (autologous neutralization), while the only LTNP tested displayed an autologous neutralization with increasing titers during the follow up. The heterologous primary viral isolates (of the cohort) are neutralized with variable titers with sera from LP but not with those of LTNP. Cohort unrelated viral isolates (SF162, QH0692 and J500) did show an association with the stage of disease depending on the neutralization's sensitivity of the isolate known from the litterature
Those preliminary results suggest that in LP the increasing viremia during the disease progression is able to induce a heterologous cross neutralizing activity that is absent in LTNP characterized by low viral load. In addition the absence of disease progression could be linked to a strong antibody response toward the autologous isolate, as detected in the LTNP.

PO 075

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DIFFERENTIAL MODULATION OF INHIBITORY AND ACTIVATORY NATURAL KILLER RECEPTORS EXPRESSION ON CIRCULATING CD3+VDELTA1+ CELLS FROM ELITE CONTROLLER HIV+ PATIENTS

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Background: Circulating T cells bearing the gamma/delta T cell receptor are rapidly affected after HIV infection: Vdelta1 T cell population, normally found among Intraepithelial lymphocytes, becomes the main component of gamma/delta T cell circulating pool. Vdelta1 T cells display NK-like cytotoxicity capability, sharing with NK cells the activatory and inhibitory surface receptors. Vdelta1 T cell expansion has been related to mechanisms such as stress-related molecules, B-cell related signals, cytokines in the context of response to microbial components, or NKR-related stimulatory signals. Vdelta 1 T cells may play a relevant pathogenetical role in lysing HIV-infected and bystander uninfected CD4 T cells.
Long-term non-Progressor (LTnP) and Elite Controller (EC) patients represent a very small population of HIV-infected patients that for a very long time and in the absence of antiretroviral treatment spontaneously control CD4 depletion (LTnP: CD4>500 cells/microl)) and HIV replication (EC: plasma HIV-RNA<1000 cp/ml), thus representing the only occurrence of natural control of HIV infection.
Aim of our work was to study circulating Vdelta1 T cell population in LTnP and EC patients. As control, HIV+ progressor (PR) patients and HIV- healthy donors (HD) were used.
Patients and methods: On the INMI LTnP/EC cohort (11 LTnP, 6 EC) circulating Vdelta1 T cell population was analysed for frequency and NKR expression, and compared to 10 HIV+ untreated progressor pa-

tients and 10 HIV- healty donors. In particular, inhibitory NKR (NKG2A, KIR3DL1, CD94, CD158A, LAIR1, NKB1, ILT2 and CD161), activatory NKR (NKG2C, NKG2D, CD244, NKP80, KIR2DL4 and NKP46), as well as DNAM1 adhesion molecule, were studied by flow cytometry.
Results: As expected, PR patients showed a significant Vdelta1 T cell expansion when compared to healty donors; on the contrary, LTnP and EC patients expansion was below the significance level. DNAM1 adhesion molecule and NKP46 activatory receptor expression on Vdelta1 T cells were significantly decreased on all HIV+ patients groups in comparison to HD. In EC, a significant increase in activatory NKP80 receptor was found in comparison to HD. Finally, a specific modulation of inhibitory receptors expression (increased CD158a and ILT2, decreased NKG2A and KIR3DL1) was found in EC in comparison to PR.
Conclusions: The specific differential modulation of Natural Killer Receptors expression on circulating CD3+Vdelta1+ cells from Elite Controller HIV+ patients may be related to the very peculiar status of these patients. Further studies are ongoing, aimed to define the functional role of these changes in EC protection.

PO 076

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LONG-TERM ANTIRETROVIRAL THERAPY IN HIV-1 INFECTED PATIENTS REDUCES CELLULAR IMMUNE ACTIVATION MARKERS TO LEVEL DETECTED IN UNINFECTED INDIVIDUALS

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Background: HIV-1 RNA persists at low levels in patients with prolonged viral suppression on antiretroviral therapy (ART), but the effect of low-level viremia on immune activation is poorly understood. Levels of T cell activation are a higher in HIV infected individuals with uncontrolled viral replication than HIV negative subjects and decrease when viral replication is suppressed on ART. In order to characterize the degree of immune response to low-level viremia, we conducted a case control study of long-term suppressed patients on ART and compared levels of T cell activation markers in HIV-1 infected and uninfected individuals.
Methods: Methods: HIV-1 infected patients enrolled in natural history studies of HIV-1 infection at the NIH NIAID/CCMD clinic, on first-line ART, HIV-RNA <50 copies/ml for at least 7 years, no viral blips (≥ 2 consecutive HIV-1 RNA ≥ 500). Samples from HIV-1 uninfected individuals were obtained from healthy donor volunteer program at NIH. HIV-1 infected and uninfected individuals were matched with respect of gender, age and race. Standard immunophenotyping was performed, relative levels of immune activation were determined as expression of HLA-DR and CD38 on CD8+ T cells. HIV-1 RNA was measured by bDNA. Relative levels of cell subtype analyzed with parametric statistical methods and corrected for multiple comparisons. Values expressed as median (IQR) or frequencies (%).
Results: HIV-1 positive patients (pts, N=31) were compared to HIV-1 negative controls (N=43); 24(77%) and 26(61%) were males in pts and controls respectively. Age was 44(42-50) and 42(24-51) years respectively. Race distribution was: White 14(45%) and 28(65%), African-American 7(22%) and 3(7%), Asian 2(6%) and 1(2%), Hispanic 4(13%) and 3(7%) in pts and controls respectively. Results are shown in Table-1. After seven years on ART we found a significant decline in relative levels of CD8+HLA-DR+ and CD8+CD38+ T cells compared to pre-therapy ($p<0.0001$ and $p<0.0001$ respectively). Relative levels of CD8+HLA-DR+ T cells, CD8+CD38+ T cells and CD8+CD38+HLA-DR+T in HIV-1 infected patients after long-term viral suppression on ART did not differ from levels observed in HIV-1 uninfected individuals ($p=0.099$, $p=0.176$ and $p=0.604$ respectively).

Table-1

	HIV-RNA (Log copies/ml)	CD4 + (cell/mcl)	CD8+ (cell/mcl)	CD8+ HLA-DR+ (% cell/mcl)	CD8+ CD38+ (% cell/ mcl)	CD8 + CD38 + HLA-DR+ (% cell/ mcl)
Pre-therapy	4.73 (4.37-504)	250 (174-361)	680 (549-909)	31 (26-40)	46 (42-53)	NA
After year 7	1.69 (1.69-1.69)	608 (444-724)	641 (487-775)	23 (15-29)	21 (16-24)	12 (8-15)
HIV-subjects	NA	804 (614-1068)	487 (310-695)	17 (11-23)	17 (12-21)	6 (10-16)

Conclusion: Long-term suppression of HIV-1 replication by ART reduces T cell activation to levels detected in uninfected subjects. These data show that low-level viremia is an insufficient stimulus for T cell activation, providing indirect evidence of the absence of ongoing HIV-1 low-level replication in patients with long-term viral suppression.

PO 077

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INCREASED EXPRESSION OF WERNER RECQ HELICASE IN PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMC) OF HIV-1 INFECTED PATIENTS

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Objectives: Werner (WRN) is a DNA helicase involved in several metabolic pathways, such as cellular genome repair, replication, and recombination. We previously described increased levels of WRN expression in PBMC from HIV-infected persons (*Human Immunology 68, 2007)* and Sharma A et al. demonstrated the role of WRN as cofactor for HIV-1 transcription and replication (*J Biol Chem 16, 2007*). Aim of the present study was to analyse the steady-state level of WRN gene and protein in total PBMC and in the main subsets of T cells (CD4+ and CD8+ T-cells) obtained from HIV-1 infected patients at different stage of disease as compared to healthy donors (HD).
Methods: WRN expression was measured by *real-time PCR;* the protein expression was analysed by immunocitochemistry with specific monoclonal antibody. Both determinations were carried-out in total PBMC and in different subsets of PBMC isolated by magnetic beads (CD4-positive and CD8-positive T lymphocytes, CD14-positive and residual cells) obtained from HD and from HIV-infected individuals in chronic or in acute phase of disease and from Long-term-Non-Progressors (LTNP) HIV-infected patients.
Results: The increase of WRN gene expression observed in HIV-infected individuals results positively correlated with patients age, with the time of HIV-1-seroconversion and, interestingly, with the stage of disease. In fact, in patients in acute phase of disease and in LTNP individuals, levels of WRN expression are similar to values measured in HD. In chronically-infected individuals, a 3.2-fold higher mean level

of WRN mRNA expression is observed in comparison with HD ($p<0.0001$). CD4 and CD8 T cells are the main subsets showing higher levels of WRN mRNA. Immunocytochemical analysis of WRN expression, performed both in total PBMC and in different subsets, concurs with data indicating increased WRN mRNA expression. Moreover, a positive correlation has been observed between WRN expression levels and CD4 absolute counts.
Conclusion: The increased expression of WRN observed in T cells from HIV-infected persons could be a mechanism finalised to assure the host genomic integrity and efficient viral replication in replication-competent cells. Targeting WRN helicase might be considered as a potential target of the antiretroviral therapy.

PO 078

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TH17 CELLS IN HIV-EXPOSED UNINFECTED INDIVIDUALS

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T(H)-17 cells are involved in bacterial defense, acute inflammation, and autoimmunity. Both HIV-1- and cytomegalovirus (CMV)-specific IL-17-producing CD4 T cells are detectable in early HIV-1 infection but are reduced to non-detectable levels in chronic and non-progressive HIV-1 infection. Th17 are infected by SIV(mac251) in vitro and in vivo, and are found at lower frequency at mucosal and systemic sites within a few weeks from infection.
The role of Th17 cells in the protection from HIV-infection was analysed in a choort of HIV-exposed unifected individuals.
We enrolled in the study 31 exposed uninfected individuals (ESN), 83 HIV+ patients (HIV+) and 35 healthy controls (HC). Unstimulated, HIV- and CMV-specific IL17-secreting CD4+ T cells and single nucleotide polymorphisms (SNPs) in IL-17 gene (IL-17A: rs8193037, rs3819025, rs7747909, rs3748067, rs2275913 and IL-17F: rs763780, rs11465553, rs2397084, rs11465551) were analysed.
The percentages of unstimulated, gag- and CMV-specific IL17A-secreting CD4+ T cells were significantly augmented in ESN compared to HIV+ and to HC. The higher Th17 function detected in ESN was associated with a G/A genotype of IL-17A rs8193037 SNP.
ESN are characterized by a higher frequency of the rs8193037 G/A genotype in IL-17A locus associated with a higher Th17 synthesis. These data suggest that Th17 cells are involved in protection from HIV infection; therapeutic approaches that reconstitute an adequate Th17 activity may be beneficial in the treatment of HIV infection.

PO 079

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ROLE OF NEDD8 IN HIV-ASSOCIATED LIPODYSTROPHY

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Background: The pathogenetic bases of HAART associated lipodystrophy is still poor known, even if it is clear that adipose tissue and its metabolism are sensitive to antiretroviral therapy alone and or in combination with HIV infection. NEDD8 system, is essential for the regulation of protein degradation pathways involved in cell cycle progression, morphogenesis and tumorigenesis. We investigated the possible involvement of NEED8 in adipogenesis and, consequently in HIV related lipodystrophy.
Methods: One hundred HIV-1 infected patients were included in the study. Using a in vitro model of adipogenesis we evaluated the effects on aipogenesis of the forced expression of NEDD8 together with Efavirenz, Stavudine, Saquinavir, Amprenavir and Indinavir, belonging to the three main classes of anti-HIV medications.
Results: we showed that NEDD8 expression level is higher in the peripheral blood of HIV-patients developing lipodystrophy. Coherently, forced expression of NEDD8 in an *in* vitro model of adipogenesis, was able to perturb expression of some key proteins involved in adipogenesis, such as C/EBPα and PPARγ, possibly acting throughout NEDD8/p27/β-catenin pathway. Moreover three out of five evaluated drugs, were able to affect adipocyte differentiation: Efavirenz, Stavudine and Saquinavir. Finally, we have shown that NEDD8 was expressed in fat tissue of lipodystrophic patients, being significantly higher in the lipodystrophic patients respect to the controls, thus further confirming the altered NEDD8 expression in the fat tissue of HIV infected patients affected by lipodystrophy.
Conclusion: Taken together our data support the hypothesis of an implication of NEDD8 through p27 and β-catenin pathway in disruption of adipogenesis and consequent lipodystrophy in patients affected by HIV infection under HAART therapy with qualitative and quantitative differences according to diverse anti-retroviral treatments. These evidences indicate the NEDD8/β-catenin/p27 pathway as a possible molecular target for prevention of lipodystrophy development in patients under HAART therapy.

PO 080

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V3-BASED GENOTYPIC PREDICTION VERSUS TROFILE™ FOR THE ASSESSMENT OF CO-RECEPTOR USAGE

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Introduction: Even though it increases the options for formulating antiretroviral regimens, the recent approval of CCR5 antagonists requires that patients should be preemptively tested for HIV co-receptor tropism. Failure to screen for CXCR4 usage reduces the likelihood of viral suppression and augments the risk of developing antiretroviral resistance. Currently, the assessment of co-receptor usage is based on the commercial Trofile™ performed only in a centralized laboratory and, hence, is complicated and costly. Therefore, easier and less expensive methods for determining HIV-1 co-receptor tropism are required. Several algorithms predicting HIV-1 co-receptor usage based on V3 env sequencing have been developed, but correlation between these different approaches is still unclear and discrepancies have emerged with respect to Trofile™. This study aimed to determine the inter-agreement of different V3 interpretative algorithms and their sensitivity and specificity, with respect to the phenotypic assay, in a group of HIV-1-positive patients infected with different HIV-1 subtypes at various levels of immunological impairment.
Methods: Blood samples were obtained from 70 HIV-positive subjects (72% males, 27% with non-B subtype) for virological and immunological evaluation with simultaneous Trofile™ and V3 env sequencing. The V3 sequences were interpreted using free web-available tools (PSSM, geno2pheno); moreover, a net charge (nc) of ≤5 was considered predictive of R5 phenotype, unless this was accompanied by either an arginine (R) or lysine (K) amino acid residue at positions 11 or 25 (rule 11/25+nc). According to Trofile™, isolates were classified as R5, X4, or dual-mixed (DM). The sensitivity and specificity of each genotypic method were calculated considering the phenotypic assay as gold standard. The agreement between methods was analyzed using *Cohen's k* statistics.
Results: Trofile™ classified 7% and 26% isolates as X4 and DM, respectively. The presence of a X4 or DM strain was associated with a lower CD4 number (p=0.03), independent of viral load and use of antiretroviral therapy. A sensitivity of 42%, 35% and 57% was found for geno2pheno, PSSM and 11/25+nc rule, respectively, while specificity was 92% for PSSM and 71% for geno2pheno-11/25+nc rule. The highest overall concordance was obtained between geno2pheno and PSSM (0.52), both of which showed a scarce level of concordance with Trofile™ (0.1 and 0.32, respectively). The rate of agreement between genotypic and phenotypic tests was two-fold higher in B subtypes (0.61). Both the sensitivity and specificity of each genotypic method, and the agreement between methods, increased if DM strains were excluded from the analysis.
Conclusions: A low sensitivity for co-receptor usage emerged for all genotypic algorithms compared to Trofile™, principally due to the presence of DM isolates and non-B subtypes.

PO 083

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EXPRESSION OF NATURAL KILLER CELL RECEPTOR GENES IN HIV-INFECTED PATIENTS LACKING CD4 RECOVERY ON LONG-TERM HAART

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Background. Natural killer (NK) cells provide a major component of the antiviral immune response by recognising and killing virally infected cells. NK cells modulate their activity through a combination of inhibitory and activatory receptors such as the killer immunoglobulin-like receptors (KIRs) that bind to human leukocyte antigen (HLA) Class I molecules. Genetic diversity of immune response genes, such as HLA and KIR loci, holds promise for explaining the variability in outcome to viral infection amongst individuals. We addressed the influence of KIR genotypes on the immunological response to antiretroviral therapy (cART) in a population of chronically infected HIV-patients.
Methods. We studied 62 HIV-infected patients with complete virological response but different immunological response to at least 12 months of cART: 13 immunological non responders (CD4<200/μl) and 49 full responders (CD4>350/μl). 44 HIV-negative subjects were evaluated as healthy controls. Molecular KIR (presence or absence of KIR2DL1, 2DL2, 2DL3, 2DL4, 2DL5A, 2DL5B, 2DP1, 2DS1, 2DS2, 2DS3, 2DS4*001/2, 2DS4*003/7, 2DS5, 3DL1, 3DL2, 3DL3, 3DP1*003, 3DS1) were typed using polymerase chain reaction-based genotyping. Fisher exact test was used for statistical analysis.
Results. A statistical significant difference in the expression of natural killer cell receptor genes was observed in the analysis of the different pattern of immunoreconstitution after cART introduction. Interestingly, immunological non responders displayed a strong significantly lower frequency of KIR2DL3 compared to full responders (82% versus 15%, p<0.001). Conversely, HIV-infected full-responders expressed levels of KIR2DL3 comparable to healthy controls (82% versus 93%). No differences in the other KIR genotypes were detected in immunological non responders compared to full responders HIV-patients. Globally, the expression of other KIR genes was not significantly different between HIV-infected and uninfected patients.
Conclusions. This study evidence the important role of the Expression of natural killer cell receptor genes in modulating different pattern of immunoreconstitution after cART. Compared to complete viro-immunological responders, immunological non responders display a significant reduction in KIR2DL3 expression. Further studies are needed to assess the mechanisms and molecular interactions between KIR, HLA and c-ART-induced immunological recovery.

PO 084

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GENERATION OF VIRUS-LIKE PARTICLES EXPRESSING DIFFERENT HIV-1 GLYCOPROTEINS FOR INDUCTION OF BROADLY NEUTRALIZING ANTIBODIES

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Elicitation of a potent and broadly neutralizing antibody response is the main goal of an effective HIV-1 vaccine. Considering that all the described and available broadly neutralizing MAbs target the envelope glycoproteins of HIV-1, a vaccine aiming to induce such a humoral broadly neutralizing response must be based on HIV-1 envelopes. In particular, given that soluble proteins fail to efficiently induce a potent immune response, it has been shown by us and others that the expression of env glycoproteins on the surface of particulate structures, such as virosomes, pseudovirions or virus-like particles (VLPs), could be a more efficient way to deliver conformational epitopes to the immune system. In particular, VLPs generated in our laboratory expressing a HIV-1 envelope gp120 of the subtype A have been previously shown to induce cross-clade neutralizing antibodies at systemic as well as mucosal sites. Moreover, it has been lately proposed that a broadly neutralizing antibody response could be induced by focusing the immune response on envelope regions known to be target for broadly neutralizing monoclonal antibodies.
Aim of this study is to produce in a Baculovirus expression system, within the FP7 EU-funded NGIN project, VLPs based on HIV Pr55gag protein, displaying on their surface either the gp140 HIV-1 envelope glycoprotein of the subtype A or the HIV-1 gp41 sequences covering the ectodomain region.
Molecular constructs containing different transmembrane sequences have been generated for the A-clade gp140 and the gp41 regions to evaluate the expression of envelope molecules on the surface of VLPs. Moreover, mutations in the gp140 glycoprotein sequence have been introduced in order to stabilize gp120-gp41 association as well as gp41-gp41 interaction and overcome the structural instability of env trimers. Recombinant Baculovirus DNAs have been used for VLP production in High5 insect cells and purified particles have been analyzed for protein expression.
The generation of VLPs expressing on their surface either trimeric gp140 env glycoproteins or gp41 domains will allow to evaluate the induction of humoral response *in vivo* and the broadness of its neutralizing activity against a panel of autologous and heterologous field isolates.

PO 085

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ANTI-HIV-1 RESPONSE ELICITED IN RABBITS BY ANTI-IDIOTYPE MONOCLONAL ANTIBODIES MIMICKING THE CD4-BINDING SITE ON GP120

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The anti-human immunodeficiency virus type 1 (HIV-1) immune response is erroneously focused on highly variable regions of HIV-1 surface glycoproteins not fundamental to viral replication. However, crucial conserved portions (as the CD4-binding site - CD4bs - on gp120) exist but are not exposed to the immune system. Classical antigen-based vaccine approaches are not able of stimulating antibodies against these regions. In this study we describe the generation of two anti-idiotype (AI) murine antibodies recognizing anti-CD4bs IgG purified from long-term non-progressor (LTNP) patients. The mAbs were shown to react with b12, the most potent anti-CD4bs human mAb, and to elicit in rabbits anti-HIV-1 antibodies confirming them as CD4bs mimotopes. The same mAbs were also used to detect the presence of anti-CD4bs antibody subpopulations in the serum of infected patients.
To obtain the murine mAbs with AI features, anti-CD4bs IgG were purified from LTNP through several purification steps. The purified IgG were then used as Fab fragments to immunize mice for hybridoma generation. Hybridomas P1 and P2 only reacting in ELISA with the anti-CD4bs IgG, and not with standard IgG, were used to immunize rabbits. CD4bs-mimicking P1 and P2 antibodies recognized the idiotype of the widely neutralizing anti-CD4bs b12 human mAb, and inhibited its binding to gp120. P1 and P2-immunized rabbit sera showed a strong anti-gp120 titer associated to a neutralizing activity in a pseudovirus assay (HXB2 strain). In particular, 3/5 rabbits in the P1 group and 1/5 in the P2 group showed an 80% neutralization at dilutions ranging from 1:20 to 1:150. In the case of two rabbits an 80% neutralization was also shown against virions bearing glycoproteins from a different strain (MN).
This proof-of-concept study describes the first epitope-based vaccinal approach performed recurring to CD4bs-mimicking AI molecules. Although comparison of different immunization protocols will be necessary to improve the strength and the breadth of the neutralizing response, these data document that immunogens designed on the idiotype of broadly neutralizing Abs are feasible and could help in the design of future anti-HIV strategies.

PO 086

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MOLECULAR IMMUNE SIGNATURES OF HIV-1 VACCINES

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We have recently shown that HIV-1 Pr55gag Virus-Like Particles (HIV-VLPs), produced in a baculovirus expression system and presenting a gp120 molecule from an Ugandan HIV-1 isolate of the clade A (HIV-VLP_As), induce maturation and activation of monocyte-derived dendritic cells (MDDCs) with a production of Th1- and Th2-specific cytokines. Furthermore, HIV-VLP-loaded MDDCs are able to induce a primary and secondary response in autologous human CD4+ T cells, in an *ex vivo* immunization assay.
In the present study we show that similar data can be obtained directly on fresh peripheral blood mononuclear cells (PBMCs) and the HIV-1 seropositivity status, with either low or high viremia, does not significantly impair the immune activation status and the responsiveness of circulating monocyte CD14+ cell populations to an immunogenic stimulus. Some HIV-1 seropositive subjects, however, show a complete lack of maturation induced by HIV-VLPs in CD14+ circulating cells, which does not consistently correlate with an advanced status of HIV-1 infection.
The established Th2 polarization in both HIV seropositive groups is efficiently boosted by HIV-VLP induction and does not switch into a Th1 pattern, strongly suggesting that specific Th1 adjuvants would be required for a therapeutic effectiveness in HIV-1 infected subjects.
Moreover, global transcriptional profile of PBMCs stimulated with VLPs has been evaluated, showing that baseline activation of chemokine production was observed in PBMC from HIV infected patients and immune stimulation with HIV-VLPs was not blunted.
These results indicate the possibility of screening PBMCs for donor susceptibility to an immunogen treatment, which would greatly simplify the identification of "responsive" vaccinees as well as the understanding of eventual failures in individuals enrolled in clinical trials.

PO 087

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A NEW ANTIGEN-SCANNING STRATEGY TO MONITOR T-CELL IMMUNE RESPONSES

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Delineation of the immune correlates of protection during natural infection and after vaccination is a mandatory step for vaccine development. Although the most recent techniques allows a sensitive and specific detection of the cellular immune response, there is not yet a consensus on the methods to assess the magnitude and breadth of these responses. Within the EU-granted AVIP project (http://www.avip-eu.com/) we have developed a new scanning strategy based on overlapping peptides (VOPSD) to evaluate the immune response toward candidate vaccine antigens from different HIV-1 subtypes.
T cell responses against the HIV-1 antigens Tat and Nef were measured in two cohorts of HIV-1+ individuals and two cohorts of healthy blood donors by both a standardized IFN-gamma ELISPOT assay and a multiparametric immunocytofluorimetric assay combining T-cell specific markers. Overlapping sets of peptides spanning the HIV-1 Tat (BH-10 strain; aa 1- 86) and Nef proteins (Bru strain; aa 1-205) were used. For Tat, both standard strategies (15mers or 20mers overlapping by 10aa) and the new set of VOPSD peptides were tested. For Nef only one peptide set of 20mers overlapping by 10aa was compared to the Nef sets of VOPSD peptides.
In HIV-seropositive individuals the new AVIP Tat peptide pools showed a significantly higher sensitivity (18 vs 9 responses; $p<0,0006$) than either the 15mers or 20mers sets. For Nef VOPSD peptides generated strongest responses ($p<0,0001$) enhancing both CD4 and CD8 T-cell responses as compared to the 20mers sets.
In HIV-seronegative individuals, the AVIP peptide sets generated low background responses comparable with those of the standard pools.
The VOPSD peptide sets gave highly specific and sensitive responses performing significantly better than the corresponding 15mers or 20mers peptide pools. This new strategy represents a powerful tool for screening novel HIV-1 candidate vaccine antigens in cohorts of European and African individuals.

PO 089

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GENERATION OF NOVEL RECOMBINANT HIV-1 GLYCOPROTEINSFOR EXPRESSION ON VIRUS LIKE PARTICLES

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A prophylactic vaccine represents the ultimate strategy for blocking the HIV transmission in the general population. To this challenging unprecedented scientific goal, in the last years we have developed a human immunodeficiency virus type 1 (HIV-1) vaccine model based on HIV-1 Pr55gag virus-like particles (HIV-VLPs), produced in a baculovirus expression system and presenting a gp120 molecule from a Ugandan HIV-1 isolate of clade A (HIV-VLPAs). The HIV-VLPAs show the induction in BALB/c mice of systemic and mucosal neutralizing antibodies as well as cytotoxic T lymphocytes, by intraperitoneal as well as intranasal administration.
In the present study, the generation of novel chimeric HIV gp120 and gp140 envelope glycoproteins, presenting heterologous Signal Sequences and/or Trans-Membrane regions, has been planned to improve the density and the trimeric conformation of the molecules presented on the surface of the HIV-VLPs. Moreover, aminoacid substitutions in the gp140 glycoprotein sequence have been designed in order to stabilize gp120-gp41 association as well as gp41-gp41 interaction.
HIV-1 gp120 or gp140 chimeric genes, based on the Ugandan HIV-1 isolate of clade A, have been generated and transposed into baculovirus-based bacmids for expression in insect cells. Analyses of the VLPs expressing such novel chimeric HIV envelope glycoproteins are currently ongoing.
The development of novel HIV envelope glycoproteins presented as stable trimeric complex on the surface of VLPs and possibly exposing broadly conserved epitopes should allow the efficient induction of systemic as well as mucosal humoral response with a broad neutralization activity on different HIV field isolates.

PO 090

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SEXUAL AND NON-SEXUAL TRANSMISSION OF HHV-8: IMPORTANCE OF ORAL TRANSMISSION AND GENOTYPING

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Several epidemiological data support HHV-8 sexual transmission: A)virus seroprevalence is higher in male homosexual individuals, particularly when affected by other sexual transmitted diseases. B)there is evidence on HHV8 transmission through seminal liquid in HIV affected patients C) there is association between HHV8 infection and the number of sexual partners and it is also interesting the significant co-infection by HHV8 and bowel infections, particularly spread over homo- and bisexual population, probably due to sexual-associated oro-fecal exposure D)although infection among heterosexual population is significantly lower, studies on prostitutes, demonstrate a higher seroprevalence in this group compared to female general population. Virus has been detected in prostatic epithelial cells, while it was absent in cervical cells, suggesting this is not a relevant replication site.
In Italy does not exist a numerous survey on HHV8 sexual transmission; nonetheless a study performed in Western Sicily points out the role of sexual behaviour in the transmission of the infection in adults. Crude seroprevalence to HHV8 antigens was 11.5% in the general population, and it increased significantly with age from 6% under age 16 to 22% after age 50. Significantly higher HHV8 seroprevalence rates were detected among HIV positive and negative homosexual men (62% and 22%, respectively), men who had sex with prostitutes (40% and 29%, respectively); female prostitutes (42% and 30%, respectively), and clients at a sexually transmitted disease clinic (male: 60% and 33%, respectively, female: 63% and 43%, respectively). In contrast, heterosexual intravenous drug users had seroprevalence rates comparable to those found in the general population.
The last studies concentrate on HHV8 non-sexual route of transmission, probably occurring during childhood due to close personal contact. Saliva may be infact a potential source of HHV8 spreading in general population. Also in our studies performed on classical Kaposi's sarcoma (cKS), a significantly higher seroprevalence among familial members of cKS patients than in healthy controls living in the same geographic area and the presence of the same HHV8 genotype within the same family suggests intrafamilial transmission via a non sexual route. Moreover we found a significant prevalence of genotype A in cKS patients with fast progression; these data would suggest a more careful monitoring and perhaps aggressive therapies in these patients.

PO 091

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GBV-C–DRIVEN CROSSTALK BETWEEN DIFFERENT COMPARTMENTS OF INNATE IMMUNITY AS POSSIBLE MEDIATOR OF PROTECTION IN HIV CO-INFECTED SUBJECTS

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GBV-C coinfection has a protective role in HIV infection, and increases the duration of suppression of HIV-1 viremia in patients under HAART. We analyzed the possible role of GBV-C as activator of innate immunity, possibly involved in the protection. To this aim, we measured the activation of the IFN system and of Toll Like Receptors genes in PBMC, and the expression of activation markers on circulating Dendritic Cells (DC) form HIV-infected patients. In addition, we measured the ability of GBV-C to activate these functions in normal PBMC *in vitro*.
The study included GBV-positive and -negative patients with HAART-driven suppression of HIV-1 viremia. The mRNA levels for a number of genes from the TLR family and several Interferon related genes (IRG) were generally higher in PBMC from GBV-C-positive when compared to GBV-C-negative patients, with highly significant differences for IFN-γ, PKR and TLR-9. IFN-γ mRNA levels correlated with those of all the IRG and with GBV-C viral load. Also the frequency of circulating plasmacytoid DC (pDC) expressing the CD80 activation marker was increased in GBV-C-positive patients, and was correlated with GBV-C viral load. The results from the *in vitro* experiments with normal PBMC showed that GBV-C increases the mRNA levels of IFN-γ and of the same set of TLR increased i*n vivo*, with the addition of TLR-3. In addition, GBV-C induced an increase of CD80 expression by pDC, that was reduced by antibody to IFN-γ, suggesting that IFN-γ was actually mediating the GBV-C stimulating effect on pDC. This was supported by the observation that exogenous IFN-γ induced a similar stimulation of pDC.
Our data indicate that, in HIV-positive patients, GBV-C coinfection promotes the coordinate activation of a set of TLR genes involved in IFN induction, of IFN-γ and of downstream IRG expression, that, in turn, may rise the activation/maturation of circulating pDC. The crosstalk between different compartment of innate immunity triggered by GBV-C, involving both soluble and cellular components, may have a role for in boosting the antiviral response to HIV infection.

PO 092

Infection 2009; 37 (Suppl. II): 88

HIV-1 TAT PROTEIN ENHANCES *IN VITRO* OSTEOCLASTOGENESIS

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Although the upgrading of antiretroviral therapy of HIV-infected patients have determined a significant increase in life expectancy for these subjects, it allowed the emergence of complications involving other organs than the immune system. Indeed HIV infection per se and HAART therapy can affect the homeostasis of several cell types and tissues as well as hormonal status, metabolism and cytokine networks. A large number of HIV seropositive patients showed an impressive evolution of demineralization and bone loss. These pathological complications represent an outstanding issue for patients' management and therapy especially for the complicances related to the increased fracture risk. Bone is a connective tissue characterized by hardness and plasticity, consisting of cells dipped in a mineralized extracellular matrix. The cellular fraction consists of three cellular types: osteoblasts, osteoclasts and osteocytes. Osteoblasts produce and secrete the extracellular bone matrix. where osteocytes are trapped and form a functional syncitium able to sense mechanical stress. Mechanical stress and calcium homeostasis are the main stimuli that determine the resorbtion process, which is accomplished by osteoclasts. These cells derive from the monocyte lineage and are able to resorb bone by the creation of an acid environment and the secretion of several lytic enzymes. Bone abnormalities in HIV positive individuals can be linked both to a direct effect of virus on bone cellular population or cytokine-hormonal regulative networks and to side effects of HAART therapy. To disclose one of the mechanisms involved in the HIV-1 related bone damage, we have investigated the interaction between HIV-1 Tat protein and human osteoclasts and its effects on cell differentiation and activity.Among the HIV-1 accesory proteins Tat plays a pivotal role in the viral replication and in virus/cell interaction acting as transactivating factor to increase viral expression. Besides its role in viral life cycle Tat is able to act on cellular targets deregulating cellular pathways in several cell types.To determine whether Tat affects osteoclast differentiation, PBMCs were differentiated by addition of M-CSF and RANKL in presence or absence of recombinant HIV-1 Tat protein. Osteoclastogenesis was then evaluated quantifying osteoclast specific genes (TRAP, cathepsin K and calcitonin receptor) expression by means of real time RT-PCR. At day 12 and 15 the expression of osteoclasts markers was incresed of 4-6 folds indicating the enhancement of osteoclastogenesis induced by Tat. In parallel, the microscopic evaluation showed a significant increase of polinucleated giant cells in cultures treated with Tat compared to controls confirming the up-regulation induced by Tat. Our observations indicate that Tat positively modulates RANKL/M-CSF mediated osteoclast formation and activation, playing a basic role in the enhancement of osteopenia/osteoporosis detected in HIV-positive patients.

PO 093

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HIGH FREQUENCY OF TORQUE TENO VIRUS (TTV) INFECTION IN HIV-EXPOSED SERONEGATIVE INDIVIDUALS (ESN) AND THEIR HIV-POSITIVE SEXUAL PARTNERS

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Background. The sexual transmission of TT virus is poor understood because of the extensive route for TT virus transmission.
Methods. To determine the frequency and possibly the sexual transmission of this virus,
specimens obtained from a group of 46 exposed seronegative individuals (ESN) and their sexual partners HIV infected, were analysed by amplification of the Untraslated (UTR) region and the Open Reading frame-N22 (ORF1-N22) domain, respectively. One-hundred blood donors (BD) were tested as a control group.
Results. By amplification of the UTR region TTV DNA was detected in 40/46 (87%) ESN and 41/46 (89%) respective HIV infected sexual partners, resulting in thirty-five (77%) couples TTV infected. In the BD the prevalence of TT viremia was assessed in 43/100 (43%) individuals.
By amplification of the N22 domain 31/90 (34%) available specimens were found TTV DNA positive. A lower proportion of TTV DNA positivity (12%) was detected in BD.
Five/44 (11%) couples resulted TTV-ORF1 positive. The transmission of TT virus was confirmed in 1 couple showing 99.5% sequence identity.
Comparison among the 3 groups indicated that TTV DNA detectability by amplification of UTR and N22 regions was higher in ESN and respective HIV infected sexual partners than in BD: $p<0.0001$ and $p=0.0011$, respectively.
Conclusions. TTV is highly frequent in the ESN as in their HIV positive sexual partners. Despite this evidence, the sexual transmission of TT virus was demonstrated in 2% of couples, suggesting that this is an infrequent event probably because of the early and extensive exposure to this virus.

PO 095

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DISAPPEARANCE OF MAJOR TIPRANAVIR MUTATIONS DURING SALVAGE ANTIRETROVIRAL THERAPY CONDUCTED WITH THE SAME PROTEASE INHIBITOR, IN THE ABSENCE OF AN OPTIMIZED THERAPEUTIC BACKGROUND. AN UNPREDICTABLE SCENARIO

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Background: The importance of each single genotypic mutations induced by protease inhibitors (PI), has been translated into a "score", which in the case of tipranavir has been validated as a measure of its pharmacological activity, in patients pre-treated with other PI.
Methods and Results: A p treated with antiretrovirals since 17 years, experienced multiple failures.Following increased viremia (55,000 copies/mL), and a drop of CD4+ T-lymphocytes (208 cells/μL), a modification of cART was needed. A complete, multi-class resistance was documented, when excluding tipranavir, which showed a limited activity (as expressed by a "mutational score" of +7). Although changes in the nucleos(t)idic background were not feasible, and our patient refused enfuvirtide adjunct, 6 weeks later HIV viremia dropped to 80 copies/μL, while CD4+ T-lymphocyte count increased (335 cells/μL). Within three months, viral replication was suppressed, but 4.5 months after the introduction of tipranavir/ritonavir without an "optimized" background, the re-appeatance of a detectable viremia (125 copies/mL), allowed us to perform another resistance assay, which surprisingly demonstrated a different mutational profile of tipranavir: an increased tipranavir activity depended on the reduction of the mutational score, from +7, to +4. Two main mutations (I54V ad M36I) disappeared, while the I84V emerged, in association with three minor mutations. Re-assured from the very favorable results, our patient accepted enfuvirtide adjunct, too. Three more months layer, an undetectable viremia was obtained, as well as stable CD4+ count (323-345/μL), which was confirmed in the subsequent eight-month follow-up.
Conclusions: In the presented patient, notwithstanding an unfavorable mutational profile, and the initial,lack of use of other active drugs, the isolated tipranavir adjunct proved effective beyond expectancies, and a mild viremic blip allowed to appreciate an increased tipranavir susceptibility gained during time. The reversal of key tipranavir mutations in a patient on salvage (but non "optimized" antiretroviral therapy), has not literature equivalents to our knowledge, and encourages the debate on the role of each single protease gene mutation, and the application of appropriate "mutational scores" to all available PI.

PO 096

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SUCCESSFUL RESCUE THERAPY WITH MARAVIROC AND ETRAVIRINE (TMC-125) IN PATIENT WITH EARLY VIROLOGICAL FAILURE TO RALTEGRAVIR

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We describe the clinical outcome of a heavily ARV-experienced patient failing a previous raltegravir-including regimen during a rescue therapy based on etravirine (ETV) and maraviroc (MVC).
Case report: We report the case of a 32-year-old Caucasian female with multi-drug resistant HIV-infection. The patient was also affected by β-thalassemia, pulmonary hypertension, wasting syndrome.
In October 2007, during a HAART regimen including DRV and 3TC, the patient presented persistent fever, CD4 were 78/mmc, HIV-RNA 5.7 log cp/ml. The GRT revealed resistance to all currently available ARVs. Considering the clinical conditions, RAL was added to HAART- regimen. After 2 weeks, HIV-RNA was 2.9 log cp/ml, CD4 188/mmc, RAL Ctrough 675 ng/ml. At day 30 and 60, RAL Ctrough were 1263 and 461 respectively.
In January, patient experienced virological failure. The GRT demonstrated the emergence of the N155H/N mutation in integrase gene (IN). The analysis of previous stored samples revealed the presence of N155H/N already at week 4 of RAL. The CCR5 tropism screening was performed and in February a HAART regimen with SQV, MVC and ETV was started. After 2 months, HIV-RNA achieved <50 cp/ml. At month 12 of follow-up, HIV-RNA is stably <50 cp/ml and CD4 were 454/mmc.
Discussion: The short-term efficacy of RAL-containing regimen at first and the rescue therapy based on ETV and MVC subsequently in this heavily ARV-experienced patient is really promising.
In our case, on the basis of the clinical conditions, a salvage RAL-based therapy without other active drugs was started and, probably, this RAL "mono-therapy" caused the short-term appearance of INI-mutations.
Resistance to RAL develops via 2 main non-overlapping, genetic pathways (N155H or Q148K/R/H), and possibly through Y143R. The addition of specific secondary mutations to either N155H or Q148H/R/Q primary mutations generally enhanced resistance to RAL, and in some cases restored the reduced replication capacity induced by the primary single mutation.
In our case, despite the emergence of N155H in quasispecies after 4 weeks, the viral load remaining under <300 cp/ml up to 8 weeks and successively rebounded with the emergence of N155H but no other mutations in PR and in RT. This evidence suggests that the N155 pathway may confer an incomplete clinical resistance to RAL differently from the Q148 pathway.
Further studies occur to establish the clinical role of IN polymorphisms in the INI resistance development. In our case, before RAL starting, the IN-GRT documented only some natural polymorphisms, including the V201I, recently associated with virological RAL failure.
In our patient, the PK profile was consistent with published data and confirmed complete adherence to regimen. At this time, the data for RAL are not sufficient to recommend routine use of therapeutic drug monitoring. Further studies occur to determine the feasibility of a gIQ, perhaps based on both polymorphisms and resistance mutations.

PO 097

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FAILURE TO DARUNAVIR/RITONAVIR CAN EITHER INCREASE OR DECREASE TIPRANAVIR/RITONAVIR GENOTYPIC RESISTANCE SCORE IN HIGHLY TREATMENT-EXPERIENCED HIV-INFECTED PATIENTS.

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Objective. To evaluate whether failure to a regimen including darunavir/ritonavir (DRV/r) worsens tipranavir/ritonavir (TPV/r) genotypic resistance score (GRS) in highly treatment-experienced HIV-infected patients (pts).
Methods. TPV/r weighted GRSs (Scherer et al, 2007) before the start and at failure to a regimen including DRV/r were compared. Pts were included in the analysis if they were naïve for TPV/r and had genotypic drug-resistance tested both before the start (baseline, BL) and at failure to DRV/r. DRV/r GRS was calculated according to that proposed by De Meyer et al, 2008. Results are presented as median (minimum, maximum).
Results. Ten pts fulfilled inclusion criteria. At BL, HIV-RNA was 4.8 (3.55, 6.01) $\log_{10}$ copies/ml, CD4+ 161 (48, 334) cells/μl, antiretroviral treatment duration 12 (9, 16) years, DRV/r GRS 3.5 (1, 6), TPV/r GRS 4.75 (0.5, 12); in 4 pts the TPV/r GRS was ≤3 [the proposed clinical cut-off (CCO) for an optimal virological response to TPV/r] and in 1 it was >10, [the proposed CCO for lack of virological response to TPV/r (Schapiro et al, 2007)]. All of the pts were failing a PI/r-containing regimen (lopinavir/r in 6, fosamprenavir/r in 4) and started a new regimen with DRV/r and an optimized backbone: 9 received lamivudine or emtricitabine, 5 enfuvirtide, and 5 tenofovir.
After 101 (34, 168) weeks, HIV-RNA was 4.36 (4.12, 5.49) $\log_{10}$ copies/ml and CD4+ 242 (56, 306) cells/μl. PI mutations more frequently selected at DRV/r failure were 32I, 33F, and 10F. DRV/r GRS was 5 (3, 8), and TPV/r GRS 4.5 (-1, 10.5); the TPV/r GRS was ≤3 in 4 pts and >10 in 1. An increase in the DRV/r GRS was observed in 9 of 10 pts.
TPV/r GRS increased in 3 of 10 pts; in 2 of these 3 it was ≤3 at BL and >3 at DRV/r failure. Of the 4 pts with a TPV/r GRS of ≤3 at BL, 2 still showed values of ≤3 and 2 an increase to values >3 at DRV/r failure; TPV/r GRS remained unchanged in 3 and reduced in 4 pts; in 2 of these 4 it was >3 at BL and ≤3 at DRV/r failure. No patient with TPV/r GRS <10 at BL had a GRS >10 at DRV/r failure.
PI mutations selected by DRV/r and associated with an increase in TPV/r GRS were 47V, 54V, and 74P (one case each). PI mutations selected by DRV/r and associated with a decrease in TPV/r GRS were 50V and 54L.
Conclusion. The majority of these highly treatment-experienced pts had a BL TPV/r GRS predicting a limited virological response to TPV/r. The TPV/r GRS did not increase with failure to DRV/r in most cases, and actually reduced in some of them. These results suggest that TPV/r may remain a viable therapeutic option in TPV/r-naïve pts failing DRV/r; however this possibility must be verified by re-testing drug-resistance at DRV/r failure, because either a switch to a TPV/r resistant HIV variant or a switch to a TPV/r sensitive HIV variant may occur. More study is necessary to understand why failure to DRV/r may lead to divergent degrees of resistance to TPV/r.

PO 098

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Comparison of the Duration of First and Second HAART Lines in Patients Undergoing HIV Resistance Testing in 2000–2001 vs 2005-2006 in the ARCA Database

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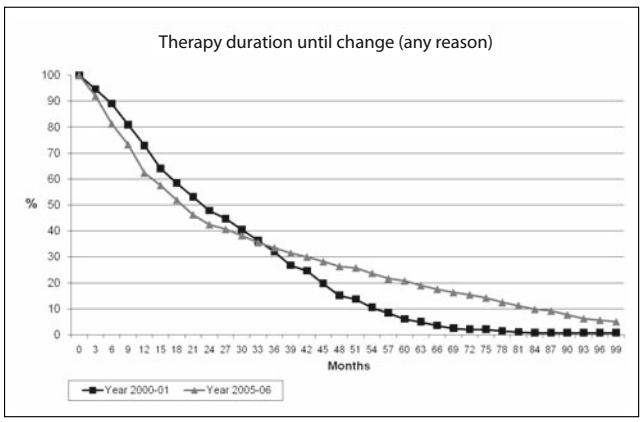
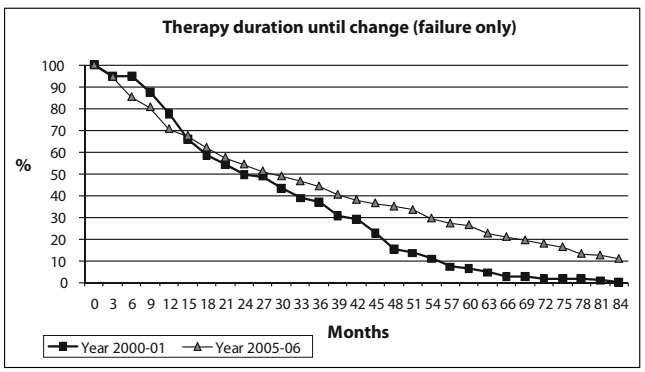
Background: the efficacy of antiretroviral therapy has changed over time as a consequence of the availability of novel drugs and drug classes with increased potency, convenience and tolerability. We planned a retrospective analysis of data available from patients undergoing Genotype Resistance Testing (GRT) in a large Italian observational Cohort, to investigate whether the durability of first and second HAART lines did actually change in the biennium 2005-2006 compared with 2000-2001.
Methods: we extracted data from the observational cohort database ARCA for all patients accessing GRT during their first or second line of HAART in 2000, 2001, 2005, 2006. For each patient, age, sex, treatment history, duration of current HAART line at the time of GRT, HIV RNA at multiple time points and CD4 T-cell counts at the start of treatment were collected. Standard parametric and non-parametric (Shapiro-Wilk test) univariate analyses were used to examine the differences in HAART duration and other variables across groups.





Results: 621 patients were considered, with a mean age of 44.7±9.8 years, 71.7% males; 284 patients in 2000-2001 and 337 in 2005-2006; 317 patients in first HAART line, 304 in second. Major reasons for accessing GRT were: virological failure (48.4%); treatment interruption due to adherence loss (10.9%); treatment discontinuation due to toxicity (9.3%). Duration of therapy in 2005-2006 was significantly longer either lumping all patients (27.9±20.2 vs 33.7±32.2 months; p=0.011) or considering virological failures only (29.0±18,9 vs 38.2±32,2 months; p=0.008). A survival curve representing the number of patients performing GRT at different time intervals during therapy indicated that more patients in 2005-2006 accessed GRT than in 2000-2001. Some of these excess GRTs were performed soon after the start of therapy. Furthermore, more patients in 2005-2006 reached a fully suppressed viremia at least once during their first and second line of HAART (39.8% vs 23.2%; p<0.001). Among major IAS mutations, only those related to NNRTI resistance increased significantly in 2005-2006 (0.45±0.74 vs 0.75±0.92; p<0.001), whereas no significant difference was scored for M184V, TAMs, major NRTI and major PI mutations.
Conclusions: Both the length and the efficacy of the first two lines of HAART significantly increased in patients treated in clinical practice in recent years. Early access to GRT increased in parallel, in line with enhanced attention to close monitoring of virological endpoints.

PO 099

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EMERGENCE OF HIV-1 RESISTANCE MUTATIONS AT TREATMENT FAILURE AND CORRELATION WITH PLASMA ANTIRETROVIRAL DRUG LEVELS

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Introduction: Relevance of suboptimal drug exposure in determining antiretroviral resistance has been poorly analyzed. We explored if protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) plasma concentrations could predict emergence of HIV-1 resistance mutations at treatment failure.
Methods: We retrospectively selected HIV-infected patients with a genotypic resistance test (GRT) performed at virological failure (GRT2), a plasma PI or NNRTI trough concentration measured before failure and a previous GRT (GRT1), collected before drug concentration measurement. Drug levels were classified as: (1)Undetectable, if below limits of quantification of HPLC-UV assay (<0.05mg/L); (2)Suboptimal, if between limits of quantification and efficacy thresholds; (3)Therapeutic, if above efficacy thresholds for drug susceptible virus. The number of acquired resistance mutations (IAS2008) was evaluated by comparing GRT2 with GRT1. Genotypic sensitivity scores (GSS) for failing regimens and the number of active drugs were calculated on both GRT using ANRS, HIVDB and REGA algorithms.
Results: A total of 43 patients (62.8% males, 86% Caucasian, median age 40 years, IQR36-48) accounting for 67 failure episodes (57 on PI-based, 49 boosted and 8 unboosted, and 10 on NNRTI-based regimens) were included.
In patients on PI-based regimens, median number of PI resistance mutations (minor+major) was 5 (IQR2-11) in GRT1 vs 8 (IQR3-12) in GRT2 (*p=0.033*); GSS of the failing regimen significantly decreased at failure as revealed by all investigated interpretation systems (ANRS *p=0.006*; HIVDB *p=0.048*; REGA *p=0.022*). Newly-acquired PI resistance mutations were observed in 8.3% of patients with undetectable PI levels vs 53.3% of those with detectable levels (*p=0.007*). No differences in acquiring resistance mutations were observed between patients with therapeutic and subtherapeutic PI levels. In multivariate analysis, undetectable PI levels confirmed to negatively predict the emergence of resistance mutations (*p=0.038*). Fewer patients with undetectable PI levels showed a decrease of the total number of active drugs when compared with those with detectable levels (ANRS 8.3%vs46.7%, *p=0.019*; HIVDB 16.7%vs40%, *p=0.182*; REGA 8.3%vs40%, *p=0.045*). Among explored factors, Caucasian ethnicity showed an independent inverse association with undetectable PI levels.
No patient treated with NNRTI-based regimens had NNRTI resistance mutations in GRT1; all acquired NNRTI resistance mutations and worsened their GSS in GRT2. Subtherapeutic (but detectable) NNRTI levels were observed in 2/10 cases. No differences in acquiring resistance mutations were observed comparing patients with NNRTI levels above or below efficacy threshold.
Conclusions: A PI measurement below limits of quantification of the assay predicted the lack of emergence of PI resistance mutations at failure. PI levels can help interpreting reasons for treatment failure and guide types of intervention needed.

PO 101

Infection 2009; 37 (Suppl. II): 92

ACUTE SEROCONVERTIONS BUT NOT TRANSMISSION OF DRUG RESISTANCE IS DECREASING AS EFFECT OF A MARKED REDUCTION OF HIV-1 VIREMIA IN A POPULATION OF POTENTIAL TRANSMITTERS OVER THE LAST 10 YEARS

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Background: HIV-1 transmission at population level is mainly driven by HIV-1 viremia of infected patients. The relationship between viremia levels of drug-failing patients (potential transmitters, PTs), number of HIV-1 observed seroconversions and transmitted drug resistance (TDR) in newly diagnosed drug-naive patients with unknown duration of infection (NDs) and seroconverters (SCs) have been evaluated by an ecological longitudinal study.
Methods: We analyzed 95,832 HIV-1 RNA values of 4,615 treated patients attending three Clinical Divisions at 'L. Sacco' Hospital during the last 10 years. HIV-1 RNA levels and CD4 cells for these patients ranged from 1.69 to 6.63 Log cp/ml and from 0 to 988 cells/μL. NDs and SCs were 295 and 100 (25.3%), respectively. HIV-1 RNA levels ranged from 1.70 and 2.5 to 5.70 and 6.48 Log cp/ml; CD4 cells ranged from 2 and 17 to 1,870 and 1,305 cells/μL for NDs and SCs, respectively.
An home-made procedure or commercial kits have been used to obtain *pol* sequences. Resistance mutations were identified from 2008 IAS-USA list.
Differences among proportions and temporal trends were tested using the chi-square and the Cochran-Armitage test, respectively.
Results: Gender and modality of infection of PTs were: 72.2% males and 37.8%, 34.9%, 22.6% for IDUs, HEs, MSMs, respectively. By dividing the study period in 5 biennial intervals the proportions of patients below 1000 copies/ml HIV-1 RNA significant increased from 49.5%, 56.6%, 66.1%, 70.0% to 81.6% overtime (p<.0001).
NDs were males in 80.7% of cases; MSMs and HEs accounted for 44.9% and 49.8% of cases, respectively, while SCs were males in 89% and MSMs or HEs in 65.3% and 30.6% of cases, respectively. A significant decrease of SCs proportions could be detected among newly diagnosed subjects in the last 3 biennial intervals (from 34.6% and 29.2% to 15.0% p=.0003).
Among SCs, male gender and MSMs risk factor rose, although not significantly, from 85.7% to 90.9% and from 58.8% to 68.2%.
Overall, TDR was 11.9% (47/395) fluctuating from 14.8% to 10.2% and 11.6% in the study period. A trend toward a significant difference in TDR distribution between SCs (17/100, 17%) and NDs (10.2% 30/295) was observed (p=.07). Of note, 65.9% (31/47) of patients with TDR were MSMs (88.2%, 15/17 for SCs and 46.6%, 14/30 for NDs). No primary resistance was detected in female SCs, while it was 10% (3/30) in female NDs.
Conclusions: New potent antiretroviral combinations, in addition to first generation HAART, achieved a robust reduction of HIV-1 viremia in an Italian metropolitan area at high prevalence of HIV-1 infection. In turn, this therapy achievement reduced the proportions of SCs overtime. Nonetheless, TDR in naïve patients remained at substantial level and clustered in males who acquired HIV-1 infection through sex with man, thus representing an ongoing public health concern.

PO 102

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ULTRASONOGRAPHIC CAROTID EVALUATION IN PATIENTS WITH HUMAN IMMUNODEFICENCY VIRUS INFECTION: ONE YEAR FOLLOW-UP

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Introduction: Previous data reported an increased incidence and a more rapid progression of subclinical carotid atherosclerosis (1), as an higher risk of stroke (2) in Human Immunodeficency Virus (HIV) pts compared to sex- and aged-matched control subjects. A recent study demonstrated that traditional risk factors for cardiovascular diseases overshadow the role of highly active antiretroviral treatment (HAART) in determining premature vascular lesions. (3) Measurement of Common Carotid Artery Intima Media Tickness (IMT) is a validate, non invasive method to evaluate atherosclerosis and it is a potent predictor of myocardial infarction and stroke (4).
Objective: To evaluate by Ultrasonographic techniques (US), carotid vessels at the baseline and after one year, in therapy naive pts with HIV infection, in order to detect the role of HAART in the progression of carotid atherosclerotic lesions in pts with HIV infection.
Methods: Thirty-three HIV pts (26m,7f; Mean age: 43.1± 11.1 (19- 69 yrs); mean duration of HIV infection: 5,1 (range:0.08-18 yrs) ;CD4 /µL : 550±278,6 (range:220-1415/µL), were evaluated by carotid-high resolution B-mode US. US examination of both Carotid arteries was performed by a 7.5 MHz linear array transducer. Intima Media Tickness (IMT) measurements was performed off-line. At the baseline all pts were therapy naïve. A second US carotid evaluation was performed after 12 months. At the follow-up 13 pts were in HAART, 15 were therapy-naïve; 5 pts dropped out.
IMT values ≥1mm were considered pathological. Vascular risk factors and metabolic assessment (age, hypertension, cigarette smoking, obesity, diabetes and increased plasma lipid levels) were analyzed at the baseline and at the follow-up. IMT of pts in HAART and pts still therapy-naive was analyzed at the follow-up.
Results: At the baseline 19 pts (58%) showed pathological findings on US carotid evaluation; in 14 pts (42%) US carotid examination was normal. At the second US evaluation, out of the 28 pts, 18 pts (64%; 8 pts in HAART, 10 pts therapy naive) showed pathological findings and 10 pts (36%; 5pts in HAART , 5 pts therapy naive) showed normal findings. Our data showed a significant difference in age, hypertension and smoke cigarette ($p<0.05$) between pts with pathological findings compared to those with normal findings. No differences in the others risk factors were found. At the follow-up the difference of the IMT increment between pts in HAART (0.17±0.2mm) and pts still therapy naïve (0.11±0.13mm) wasn't significant ($p>0.05$).
Conclusions: Clinical and US evaluation of HIV pts can help to clarify the role of the HAART in the pathophysiology of carotid atherosclerotic lesions. Subclinical atherosclerotic lesions seems to be related to older age, hypertension and cigarette smoking. The HAART seems to be not related to the progression of atherosclerosis. These findings confirm previous referred data .

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OPTHALMIC ARTERY RESISTANCE INDEX IS RELATED TO VISCERAL FAT DISTRIBUTION IN HIV-1-INFECTED PATIENTS RECEIVING ACTIVE ANTIRETROVIRAL THERAPY. PRELIMINARY RESULTS

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Purpose. HIV-1 infected patients receiving antiretroviral therapy often develop changes in body fat distribution Moreover, there is concern that human immunodeficiency virus (HIV) infection and the use of highly active antiretroviral therapy lead to accelerated atherosclerosis and increased risk of cardiovascular disease. Alteration of ocular blood flow may play a role in the pathophysiology of human HIV related endothelial damage secondary to altered fat distribution. Primary objective of our study was to evaluate whether peri-renal fat diameter (PRFD), a parameter of visceral obesity, is related to opthalmic artery resistance index (RI), indexes of atherosclerosis.
Methods. We enrolled 58 consecutive HIV-1-infected patients (42 men and 16 women) receiving active antiretroviral therapy (HAART) for more than twelve months, in a prospective cross-sectional study. Diagnosis of visceral obesity was based on ultrasound measured PRFD/BMI ratio > 0.22 using 3.75 mHz convex transducer, according to our previously published data. Ophthalmic artery RI was measured using a 7.5 mHz ultrasonographic linear probe scaning through the closed eyelid.
Results. A total of 24 patients were in the visceral obesity group and 34 were in control group. There were no differences between the two groups with regard to age, gender ratio, smoking status, risk factors, metabolic parameters, BMI, CD4 cells count, viral load and HAART duration. Protease inhibitors (PI) had been prescribed in 23 (39.65%) patients (8 with visceral obesity and 15 without obesity), without statistically significant difference between the two groups. All patients exposed to PIs received a ritonavir-boosted PI. Non-nucleoside reverse-trascriptase inhibitor (NNRTI) had been prescribed in 35 (60.34%) patients (16 with visceral obesity and 19 without obesity). At baseline the mean of ophthalmic artery RI in HIV-1-infected patients with visceral obesity were considerably higher (0.74 ± 0.05 vs 0.68 ± 0.04) than that in patients without. We further found a positive correlation between ophthalmic artery RI and PRFD ($r = 0.43$; $p = 0.0007$). Using the average ophthalmic artery RI as the dependent variable in regression analysis, age and PRFD were independent factors associated to with ophthalmic artery RI.
Conclusions. HIV-1 infected lipodystrophic patients with central fat distribution are at risk of increased ophthalmic artery RI, with positive correlation between ophthalmic artery RI and thickness of peri-renal adipose tissue. Our data demonstrated that ultrasonographic assessment of peri-renal fat diameter may have a potential to be a marker of increased endothelial damage in HIV1 infected patients with specific involvement of ocular vascular district. As a consequence, a periodic screening for visceral obesity should be considered mandatory in the HIV-1-infected patients receiving highly active antiretroviral therapy and it could identify patients at major risk to develop an ocular damage.

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Evaluation of the new Versant HIV-1 RNA 1.0 ASSAY (KPCR) for quantification of human immunodeficiency virus type 1 RNA

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Objective: To compare performance of the new Versant HIV-1 RNA 1.0 (kPCR) assay (Siemens Healthcare Diagnostics) for quantification of HIV-1 RNA in clinical samples from HIV-1-infected individuals with Versant HIV-1 RNA v3.0 (Siemens Healthcare Diagnostics) and COBASAmpliprep/COBASTaqMan HIV-1 CAP-TCM (Roche Diagnostics) procedures. Versant HIV-1 RNA 1.0 (kPCR) and COBASAmpliprep/COBASTaqMan HIV-1 assays are both based on RT real-time PCR technology; Versant HIV-1 RNA v3.0 is based on bDNA technology and was considered as reference method.
Methods: The study was conducted on 256 retrospectively collected plasma samples from HIV-1 infected individuals attending the outpatient care facility of the "Lazzaro Spallanzani" Hospital in Rome. Quantitative results were compared with correlation, linear regression, Bland&Altman and k-statistic analyses of $\log_{10}$ transformed HIV-1 RNA copy numbers.
Results: Agreement between Versant HIV-1 RNA 1.0 (kPCR) and other assays was elevated (>0.940) and high correlation coefficients were measured: *r=0.9662, p<0.0001* between Versant HIV-1 RNA 1.0 (kPCR) and Versant HIV-1 RNA v3.0 (bDNA); *r= 0.9597*, *p<0.0001* between Versant HIV-1 RNA 1.0 (kPCR) and COBAS Ampliprep/COBAS TaqMan HIV-1. Analysis of mean differences of measurement between assays, conducted according to Bland&Altman method, showed no clinically significant differences in quantification of viral load (lower than 0,2 $\log_{10}$cp/ml) along all the overlapping range.
Conclusion: Versant HIV-1 RNA 1.0 (kPCR) assay for quantification of HIV-1 RNA in plasma samples from HIV-infected individuals is based on RT real-time PCR technology. This new commercially available diagnostic system produces viral load results that can be considered equivalent to results given by the reference diagnostic system and a similar RT-real-time PCR-based procedure.

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UNCOMMON MALIGNANCIES IN HIV-PATIENTS DURING THE ERA OF THE HIGLHY ACTIVE ANTIRETROVIRAL THERAPY: A DESCRIPTION OF TWO CASES

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Large epidemiological and cohort studies clearly revealed that the risk of acquiring non-AIDS related malignancies is about two to three fold higher than in the general population, and the incidence of these tumors increased during the HAART era. We report on a case of Merkel cell carcinoma (MCC) in a male adult HIV patient, and a case of spinal subependymoma in a HIV-positive woman.
Case 1: A 66-years old patient presented on april 2008 with a painful left inguinal lymphoadenopathy. The patient, with a 25-years history of HIV infection, started HAART on 2002 with saquinavir, lamivudine and stavudine and he received also IL-2 from 2002 to 2006 in the context of an international trial. The biopsy of the inguinal mass documented massive growth of malignant cells inside the inguinal lymph nodes with the histological and immunohistochemical patterns of MCC carcinoma. At the time of diagnosis of the neoplasia the patient had HIV-RNA < 40 copies/mL and 479/mm3 T CD4 lymphocites. Six cycles of chemotherapy with carboplatin and etoposide with concurrent radiation therapy after complete excision of the tumoral mass were administered. Despite the lymphonodal involvement at presentation (MCC stage III), one year after the patient remained free of symptoms and a total body computed tomography scan and positron emission tomography did not show recurrence of the disease.
Case 2: A 44-years old woman was admitted to our department complaining burning pain radiating to the legs and footh with paresthesia lasting from five months. The patient was found to be HIV-positive in 1987 and her past history is remarkable for a chronic HCV-related hepatitis and a lumbar herpes zoster episode. She started HAART on 1999, and with the ongoing treatment (tipranavir/ritonavir + stavudine + tenofovir since 2005) her plasma HIV-RNA is below 40 copies/mL, and T CD4 cell count 424/mm3. The magnetic resonance imaging of the spine showed an intramedullary lesion of the thoracic tract with an enlargement of the ependimal channel along the first to the fourth thoracic vertebral body. The lesion appeared contrast-enhancing. Intraspinal thoracic subependymoma was diagnosed, and surgical resection of the mass was performed.
Conclusions: The HAART has dramatically reduced the incidence of AIDS-defining infectious and neoplastic diseases, but other malignancies are diagnosed in the HIV-positive patients with an increased incidence than in the general population. HIV positive individuals have a relative risk for MCC of 13.4, and, like HHV-8 virus for the Kaposi sarcoma a novel polyomavirus seems to be involved in the pathogenesis of MCC. There is not evidence that the incidence of brain tumors other than primary EBV-related cerebral lymphoma is increased in the HIV-infected population. Intraspinal subependymoma are very rare tumors and their symptoms could be easily misinterpreted with the symptoms due to HIV- and drug-related peripheral neuropathies.

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EVALUATION OF GLOMERULAR AND TUBULAR FUNCTIONS IN HIV INFECTED PATIENTS NAIVE TO ANTIRETROVIRAL THERAPY ENROLLED IN A STUDY OF TDF/FTC + EFV OR ATV/R (INCA STUDY OF THE MASTER COHORT)

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Objectives: to compare different measurements for estimating creatinine clearance (ClCr) and evaluate tubular function in HIV patients naïve to antiretroviral therapy.
Methods: We used the baseline tests available in an ongoing prospective randomized trial. In this study, we are evaluating actual ClCr, proteinuria, proteinuria/creatininuria ratio (P/Cr_R) and microalbuminuria through 24-hour urine collection. Serum cystatin C and plasma/urine electrolytes are being evaluated. To compare actual with estimated clearance, CrCl is calculated using MDRD and Cockroft-Gault (C-G) formulas.
Results: 63 patients were studied so far. For glomerular function, all patients had actual 24-hour CrCl >50 mL/min; of these patients, 7/63 (11%) had abnormal values (<90 mL/min) and 7/60 (12%) had abnor-

mal 24-hour microalbuminuria (>30 mg). Patients with abnormal actual CrCl had normal microalbuminuria, while those with abnormal microalbuminuria had normal actual CrCl. Consideration of estimated CrCl apparently detected more abnormalities than the actual measurements because 15/63 (24%) of patients demonstrated MDRD or C-G alterations. However, 9/63 (14%) had both abnormal MDRD and abnormal C-G CrCl. Interestingly, only 2 patients had alterations of the three CrCl measures (actual, MDRD, and C-G) and one patient also had abnormal microalbuminuria. Regarding tubular function, 4/62 (6%) patients had 24-hour P/Cr_R alterations (>1); none of these had signs of glomerular abnormalities. Cystatin C was abnormal in 3 patients (1 had abnormal C-G CrCl, 1 had abnormal P/Cr_R and 1 had normal kidney function).
Conclusions: Great discordance was found among different measures to estimate CrCl. Also, great discordance was found between them and 24-hour microalbuminuria as adjunctive parameter for glomerular function. This suggests that multi-parametrical assessments of glomerular function should be performed. Even though glomerular function was normal, some naïve patients had possible signs of tubular alteration. Prospective evaluation of patients enrolled in the INCA study is important to establish the predictive value of these alterations (and their patterns) for the evolution of glomerular and tubular functions under TDF ± PI/*r*.

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LIVER FIBROSIS ASSESSMENT IN A COHORT OF HIV POSITIVE PATIENTS WITHOUT OVERT CAUSE OF LIVER DISEASE

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Background: Progressive hepatic fibrosis, is a wound-healing process following chronic liver injury from many causes, including persistent viral infection, alcohol or drug toxicity. The aim of the present study was to assess liver fibrosis in HIV positive patients with no evidence of liver disease to investigate estimates for normal values and factors associated with liver fibrosis.
Methods: Liver fibrosis was assessed using transient elastography (TE) in all consecutive HIV-infected patients without overt cause of liver disease who attended our institution between September 2007 and December 2008. Hepatic stiffness was measured in kiloPascal units (kPa) and was interpreted on the basis of Metavir score: no or mild fibrosis (score, F0-F1) when liver stiffness is 7.1 kPa, and fibrosis or cirrhosis (F2-F4) when >7.1 kPa. Clinical, biochemical, and behavioral variables were matched with Liver stiffness measurement (LSM) by univariate and multivariate analyses.
Results: A total of 175 patients (80% male; mean age 45 years; 60% MSM) were analyzed. Mean CD4 cell count was 417 cells/mL. 114 (65%) patients had HIV RNA level of < 50 copies/mL; 152(87%) were receiving antiretroviral therapy (mean duration of HAART 6,3 years). ALT level (mean) was 31 IU/L, AST (mean) 27 IU/L. 37 (21%) patients introduced metabolic syndrome (NCEP criteria). Mean liver stiffness value was 5.7 kPa (F0). Overall, 23 (13%) of the patients had scores indicating significant liver fibrosis (F2-F4). At univariate analysis gender, liver enzyme activity, and all parameters included in the metabolic syndrome were related to LSM. There was no significant association between LSM and age, risk practice, CD4+ count, HIV RNA level, specific drug regimen or cumulative period of HAART. At multivariate analysis significant hepatic fibrosis was associated with AST level ($p < 0.001$), ALT level (p 0.010) and metabolic syndrome (p 0.06).
Conclusions: Patients HIV positive without overt cause of liver disease show a spread of liver fibrosis that does not differ from that one of the general population.

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CORRELATION BETWEEN VIRAL TROPISM DETERMINED BY TROFILE PHENOTYPIC ASSAY AND GP120-V3 GENOTYPING OF HIV RNA AND DNA IN 37 PATIENTS AT BASELINE AND DURING FOLLOW-UP

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Background. Determining co-receptor tropism using genotyping tests is essential to save time and costs and in patients with low viremia. Nowadays the only clinically validated assay for determining viral co-receptor tropism is the phenotypic Trofile assay. We wanted to assess a comparison of the Trofile result and a genotypic assay for the detection of tropism in plasma viral RNA and whole blood viral DNA.
Methods. The Trofile assay, to assess co-receptor Phenotype, was performed at Monogram Biosciences on a serum sample. It use the following classification: CCR5-using, CXCR4-using or DM (indicating dual and/or mixed-tropic virus) or non reportable. V3 envelope (env) genes from plasma samples at Trofile time, and from plasma and whole blood (WB) at follow-up, were amplified and sequenced in both strands by infrared-labeled primers on a Licor IR2 system. Coreceptor tropism was inferred by geno2pheno[coreceptor]. Both results from the "clonal" and the "clinical" interpretation of geno2pheno were analysed.
Results. 37 patients of a single centre, were analyzed for viral co-receptor tropism (Trofile). 65% were males, median age 43 years (IQR 40-48 years), median CD4 were 235 cells/mm^3(IQR 71-495 cells/mm^3) and median HIV RNA 3.88 log copies/ml (IQR 3.57-4.52 log copies/ml). HIV co-receptor phenotypic assay showed 21 CCR5-tropic, 1 X4-tropic, 9 dual mix, 6 of samples were non reportable. 16 samples had VL<1,000 cp/mL (median VL 234 [52-410]); 11/16 had VL<400. Proviral DNA was genotyped in 12/12 WB samples, including 10 with VL <1,000 cp/mL (median VL 49 cp/mL [49-138]), 9/10 with VL<400. The concordance between the "clinical" and the "clonal" interpretation was 76% on RNA and 82% on DNA. The concordance of the tropism assignment using plasma viral RNA and WB viral DNA was 100% for both "clinical" and "clonal" interpretation.
All samples with not reportable Trofile results were genotyped. Baseline plasma RNA genotypes were tested in 25 patients and detected D/M or X4 with sensitivities of 50% ("clinical") and 87.5% ("clonal") and specificities of 85.7% and 71.4%, respectively.
Follow up RNA was genotyped in 14 patients in 1-4 samples (on MVC: 6 with VL≥400 cp/mL, 4 with VL<400 cp/mL after a median of 45 days [1st sample] to 149 days [last sample] from MVC start). Tropism switches were observed in 2 patients (1 Trofile R5 switching from genotype R5 to X4 ["clonal" interpretation] and 1 Trofile D/M switching from X4 to R5 ["clinical" interpretation]) . Follow-up DNA was genotyped in 12 patients (9 on MVC, a median of 129 days after MVC start): no tropism switches were observed in these samples.
Conclusions. This test, using both HIV RNA and DNA, is an useful Trofile alternative for samples with low VL, those N/R by Trofile and for monitoring follow-up of patients treated with CCR5 antagonists. Low sensitivity in detecting X4-tropic variants (Trofile) using geno-2pheno "clinical" interpretation suggests of re-calibrate this interpretation.

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MULTIPLEX PCR FOR SIMULTANEOUS DETECTION OF HIV AND HCV FROM DRIED BLOOD SPOT

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HIV-1 and HCV co-infection is a relatively common clinical occurrence in Europe and in USA affecting approximately 25% of HIV-1–infected patients and 10% of HCV-infected individuals.
Early diagnosis of viral infections is fundamental both to reduce the probability of transmission and to increase the efficacy of antiviral therapy. One solution that has been proposed for improving access to HIV and HCV diagnosis is the use of dried blood spots (DBS). A drop of blood is obtained from a finger prick, applied to a piece of filter paper, air-dried, and stored until analysis. Blood spotted onto filter paper facilitate the collection, transport and storage of blood samples for laboratory use. The first application of this method was achieved by Guthrie, in 1963, who demonstrated the feasibility of collecting neonatal blood samples onto filter paper for phenylketonuria testing of newborns. Nowadays several studies have reported the successful extraction of DNA and RNA suitable for molecular applications from dried blood spots (DBS) collected on filter paper. Indeed, once dried, the blood specimens on filter paper are no longer infectious and nucleic acids are stable over time under differing conditions of temperature and humidity.
The combination of DBS and PCR highlights the simplicity and stability in the sample collection with the analytical accuracy in the diagnostic procedure. For this reason this diagnostic technique can be particularly useful in paediatrics, where it represents a less invasive practice than venopuncture, in the massive screening of high risk population such as drug abusers or in countries where health facilities are not accessible.
This work was aimed to the develop a SYBR Green-based multiplex real time RT-PCR for the simultaneous detection of HCV and HIV-1 genomes in dried blood spot. Viral genomes were identified in the same sample by their distinctive melting temperature (Tm) which are 81.6 and 86.5 °C for HIV-1 gag 142 bp amplicon and HCV 5′-NCR region 226 bp amplicon, respectively. Analysis of known scalar concentrations of reference plasma indicated that the multiplex procedure detects at least 500 copies/ml of both HIV-1 and HCV. In addition, we also assayed HIV-1 and HCV viral load in co-infected patients and in blood donors, confirming the sensitivity and specificity of the assay.
This method may represent a useful alternative method for the detection of HIV-1/HCV co-infection, reliable for a rapid and relatively inexpensive screenings.

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IMPROVING THE PERFORMANCE OF HIV-1NON-B SUBTYPE RNA QUANTIFICATION

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Commercial viral load assays to quantify HIV-1 RNA levels were originally optimized for detecting subtype B sequences, predominating in industrialized country. Later on, with the continued evolution of HIV-1 pandemic, increasing numbers of non-B subtype and intersubtype recombinant form (CRF and URF) infections are spreading worldwide, including also North America and Western Europe, originally considered clade B restricted. For this reason, viral load assays have been continuously improved to ensure accurate quantification of HIV RNA regardless of the infecting subtype, since HIV variability within target region used for viral load quantification can directly impact the performance of diagnostic assays.
We report the results obtained in some non-B strains infected patients by using a new version of Roche TaqMan real time assay to quantify HIV viral load.
In particular, HIV-1 infection was diagnosed in three patients (A, B and C) resulted anti-HIV positive with 4th generation combined antigen/antibody test and anti-HIV-1 reactive by western blot. In A, in spite of the absence of antiretroviral therapy, plasma HIV-1 RNA was repeatedly undetectable ("target not detected") with both Cobas AmpliPrep-Cobas Amplicor HIV-1 test vs 1.5 and COBAS AmpliPrep/COBAS TaqMan HIV-1 test vs 1 (Roche Molecular Systems, Branchburg, USA), targeting highly conserved regions of the HIV-1 *gag* gene. In B and C, COBAS TaqMan HIV-1 assay gave an undetectable viral load result for the first examined plasma sample but HIV-1 RNA was quantified in the following samples. Conversely, amplification and sequencing of *pol* region, carried out with the ViroSeq™ HIV-1 Genotyping System, v2.0 (Abbott Diagnostics, Weisbaden, Germany), gave a positive result in all the examined samples. The obtained sequences were submitted to the Stanford HIV database, the Los Alamos and the BioAfrica subtyping websites, and the patients resulted harboring HIV-1 subtype G and URF A/G *pol* sequences. Molecular characterization of *gag* region, performed with primers described by Swanson et al., showed oligonucleotide mismatches in the hybridization domain of both primers and probe included in Cobas Amplicor HIV-1 assay vs 1.5.
Plasma samples were then analyzed by using the new Roche CAP/COBAS TaqMan HIV-1 test vs 2, characterized by multiplex amplification and detection with primers and probes targeting 2 conserved sequences on *gag* and LTR HIV-1 regions. HIV-1 RNA was detected in all the analyzed samples with a viral load of 10^4 $\log_{10}$ / ml.
Our data show the importance to re-evaluate the reliability of commercial kits designed mainly on the basis of HIV-1 subtype B sequences. This issue is becoming more and more important in consideration of the diffusion of non-B subtypes and recombinant forms outside the African continent.

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USE OF TENOFOVIR DISOPROXIL FUMARATE (TDF) AND EMTRICITABINE (FTC) IN PREGNANCY: FINDINGS FROM THE ANTIRETROVIRAL PREGNANCY REGISTRY (APR)

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Background: The beneficial role of antiretrovirals (ARVs) in the prevention of mother-to-child transmission (PMTCT) of HIV was first demonstrated in 1994 in ACTG Study 076 using zidovudine (ZDV) monotherapy. However, the safety of prenatal ARV exposure to the fetus has not been established. Use of TDF-containing regimens in pregnancy and inclusion of TDF in treatment strategies for PMTCT have been demonstrated to be well tolerated while reducing MTCT both in animal models and in humans.
Methods: The APR is an international, prospective, registry designed to collect and evaluate data on the outcomes of pregnancy exposures to ARVs. This Registry is intended to provide an early signal of teratogenicity associated with prenatal use of ARVs. Sufficient numbers of 1st trimester exposures to 14 ARVs have been monitored to detect at least a 1.5-fold increase in overall birth defects for ZDV and 2-fold increase in overall birth defects for TDF and FTC.

Results: Through 31 July 2008, there were 11,950 prospective pregnancy cases reported to the Registry. APR began collecting data from exposure to TDF in 2001.No overall increase in congenital anomalies in infants following any 1st or 2nd/3rd trimester ARV exposure has been seen compared to the general population. Prevalence of anomalies with any ARV exposure in the 1st trimester 2.9/100 live births (95% CI: 2.4-3.5) [126/4329]; with 2nd/3rd trimester exposure 2.6/100 live births (2.2-3.0) [145/5618]; with 1st trimester exposure to TDF 2.3% (1.3-3.9) [14/606]; with 2nd/3rd trimester exposure 1.5% (0.5-3.4) [5/336]; with first trimester exposure to FTC 3.2% (1.4-6.2) [8/252]; with 2nd/3rd trimester exposure 1.5% (0.2-5.3) [2/134]; with first trimester exposure to ZDV 3.1% (2.5-3.7) [94/3068]; with 2nd/3rd trimester exposure 2.7% (2.3-3.1) [161/6063].
Conclusion: To date no increase in prevalence of congenital anomalies in live births with exposure to TDF (n=942) or FTC (n=386) has been seen through prospective voluntary reporting to the APR. Birth defect prevalence with exposure to TDF was similar to birth defect rate with exposure to ARVs overall. Further studies are warranted in women receiving TDF or TDF/FTC during pregnancy and for PMTCT.

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EFFECT OF HCV INFECTION ON GLUCOSE METABOLISM IN PREGNANT WOMEN WITH HIV RECEIVING HAART

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Objective: A prospective study was designed in order to evaluate the rate and determinants of glucose metabolism abnormalities (GMA) among HIV-1 infected pregnant women receiving highly active antiretroviral therapy (HAART).
Methods: Blood samples were collected during pregnancy in fasting conditions and following a 100 g oral glucose tolerance test among HIV-infected pregnant women consecutively followed at a single HIV reference centre in 2001-2008 within a national study. GMA were defined by glucose intolerance (IGT) or gestational diabetes (GDM), according to the National Diabetes Data Group criteria. Predictors of GMA were assessed in univariate and multivariate analyses.
Results: Overall, 77 women with no history of diabetes or GMA were eligible for analysis. All were on stable HAART from at least four weeks at the time of sampling with either PI (79.2%) or nevirapine (20.8%). Most commonly used PI were lopinavir (n: 29, 47.5%) and nelfinavir (n: 25, 41.0%), followed by atazanavir (n: 4, 6.6 %) and saquinavir (n: 3, 4.9 %). With the exception of nelfinavir, all the other PI were used with low-dose ritonavir as a pharmacological booster. GMA during pregnancy were observed in 19 women (24.7%; GDM: 5, 6.5%; IGT: 14, 18.2%). In univariate analyses, the stronger association with GMA was found for coinfection with HCV, with a three-fold increase in risk associated with this condition (odds ratio: 3.64, 95% CI 1.10-12.0, p=0.034). Pregnancies with GMA were also characterised by trends for a slightly higher age (average difference: 2.7 years, p= 0.064) and a longer time from infection (average difference, 99 weeks, p=0.162). No differences were observed between pregnancies with and without GMA with respect to CD4 counts, HIV-RNA, HIV clinical status, treatment history, parity, ethnicity, and familiar history of diabetes. Women with GMA had a trend for a higher rate of preterm delivery (36.8 vs. 19.0, p= 0.116). In a multivariate analysis, after adjusting for age, time from HIV diagnosis and ongoing antiretroviral treatment (PI or nevirapine), GMA in pregnancy were significantly associated with HCV coinfection (adjusted odds ratio: 3.64, 95%CI 1.07-12.4, p= 0.039). No maternal or neonatal complications were observed.
Conclusion: Glucose metabolism abnormalities represent a relevant issue in the management of HIV-1 infected pregnant women. Our data suggest that these abnormalities are relatively common in this particular group. Women with HCV coinfection have an increased risk of developing glucose metabolism abnormalities during pregnancy and should be monitored for potential complications.

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EVALUATION OF CAROTID INTIMA-MEDIA THICKNESS AND CARDIOVASCULAR RISK FACTORS IN A COHORT OF YOUNG PATIENTS WITH VERTICALLY ACQUIRED HIV-1 INFECTION

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Background: The use of surrogate cardiovascular markers in the setting of cardiovascular disease in HIV-infected patients is intriguing to many clinicians. We investigated markers of early vascular disease and carotid intima-media thickness (C-IMT) in a cohort of ART-treated young patients with vertically acquired HIV-1 infection.
Materials and Methods: Cross-sectional study of HIV-1 infected young patients. Neck ultrasonography (US) was performed with a 4-14 MHz linear probe (MyLab 70, Esaote, Genoa, Italy). C-IMT was evaluated on both sides by US in the supine position. We evaluated fasting glucose and lipid profile, biomarkers of vascular dysfunction (C-reactive protein [CRP], D-dimer), arterial blood pressure, height, weight, and BMI. We collected past clinical and ART history Correlation analyses between variables were carried out by Pearson correlation test.
Results: There were 41 patients (21 female, median age 16 years [range, r, 4-25]), 6 in CDC class C, 9 smokers, none with hypertension. The median weight, height and BMI was 53 kg (r 16-89.8), 163 cm (r 100-180) and 19,6 kg/m^2 (r 13,4-29,8), respectively. Only one patient was naïve to ART, while 29 (73%) were receiving a PI-based regimen. The median time of exposure to ARV was 141 months (r 0-248), with a median exposure to NNRTI and PI of 24 (r 0-73) and 38 (r 0-145) months. At the time of the study, the median (r) viral load was 49 cp/mL (49-500000), CD4+ cells count 583 cells/mmc (21-1508), triglycerides 83 mg/dL (29-491), total-cholesterol 142 mg/dL (67-235), high-density lipoprotein cholesterol 45 mg/dL (16-109), low-density lipoprotein cholesterol 91 mg/dL (25-179), apolipoprotein A 1,3 mg/dL (0,7-2), apolipoprotein B 0,7 mg/dL (0,3-1,2), glucose 82 mg/dL (67-97), glycated hemoglobin 5,1 % (4,4-5,7), CRP 3,3 mg/dL (3,3-47,2), insulin 8,2 mIU/L (2,3-44,4), and D-dimer 139,7 ng/dL (50-1318). About vascular measurements, only 3 patients presented increased C-IMT: mean C-IMT correlated significantly ($p<0.01$) with the BMI and insulin levels. No significant correlation was found between mean C-IMT and the use of a type of ART, while the BMI correlated with the time of exposure to ARV.
Conclusions: Long-term HIV infection in youths is a risk factors for vascular changes and most of them could be at risk of having coronary heart disease in adulthood. We did not found a direct correlation between IMT and the use of a type of ART, but the indirect correlation between the time of exposure to ART, BMI and C-IMT, suggest that longitudinal studies are required to differentiate the relative impact of HIV disease and ART and to assess the potential for prevention.

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DETECTION IN HIV POSITIVE WOMEN OF PREVALENT HPV GENOTYPES AND THE INCIDENCE OF RELATED CERVICAL PATHOLOGY

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Introduction: HIV positive patients are at greater risk for CIN and persistent HPV infections. Aim of this study is to evaluate the prevalence of HPV in cervical speciments and to analyse the relationship of HPV genotypes , the risk factors and ART in incidence of cervical pathology in a cohort of HIV positive women.
Methods: From June 2006 up to December 2008, 72 HIV-positive women were enrolled in a gynaecological prospective study and performed 103 examinations. All subject underwent gynaecologic examination including a HPV cervical sample collection, STD screening, Pap smear, a colposcopic examination and, if necessary, a cervical biopsy. HPV test was carried out using PCR with consensus primers (GP5+/GP6+) followed by typing with reverse line blot. A questionnaire was utilized to gather demographic information and obtain information on known risk factors associated with HPV infections such numbers of partners, smoking and other STDs. Details of antiretroviral therapy, cytological assessment, and clinical examination were related to HPV types.
Results: The main parameters at examination were: median age 41 ys , median CD4+ 454/mmc, HIV-RNA < 50 copies/ml in 74.7 % of cases, 91.2 % on ART. Abnormal cytology was detected in 17 examinations (16.5 %): H-SIL 1/103 (0.97%), LSIL in 11/103 (10.6 %) and ASCUS in 5/103 (4.9 %). All subjects underwent colposcopy and the final diagnosis was negative in 77 examinations (74.7 %), CIN 1 in 23.3 % (24/103) and CIN 2 in 1.9 % (2/103) . 36,9% (38/103) and 21 % (20/103) of the women resulted positive to HR-HPV and LR-HPV respectively. Among the HR HPV women, a single infection was detected in 52.6 % (20/38) , whereas a multiple infection with HR was detected in 47.3% (18/38) of the women. HR-HPV genotypes other than HPV-16 (HPV 45, 33 and HPV 58) are frequently detected in HIV infected women. The two CIN 2+ lesions were sustained from HPV 35 and 39 respectively. The only statistically significant factors associated to HPV prevalence in multivariate analysis were heavy smoking cigars (n cigarettes > 20 OR=3.96 95% CI 1.4-11.0) and the number of sex partners (n partners > 2 OR= 1.88, 95% CI 0.6-5.6).
Conclusion: Few data are available on ART and on its role in HPV-associated cervical disease in HIV positive women. ART decreased the risk of cancer associated with very low CD4 as Kaposi Sarcoma but has a modest impact of HPV-related cancer. Immune restoration may decrease the severity and recurrence of HPV infection although infection occur more often in HIV-positive patients with low CD4. HIV-positive women showed a higher prevalence of multiple genotypes that correlates neither with CD4 counts nor with cervical dysplasia. Infection with HIV may enhance HPV proliferation through mechanisms other than CD4 immunosuppression. Therefore, it remains important to closely monitor HPV-related disease in women with HIV who are receiving ART. The risk for precancerous lesion and cancer seen among HIV+ women depends largely on screening practices and adequate follow up of cervical lesions.

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ROLE OF HOST GENETIC DETERMINANTS OF INNATE IMMUNITY IN MOTHER-TO-CHILD TRANSMISSION OF HIV-1

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Background: Mother-to-child transmission (MTCT) of HIV-1 is multifactorial. Innate immunity may contribute to host-viral interactions and impact the risk of MTCT. Defensins, which provide microbial barriers, and Toll-like receptors (TLRs), which recognize and bind pathogen-associated molecular patterns, play crucial roles in the host's innate immune response. The aim of the present study was to investigate the influence of single nucleotide polymorphisms (SNPs) and haplotypes of the beta-defensin-1 (DEFB1) and TLR9 genes on MTCT.
Patients and Methods: The study was conducted in 300 children (118 HIV-1 infected and 182 HIV-1 uninfected) born to HIV-1 infected mothers. None of the mothers underwent antiretroviral prophylaxis and 94% of children were born by vaginal delivery. DNA, extracted from peripheral blood mononuclear cells, was evaluated for -44C/G(rs1800972) and -52G/A(rs1799946) SNPs of the DEFB1 gene and 1635A/G(rs352140) and 1174G/A(rs352139) SNPs of the TLR9 gene by TaqMan allelic discrimination assay. Statistical analysis was performed using SNPStats and Haploview programs.
Results: The -52GG genotype and the -44G/-52G haplotype of DEFB1 were associated with a low risk of MTCT [odds ratio (OR)=0.52 (95% confidence interval 0.31-0.86) and OR=0.50 (0.31-0.83). The 1174A/1635G and 1174G/1635A haplotypes of TLR9 were also associated with a low risk of HIV-1 infection in infants [OR=0.15 (0.05-0.48), and OR=0.18 (0.06-0.55), respectively]. Maternal viral load at delivery was available in 109 cases; the protective effect of these genetic variants on MTCT was confirmed in this subgroup of infants even in multivariate analysis after adjustment for maternal viral load [OR= 0.38(0.14-1.05) and OR=0.48 (0.19-1.10) for -52GG and -44G/-52G of DEFB1, and OR=0.12 (0.05-0.79) and OR=0.08 (0.01-0.78) for 1174A/1635G and 1174G/1635A of TLR9, respectively].
Conclusions: Overall, results demonstrate a significant correlation between genetic variants of the DEFB1 and TLR9 genes and risk of MTCT of HIV-1, thus confirming the role of innate immunity in perinatal HIV-1 infection. Strategies aimed at activating this innate immunity may contribute in preventing pediatric HIV-1 infection and AIDS.

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INFANT FEEDING MODALITIES AND MORBIDITY IN HIV INFECTED WOMEN IN RESOURCE-POOR COUNTRIES. A MULTICENTER STUDY IN SUBSAHARAN AFRICA

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Background. The optimal feeding modality of infants born to HIV-infected mothers in resource-limited settings is still the subject for debate. WHO guidelines recommends exclusive formula feeding wherever it is available, feasible, affordable, safe and sustainable (AFASS). In all other instances, exclusive breastfeeding and early weaning is recommended. However, formula feeding has been reported to be associated to a higher incidence of infant morbidity in previous studies. Aim of our study was to assess factors associated to (i) feeding practices and (ii) infant morbidity
Methods. HIV-infected women attending post-natal visits at the collaborating centers in Burkina Faso, Cameroon, Guinea Bissau and Tanzania were administered a 16-items questionnaire (translated into French, English and Swahili) aimed at assessing factors associated to (i) feeding practices and (ii) infant morbidity. Questionnaire was designed with the help of a medical anthropologist and administered by trained personnel after having been field tested. Data have been analyzed by univariate and multivariate (hierarchical model) analysis using Epi-Info vers. 5.3.1
Results. Questionnaire were administered from January 2007 to January 2008 to 284 women. In 256 of them, feeding practice was ascertained (table).

	All (256)	Burkina Faso (164)	Cameroun (30)	Guinea Bissau (40)	Tanzania (22)
Formula feeding (never breast milk)	198/256 (77.3%) (71.7-82.3)	136/164 (82.9%)	23/30 (76.7%)	39/40 (97.5%)	0/22 (0.0%)
Exclusive breastfeeding and early weaning	23/256 (9.0%) (5.8-13.2)	8/164 (4.9%)	7/30 (23.3%)	0/40 (0.0%)	8/22 (36.4%)
Mixed feeding	35/256 (13.7%) (9.7-18.5)	20/164 (12.2%)	0/30 (0.0%)	1/39 (2.5%)	14/22 (63.6%)

Practice of formula feeding was associated with a HIV-tested partner (AOR = 4.04; 95%CI 1.12 – 14.56), while a negatively association was founded with farming activity of the mother (AOR = 0.07; 95%CI 0.03 – 0.18). At least 1 episode of fever or diarrhea in the first 6 months was reported by 143/256 (55.9%; 95% CI: 49.5 – 62.0) and by 97/256 (37.9%; 95% CI: 31.9 – 44.1) children respectively.
Exclusive breastfeeding was associated with a lower incidence of diarrhea (70% decrease), even if statistical significance was not attained (p = 0.07). Higher education level (p= 0.02) and independent cooking by the mother (p= 0.04) were also independently associated with a lower incidence of diarrhea
Discussion. Most of HIV-infected puerperas adequately fed their infant when appropriately supported and counselled. However, the use of formula feeding resulted to be a risk factor for higher infant morbidity
Acknowledgement. The study was funded by Grants n. 30G.34, 30G.35, 30G.36, 30G.37, 30G.38, 30G.39 from the Italian Istituto Superiore di Sanità (Rome). Study settings and Italian collaborating Institutions are part of the ESTHER projects and of the Collegamento Internazionale Lotta all'AIDS (CLIA)

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HIV NOTIFICATION TO THE PARTNER AMONG PUERPERAS IN SUB-SAHARAN AFRICA

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Introduction. HIV serostatus disclosure to sexual partner may lead to clear public health benefits (motivation for partner testing, behavior changes, earlier access to medical care), but it may also lead to women rejection, loss of economic support, physical and emotional abuse. Studies from developing countries suggest that a larger proportion of women compared to industrialized countries do not share HIV test result with anyone
Materials and methods. As a part of a questionnaire mainly aimed to investigate infant feeding attitudes and practices among HIV infected pregnant and puerperas populations, disclosure of HIV serostatus to familiar entourage was investigated in five Sub-Saharan African Countries (Burkina Faso, Cameroun, Guinea Bissau, Uganda, Tanzania). Descriptive and inferential data analysis was performed with EpiInfo3.5.1.
Results. All the 224 interviewed pregnant women and 273 of the 284 interviewed puerperas answered the specific questions about partner notification. Disclosure of HIV infection to the partner was reported by 138 (61.6%, CI95% 54.9-68) and 205 (75.1%, CI95% 69.5-80.1) women respectively. Among pregnant women, notification rate was lower for those who were diagnosed only during current pregnancy (38.5% vs 89.1%; OR 0.14, CI95% 0.06-0.32; p<0.0001). Disclosure to the partner was significantly associated with notification to other members of family, particularly to the women' mother (AOR 2.7, CI95% 1.03-7.16; p=0.04) and mother-in-law (AOR 16.5, CI95% 1.99-136.6; p=0.009). Among puerperas, the probability of partner notification was 6 times lower for those who do not cohabit with him (p<0.0001 in multivariate analysis).
Conclusion. Many pregnant women, with new diagnosis of HIV infection, delay partner and family notification and deal with drama by themselves. Such attitude could negatively compromise adherence to mother-to-child transmission prevention programs and delay testing and treatment of other family members.

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PREGNANCY RELATED IMMUNE-DEFICIT IN HIV-INFECTED PREGNANT WOMEN IN RESOURCE-LIMITED COUNTRIES. IMPLICATIONS FOR HAART INITIATION

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Aims. Recent international guidelines suggest that HAART in pregnant women should be initiated when CD4 cell count fall below 350 CD4/µl. Aim of our study is to assess the impact of such new guidelines on the management of HIV-infected pregnant women in resource-poor countries
Methods. All pregnant women coming to St Camille Medical Center in Ouagadougou (Burkina Faso) from 1st jan 2003 to 31st dec 2008 have been offered opt-in voluntary counseling and testing (VCT). Women testing HIV-positive underwent clinical and immunological assessments in order to identify the need to initiate HAART according to national protocol. Those women who entered follow-up at the St Camille Medical Center were also assessed 4-6 months after delivery
Results. During the study period, 476 women tested HIV infected (mean age 28,5 years; σ ± 4,92). Most infections (464/476; 97,7%) were due to HIV-1, while 9/476 were due to HIV-2 and 2/476 women had mixed infection. Baseline clinical and immunological assessment is reported in table 1 below:

Clinical stage (WHO, 2006)		Immunodeficit		
		(< 200 CD4/µl)	(200-349 CD4/µl)	(> 350 CD4/µl)
Stage I	266 (55.9%)	29	85	152
Stage II	161 (33.8%)	47	66	48
Stage III	48 (10,1%)	24	11	13
Stage IV	1 (0.2%)	1	0	0
TOTAL	476 (100%)	101 (21,2%)	162 (34,0%)	213 (44,7%)

According to WHO-2006 criteria, women with CD4 cell count below 200/µl (n. 101) or below 350/µl and WHO stage III (n. 11) have been started HAART. If new international suggestions were to be followed, additional 151 pregnant women (total: 263/476; 55.3%) with CD4 cell count < 350/µl, regardless clinical stage, should have received HAART. 152 HIV-infected pregnant women who were not eligible for HAART were followed after delivery. Table 2 reports their immunological status during pregnancy and 4-6 months after delivery and MTCT rate

CD4 during pregnancy	N. patients	Mean CD4 during pregnancy	Mean CD4 4-6 months after delivery	P	MTCT
200-349/µl	63	282 (σ±37)	356 (σ±102)	ns	4/63 (6.3%)
>349/µl	89	541 (σ±158)	611 (σ±204)	<0,05	2/89 (2.2%)
Total	152	434 (σ±178)	505 (σ±211)	<0,01	6/152 (3.9%)

Out of the 63 pregnant women whose CD4 cell count during pregnancy was between 200-349/µl, 33 were in the same immunological class even after delivery, while 30/63 (47.6%) increased their CD4 cell count over 350/µl and were therefore not eligible anymore for HAART even for the updated WHO guidelines
Conclusions: If all HIV-infected pregnant women with less than 350 CD4 cell count/µl were to be offered HAART, the number of eligible women would more than double in resource-poor settings. Toxicity and resistance monitoring, with particular regard to nevirapine toxicity for those women whose CD4 count exceeds 250/µl, would have to be strengthened. Furthermore, an important significant proportion of women experience a significant immunological restoration after delivery. These disadvantages are to be balanced with a discrete reduction of MTCT of HIV.

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FIVE YEARS (2003-2008) OF MINGHA (MY CHILD) PROJECT IN A RURAL AREA OF WEST CAMEROON: IS THE TIME FOR AN AIDS-FREE NEW GENERATION?

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Since 2003 we set up a PMTCT program (Prevention mother to child transmission) based on local guidelines and local resources. The aim of the study was to facilitate and to describe a prevention model in a setting of real life. In this analysis we take attention especially on children follow-up.
After training of the health operators, ten rural ambulatory centres located in the area of in the departments of Menoua (West Cameroon), were involved in the study. Identification of pregnant HIV women and PMTCT of HIV/AIDS are followed by medical staff supervised by Infectious Diseases Specialists according the Cameroonian national programme. A local staff was growth up during the years. Children were followed up for a minimum period of 12 months recording clinical data every month.
From 2003 to 2008, 7300 women were tested for HIV with a « *opt-out* » strategy. A high acceptance of testing was found (near 99%), but 7.6% of the women were tested at delivery. 343 subjects were HIV-positive and 220 women with their 231 children were followed by the project. ARV therapy at the beginning of the project was nevirapine alone (HIVNET 012) and after 2006 all subjects with CD4 <200 cell/mmc (11%) were treated with HART followed OMS guidelines for resource pour settings. The majority of the women had a vaginal delivery and 97% of them choose formula feeding with social and technical support from the project. In spite of all treatments and practical support, HIV transmission rate was of 6.7-9.2 %. Monthly follow-up with all growth curves will be presented for children (12 in 2003, 24 in 2004, 28 in 2005, 40 in 2006, 52 in 2007 and 8 in 2008). Clinical and immune virological parameters will be reported for both HIV infected and uninfected children.

As health operators in general, involved in the fight against HIV/AIDS in resource-limited settings, we believe that the time has come for the best standard of care to be internationally recommended even in developing countries and, wherever possible, to discuss alternative options where conditions are not favourable. We then would like to ask WHO to reconsider the possibility of recommending, in resource-limited settings, the use of ART in pre-partum for all HIV-pregnant women and during the breast-feeding period for lactating HIV-mothers, regardless of their country of residence and CD4+ cell count, wherever the local situation allows.

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PREVENTION, COUNSELLING AND ACCESS TO RAPID DIAGNOSIS OF HIV INFECTION IN A RURAL AREA OF TANZANIA

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Problem: in African countries access to antiretroviral treatment is still very limited. The Clinic of Infectious Diseases of the University of Chieti is part of a program of partnership between hospitals in the North and South of the World (Esther Project), to support the creation of an AIDS-Center in the Health Dispensary of Iguguno-Singida, in Tanzania.
Methods and results: the protagonists of the project are local people who work in a non governmental organization (ONG), the "World Vision", operating in Singida region, trained by staff of the our Clinic and coordinated by the Assumption Sisters of Catholic Community of Iguguno. The target of the Health Center is the people coming from 3 villages of Singida region: Iguguno, Senene and Lukomo. The Dispensary is equipped for the microscopic diagnosis mainly for infections such as malaria, Urinary Treat Infection (UTI) and infectious diarrhea and also has some anti-malarial drugs and antibiotics to treat them. Within the Health Dispensary, in February 2006, it was possible to open the Ukimwi (AIDS) Center, for counselling and rapid diagnosis of HIV infection. Individuals who reach the Center, after the registration of personal data, are received by an operator who informs them about ways of transmission of HIV infection, risk factors and principals symptoms of the disease. Then the operator proposes the rapid test for the diagnosis of HIV infection. The rapid test consist in an immunological dosage a visual reading for detection of anti-HIV 1, 2 antibodies on capillary blood (Abbott Determine HIV 1/2). During the period 2006-2008 2802 people have reached the Center and were undergoing to test: 1470 (52,46%) were male, 1332 (47,54%) were female, with mean age of 40,5 ± 5,3 years (33,5 years for women, 44,1 for men). After counselling, all individuals agreed to undergo the rapid test, that was positive in 102 cases (3,64%), 69 women (67,65%), with mean age of 32,8 ± 4,8 years, 33 men, (32,35%) with mean age of 42,1± 3,7 years. All patients tested positive were sent to carry out the ELISA test to determine anti-HIV 1,2 antibodies and the Western blot at the main Hospital of Singida.
Conclusions: these early data confirm the low prevalence of HIV infection in the rural areas of Tanzania, but a high incidence of infection among women of childbearing age who are the principal target of our intervention. The second part of the project includes the opening of the Clinic mother–child and the future distribution of antiretroviral drugs.

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PREVALENCE OF HUMAN HERPESVIRUS-8 (HHV-8) SPECIFIC ANTIBODIES AND IMMUNIZATION STATUS FOR HEPATITIS B VIRUS (HBV) IN NON-SEVERE FEBRILE PATIENTS IN TWO TANZANIAN HOSPITALS

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Aim of the study. To determine HHV8 and HBV role in aetiology of febrile syndrome in two hospitals of United Republic of Tanzania.
Methods. During February and March 2007 blood samples were collected from 336 patients in Chake Chake Hospital, Pemba Island, and in Tosamaganga Hospital, Iringa Region. HHV8 DNA was quantified by Real-Time PCR. HHV8 antibodies titers were determined by IFA and HBV markers (HBsAg, HBsAB e HBcAb) by MEIA.
Results. 96/313 patients had HHV8 IgG (30.7%). In Pemba the HHV8 prevalence was lower than the percentage of patients with <1:80 titer (81.0%). Only 6 seropositive subjects resulted positive for HHV8 DNA. The HBsAg, HBsAb and HBcAb prevalence was 4.3%, 37.6% e 29.3% respectively. Out of 277 patients, 70 had a past infection (25.3%). Among patients born after 2002 the percentage of immunized subjects with vaccine was greater (66.7%) and the percentage of not immunized subjects was less (15.7%) than those born before 2002.
Conclusions. HHV8 is endemic in Tanzania. In Pemba the HHV8 prevalence is less than in inland Tanzania, probably because of the diverse cultural and geographical conditions in Pemba (an island in which the prevalent religion is muslin) in respect to the rest of the country and to the reduced prevalence of HIV infection (<1.0% vs 12.0% of young-adult population). The grater part of the children had a low titer of HHV8 antibodies, while the only child with an high titer (≥1:1280) was HHV8 DNA positive: a sign of a recent infection with active viral replication. The presence of 3.9% of HBsAg in the population of children less than 4 years old suggests that, in order to effectively guarantee a universal coverage, an obligatory vaccine against HBV must be carried out to its completion in early years of infancy.

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INCREASING HIV VIRULENCE IN TWO DECADES OF THE ITALIAN HIV EPIDEMIC

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Background. The recent origin and great evolutionary potential of HIV imply that the virulence of the virus might still be changing, which could greatly affect the future of the pandemic. However, previ-

ous studies of time trends of HIV virulence have yielded conflicting results. **Methods.** We used an established methodology of the Swiss HIV Cohort Study (AIDS 2006; 20:889-894) to assess time trends in the severity (virulence) of untreated HIV infections in a large Italian cohort. We characterized virulence by the decline slope of the CD4 count (n=1423 patients) and the viral setpoint (n=785 patients) in untreated patients with sufficient data points. We used linear regression models to detect correlations between the date of diagnosis (ranging between 1984-2006) and the virulence markers, controlling for gender, exposure category, age and CD4 count at entry.
Results. Over two decades of observations, the rate of CD4 decline in newly diagnosed infections has almost doubled, while the viral setpoint has been increasing at a rate of about one log per 16 years since RNA measurements had become available. The decline slope of the CD4 count and the viral setpoint displayed highly significant correlation with the date of diagnosis pointing in the direction of increasing virulence; the trends towards increasing virulence have been stable throughout the time span of the cohort. A detailed analysis of riskgroups revealed that the epidemics of intravenous drug users started with an apparently less virulent virus, but experienced the strongest trend towards steeper CD4 decline among the major exposure categories. Therefore, two stages in the time evolution of CD4+ slopes within the riskgroups were found: in the first stage, intra-venous drug users lost their initial advantage of slower CD4+ decline compared with heterosexual subjects and men who had sex with men. After the convergence of the three categories, the second half of the observed epidemic has been characterized by a steady coupled trend towards steeper CD4 slopes in all groups.
Conclusions. Increasing virulence of the HIV epidemic has been found over time in Italy. Comparison of discordant patterns between riskgroups and epidemics hints at a converging trend, which might indicate that an optimal level of virulence might exist for the virus.

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TREATMENT AND OUTCOME OF PULMONARY ARTERIAL HYPERTENSION IN HIV-INFECTED PATIENTS: A REVIEW OF THE LITERATURE

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Pulmonary arterial hypertension (PAH) is a life-threatening complication of HIV infection. The prevalence of HIV-associated PAH (HIV-PAH) seems not to be changed over time, regardless of the introduction of highly active antiretroviral therapy (HAART). HIV-PAH treatment is similar to that for all PAH conditions and includes lifestyle modifications, general treatments, and disease-specific treatments.
We reviewed the cases of HIV-PAH reported in the Literature in order to evaluate the role of HAART and specific PAH therapy in the prognosis and outcome of HIV-PAH. The research was performed through the PubMed database, by using the following key words: *human immunodeficiency virus, AIDS, pulmonary hypertension, antiretroviral,* and *treatment*. The outcome was reported as survival at the end of the observation period of each study.
We found 509 patients with HIV-PAH described in the literature to date. At the end of follow-up period, survival rates were 55% and 22% among patients treated or not with antiretroviral therapy (ART), respectively (p=0.02). Moreover, survival rates at the end of follow-up were 76% and 32% among patients treated or not with specific therapy for PAH (PAH-ST), respectively (p<0.0000001). Survival rates were 69% and 38% among patients treated or not with ART and PAH-ST, respectively (p=0.02).
Specific therapy for PAH should be strongly recommended in patients with HIV-PAH. The role of the HAART in influencing the outcome of HIV-PAH is controversial, even if some evidences seem to indicate a beneficial effect in the clinical course of the disease.

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IS THERE STILL A NEED FOR PALLIATIVE CARE AMONG HIV-INFECTED PERSONS IN THE HAART ERA?

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Background. The use of HAART has significantly reduced AIDS-related mortality in the developed world and has determined AIDS conversion from a rapidly fatal illness into a manageable chronic disease. In the HAART era, younger HIV care providers have not had much experience in the issues surrounding end-of-life and palliative care, and it has been reported an increasing proportion of deaths due to co-morbidities such as chronic hepatitis B and C and concomitant malignancies (both AIDS- and non-AIDS defining), in addition to antiretroviral treatment failure and HAART-related toxicities. Thus, HIV disease has shifted to a trajectory more typical of chronic, progressive illness in whom palliative care should be more considered.
Objectives. In order to evaluate changes in cause of death (COD) and the need for palliative care in the HAART era we retrospectively reviewed clinical records of 664 HIV-infected patients who died at "L. Spallanzani" Institute between January 1999 and December 2007.
Methods. 664 patients were grouped into 1999-2001 (229), 2002-2004 (244), and 2005-2007 period (191). COD were grouped into 7 categories. AIDS-related categories: AIDS-related malignancy, AIDS OI. Non-AIDS-related causes: hepatitis/liver-related, other (non-opportunistic) infections, non-AIDS-related malignancy. Other/unknown. When more than one cause of death was found, the most likely underlying cause was scored independently by a panel of three physicians until a final consensus was reached.
Results. Median age was 42.9 years, 78.8% were men and 9.3% were foreign born. 485 patients were AIDS cases and represent 11.3% of 4.307 AIDS deaths reported in Italy in the same period. At our Institute, in-hospital mortality rate among HIV-infected patients declined from 5.1% in 1999-2001 to 4.4% in 2005-2007 period.
The proportion of deaths related to a non-AIDS-defining event increased from 42.4% in 1999-2001 to 50.8% in 2005-2007 period. Particularly, proportion of liver-related and non-AIDS defining malignancies deaths increased from 15.7% to 27.2% and 6.6% to 8.9%, respectively.
Conclusions. In the HAART era, HIV/AIDS is a chronic, progressive disease that may be effectively managed in many patients but it is still associated to a significant mortality. Death rates from non-AIDS-related conditions, particularly hepatic failure and malignancy, may continue to rise in future years as HIV-patients survive for longer. In this context, need for palliative care will become more important and both palliative and curative approaches should be more considered throughout the course of HIV/AIDS disease. Patients with HIV/AIDS have palliative care needs at each stage of the illness, as side effects of HAART and different symptoms arise with impact on quality of life. HIV care provider should be more informed about the utility of providing palliative care, even for patients who are not in end-of-life stage of AIDS illness.

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ANTIRETROVIRAL PROPHYLAXIS FOLLOWING SEXUAL EXPOSURE IN ITALY. THE ITALIAN REGISTRY OF ANTIRETROVIRAL POST-EXPOSURE PROPHYLAXIS (IRAPEP)

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Antiretroviral prophylaxis (PEP) following potential sexual exposure to HIV is increasingly offered in Italy. Formal recommendations were issued in 2002 and updated in 2008.
The Italian Registry of Antiretroviral PEP enrolls 98 HIV clinics nationwide; for each case, details are collected on standardized forms: demographics of the exposed individual, type of exposure, characteristics of the source, prescribed PEP regimen, occurrence of adverse effects, duration of the prophylaxis, date and reason of premature PEP interruption, if any. From 1997 to 2008, 640 sexual cases were reported; median age was 31 years (range 13-68); 43% were women.
Exposures within stable serodiscordant couples (SSC) accounted for 44% (PEP was started after a median of 2 hours from the exposure), sex with casual partners (SCP) for 40% (PEP started after a median of 12 hours), rape for 10%; in 6% of cases details were not available.
Among SCP, the source serostatus was unknown in 79%, in 19% of cases the source was reported or tested as HIV+, while in 2% the source tested negative. In 85% of cases occurring in SSC and in 65% of those occurring after SCP, the exposed subjects reported to have used condom that slipped or broke.
Almost all PEP regimens included 2 NRTI (mostly ZDV plus 3TC) plus a PI. The PI more frequently included in the regimen changed over time.
Adverse effects, mostly gastrointestinal symptoms, were reported in 281 cases.
Treatment was completed in 467 cases (73%); of the remaining 173, 45 (26%) discontinued PEP because of adverse effects, 31 (21%) because of self-withdrawal due to risk re-assessment, in 14 (8%) because the source tested negative and 76 (44%) were lost to observation during the 4 weeks PEP course.
A negative HIV test at more than 6 weeks from exposure was available for 286 subjects (46%), with no significant difference according to source serostatus or type of exposure. Four seroconversions were observed, all in MSM. Two of them were in SSC, and one after occasional intercourse; all acknowledged subsequent unprotected exposures. In the fourth case following an occasional intercourse, the patient seroconverted for HCV at three months and for HIV at 7 months of follow up, and did not reported subsequent at risk exposures.
Information on PPE, including risk assessment, potential efficacy and toxicity, should be provided to at-risk subjects and especially to serodiscordant couples possibly in advance with respect to a potential exposure, and always in the context of counseling on safe sex, reinforcing messages on primary HIV prevention and consistent condom use. The potential source of exposure is rarely available for testing in the non-occupational setting, and exposures are often not isolated. Thus, it is often impossible to determine whether seroconversion resulted from failure of PEP or from other exposures. Minimizing subsequent HIV exposures will be critical to enhancing the effectiveness of PEP. Primary prevention remains essential.

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MOLECULAR AND PHYLOGENETIC ANALYSIS OF HIV TYPE 1 NON-B SUBTYPES IN EMILIA ROMAGNA

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A unique trait of HIV is its ability to generate multiple genetic variants that may be more fit and virulent. In the past decade, an increasing spread of HIV-1 non-B and circulating recombinant forms (CRFs) has been observed. This phenomenon seems to be strictly linked to the growing number of immigrants from non-Western Countries. Even if in our country, the percentage of infection with non-B subtypes has been reported to range from 5.4% to 12.6%, little information is available on the transmission of non-B viral strains in Emilia Romagna. To improve our knowledge, we performed a retrospective biomolecular study on 1412 isolates (years 2006-2008) to evaluate the presence of non-B subtypes and to estimate the amino-acid changes able to confer a high level of resistance to antiretroviral drugs.
Complete HIV-1 PR and partial RT regions were sequenced from all HIV-1 positive samples and phylogenetic analysis was performed. The sequences were first analyzed using the REGA HIV-1 Subtyping Tool, aligned and compared with reference strains using CLUSTAL X and then edited manually using Bioedit program. The gaps were removed from the final alignment and separate PR and RT tree were only performed on the non-B identified subtypes using F84 model of substitution with both neighbour joining (NJ) and maximum likelihood (ML) tree building methods. Out of 1412 HIV-1 infected individuals analyzed, 1249 (88.5%) sequences clustered with subtype B.
The presence of non-B subtypes was found in Italian (44%) and not-Italian (55%) patients, characterized by HIV-1 subtype F1 in 30% of the subjects analyzed. Moreover, twenty-six sequences (16%) clustered with subtype C, twenty-one (12.8%) with subtype G, ten (6.1%) with subtype A1 and only one (0.6%) with subtype D.
The subtypes analysis also classified 27 (16.5%) sequences as putative CRFs (02_AG, 01_AE, 06CPX, 03AB, and 12BF). Finally thirty sequences (18.4%) remained unassigned (probably mosaicisms), even if we cannot excluded that they are a recombinant form. Most (51/90) of non Italian individuals infected with non-B subtypes were from a European countries and 39/90 were from outside Europe.
Major mutations conferring resistance to antiviral drugs were found in nine HIV-1 non-B subtypes drug naïve patients (for example K103N, Y181C); however, we found different resistance's pattern with minor mutations correlated with resistance to PIs (especially AMP/fAMP, AMP/fAMP/r, TPV/r, SQV/r).
In conclusion the interracial blending is slowly introducing novel HIV-1 subtypes with increasing nucleotide heterogeneity in infected population. Therefore, a molecular monitoring is needed to follow the constant evolution of the HIV-1 epidemic and to better establish the rate of progression to AIDS and the resistance pattern to antiretroviral drugs.

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PREVALENCE, INCIDENCE AND CHARACTERISTICS OF THE HIV POPULATION IN THE BRESCIA PROVINCE BY A COMPOSITE DATABASE: RESULTS OF THE S.E.R.I.H.A. STUDY

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Objectives To estimate prevalence, incidence and characteristics of the HIV infected population in the Brescia Local Health Agency.
Methods Population-based study of the Brescia Local Health Agency (Northern Italy) in the period 2003 to 2006. In order to capture any HIV diagnosis, a composite database was used merging data of the following: (i) Brescia Local Health Agency database which keeps records of the services provided; (ii) the internal database of the Institute of Infectious and Tropical Diseases; (iii) Registry of AIDS cases; (iv) Registry of Causes of Deaths (ICD-IX=279.1); (v) Centre for International Health for assistance to immigrant patients and; (v) Centre for Sexually Transmitted Diseases Diagnosis and Care. Logistic regression analysis was performed to study associations between CD4+ T-cell at HIV diagnosis and patients' characteristics. Methodological details for construction of the database and analyses will be shown during the presentation.
Results Prevalence of HIV patients increased constantly, from 257/100,000 inhabitants in 2003, to 280/100,000 in 2006, that is, an annual increase by 2.9%. The increase in prevalence cannot be ascribed to an increase in new cases (26 new cases/100,000 in 2004, 25/100,000 in 2005 and 15/100,000 in 2006); a marked decrease of HIV/AIDS deaths and patients loss to follow-up was observed. The average age increased continuously from 40 years in 2003 to 42 years in 2006, while the average age of new cases was stable at around 37.5 years. Females represented less than a third of prevalent cases, although their proportion appeared to increase among the new cases. At HIV diagnosis, CD4+ T-cell counts were <200/mm^3 in 25.1% of patients before 2004 -vs- 33.6% in the study period; lower CD4+ counts were independently correlated with male gender, recent year at diagnosis, increasing age, and regular immigrant status (vs- Italian or irregular immigrants for whom a specific program for early diagnosis is ongoing).
Conclusions Incidence of HIV in our population is very much higher than that estimated in other Italian areas using different methods. Early diagnosis programs ongoing in illegal immigrants should be implemented outside this population. While waiting for HIV-diagnosis notification, population based studies by merging of different databases could offer useful information for public health.

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HIV INFECTION PROGRESS AMONG HOMOSEXUALS IN NAPLES

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Introduction. The most diffused HIV infection way of transmission is the sexual one. Both heterosexual and homosexual, non protected by condom, sexual intercourses can be the cause of infection transmission.

The aim of this paper is to evaluate the HIV infection concourse and progress among homosexuals users of the Screening in Anonymity Service of Domenico Cotugno Hospital of Naples from January 2000 to December 2008 (See the table below).
Results

	Homosexuals come to the service for the first time	Average age	Homosexuals HIV positive after test	<30	>30	Homosexuals positive in comparison with all the positive subject
2000	23/305 (7.5%)	32 (21-54)	4 (17.3%)	-	4 (100%)	4/28 (14.2%)
2001	27/285 (9.4%)	30.2 (19-56)	3 (11.1%)	1 (25%)	2 (75%)	3/31 (9.6%)
2002	37/327 (11.3%)	29.3 (19-44)	4 (10.8%)	3 (75%)	1 (25%)	4/41 (9.7%)
2003	27/322 (8.3%)	29.1 (18-49)	2 (7.4%)	-	2 (100%)	2/35 (5.7%)
2004	19/324 (5.8%)	31 (18-49)	4 (21%)	-	4 (100%)	4/47 (8.5%)
2005	36/341 (10.5%)	30.5 (18-48)	10 (27.7%)	5 (50%)	5 (50%)	10/44 (22.7%)
2006	57/384 (14.8%)	32 (19-62)	13 (22.8%)	7 (54%)	6 (46%)	13/53 (24.5%)
2007	55/394 (13.9%)	32.7 (19-60)	5 (9.09%)	1 (20%)	4 (80%)	5/39 (12.8%)
2008	82/412 (19.9%)	30.2 (16-58)	17 (20.7%)	7 (41%)	10 (59%)	17/56 (30.3%)

From the table it can be deduced that:
- from 2005 it is increased the number of the service user as well as the percentage of homosexual ones;
- from 2004 it has been registered an increasing in number of homosexuals positive to the HIV test in accordance to the increase of users;
- in the last four years it is increased the percentage of seropositive subjects among young men under 30 years of age while in the past years the seropositive homosexuals were mostly young men over 30 years of age;
- from 2005 there was an increase in the percentage of seropositive homosexuals compared with the total of seropositive subjects.

Discussion. The data collected show that even if there was a major risk perception among homosexuals (increase of users), it has been observed a minor protection in sexual intercourses (increase in the percentage of seropositive homosexuals in comparison with the total of seropositive subjects) and a decrease in the infection threshold (increase of seropositive subjects among young men under 30 years of age).
Conclusions. Based on what it has been observed, it is evident the need to promote more effective informative campaigns, especially addressed to young men, in order to encourage the adoption and preservation of more safe sexual behaviours.

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RETROSPECTIVE EPIDEMIOLOGICAL SURVEILLANCE OF HIV INFECTION IN THE HEALTH AGENCY OF THE BRESCIA PROVINCE: FOCUS ON HIV AND MIGRANTS (S.E.R.I.H.A. STUDY)

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Objective: analysis of main epidemiological features of HIV infection among migrants in comparison to local population in the Brescia Province over years 2003 to 2006.
Methods: an accurate integration of the following databases was performed: (i) database of the Local Health Agency of the Brescia Province (ASL Brescia); (ii) database of the Department of Infectious Diseases of Spedali Civili Hospital of Brescia; (iii) database of AIDS cases of the Department of Medical Prevention of ASL Brescia; (iv) database of ISTAT death causes (ICD-IX=279.1); (v) databases of Sexually Transmitted Infection and Migrant Outpatient Departments of the International Health Center of the Brescia ASL. A logistic regression analysis was performed to study associations between HIV diagnosis and patients' characteristics. Incidence and prevalence of HIV in migrants were obtained taking into account also the irregular migrants. To do so, the number of total migrants was increased by 25% according to local estimation.
Results: migrants accounted for 15.3% of total HIV+ subjects (505/3308). Among them 98 (19.4%) were irregular. HIV+ migrants' area of origin was Sub-Saharan Africa in 57% of the cases, Latin America 17%, Europe 17% and Asia 6%. While the percentage of migrants in local population increased from 11.8% in 2003 to 15% in 2006, the prevalence of HIV infections in the migrant population was stable: from 331 to 310/100,000 in the same period. The incidence of HIV in migrants was more than twice higher than in local population, but a decreasing tendency was recorded: from 55/100,000 in 2004 to 39/100,000 in 2006. Compared to local HIV+ population, HIV+ migrants were younger (36.1 vs 43.2 years), with higher prevalence of women (50% vs 25%) and with less probability to take antiretroviral therapy (Italians: 83.4%, regular migrants: 77.8%, irregular migrants 30.6%)
Conclusions: the study provides evidence of the importance of a wide offer of HIV-test, optimization of HIV-disease management and easier access to therapy for the migrant population.

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LATE TESTERS IN HIV SURVEILLANCE SYSTEMS: TREND IN 1992–2008

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Background: The aim of the present study is to examine the number of new HIV diagnoses in the HIV surveillance system of Modena, and to identify risk factors associated with presenting at late stages of HIV disease.
Methods: Data were collected from persons with a new HIV antibody positive test and at least one CD4+ lymphocyte count and recorded stage of HIV disease, from 1992 to 2008 (divided in three period) . Subjects were defined as "late presenters" if they had a CD4 cell count <200 cells/ mm^3 or presented with AIDS within 3 months of the HIV positive test.
Results: During the study period 1008 persons newly diagnosed with HIV infection were notified, of whom 934 (93%) met the inclusion criteria. The proportion of men decreased over time, from 72.6% in 1992-98 to 67.6 % at the end of the study period. The median age at the time of diagnosis increased from 32.5 years in the first period to 37.3 years in the last period (p =0.04), especially in men (from 33.1 to 339.7 years, p=0.000). IDUs decrease over time (from 34.7% to 4.1%) while sexual transmission increase in HC (from 45.7% to 72.1.1%), but not in MSM (from 19.7% to 23.8%) in the first and in the past study period. Persons born outside Italy increased from 14.8% in 1992-98 to 38.1% in 2002-08 (p=0.000). The proportion of late presenters remained constant over time from 42.4% in 1992-1998 to 38.9% in 2004-2008 (p=0.106); as like of AIDS presenters from 23.2% in first period to 23.4 in the last (p=0.106). Older age (per a 5 years increase) (OR 1.31; 1.22-1.41 95%C.I. ; p=0.000); male gender (OR 2.10; 1.49-2.97 95%C.I.; p=0.000) and foreign born (OR 1.97; 1.37-2.83; p=0.000) were the only determinants of being a late presenter. A reduction in risk was observed in the last two periods, (p= 0.001; P=0.003 respectively).
Discussion: Our study shows that about 40% of patients, who presented for care in the most recent time period in the Modena province, were at an advanced stage of immune deficiency of whom half presented with an AIDS-defining disease. . Efforts are needed to encourage HIV testing and reduce the proportion who first seek HIV care at such a late stage.

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HIV/AIDS AND MENTAL ILLNESS DUAL DIAGNOSIS: EXPLORING HEALTHCARE PROFESSIONALS' PERSPECTIVE

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Background. A growing body of scientific literature emphasizes the strong linkage between HIV/AIDS and serious mental illness. In the Italian context, new care models for management of dual diagnosis are increasingly requested, because healthcare professionals (HCP) have to face up the difficulty emerging by this new situation. To bridge these gaps, the present project aimed at studying the representations of dual diagnosis, analyzing HCP's experiences, in order to understand difficulties and create future good practices in healthcare services.
Methods. Dual diagnosis representations were detected by the use of an *ad hoc* questionnaire made up of 29 questions regarding two macro-areas. The first area has detected HPC's representations in terms of their perceptions, opinions and judgements concerning four different fields of experience: a)Micro and macro-social environment, b)Healthcare system, c)HCP's role and function, d)HIV/AIDS and dual diagnosis. The second one aimed at collecting socio-demographic and role-related data to describe the different population segments identified. Questionnaires were analyzed by a two-step statistical multidimensional technique: the Multiple Correspondence Analysis (MCA), to extract the factorial dimensions summarizing the general variability of the answer patterns within the whole sample, and the Cluster Analysis (CA) to identify homogeneous groups of individuals, each characterized by a peculiar response profile.
Results. The questionnaire was administered to a proportional cluster sample of 457 HCP – 60% of whom female – drawn by HIV/AIDS (35,9%) and Mental Health (64,1%) services located in the metropolitan area of Rome. MCA helped identifying two factors, interpreted as two "Latent Affective Dimensions of Sense", that HCP use to connote their experience of dual diagnosis. The first dimension

highlighted the representation of the relation with the users in terms of *Refusal* vs. *Idealized acceptance*. The second one highlighted the representation of the context in terms of *Devaluation* vs. *Trust*. These two dimensions shaped a symbolic field within which 6 different clusters of HCP were identified, corresponding to as many different ways they represent/depict the aims of Health Service in relation to the comorbidity. Each cluster, therefore, corresponds to a specific profile of HCP: the distrusting; the familistic; the integration professional; the critic; the idealizing; the disappointing.
Comments. Our results highlight the extreme heterogeneity of the HCPs' representations in relation to HIV/AIDS-Mental illness comorbidity, and about their role in Health Service. The differences observed, moreover, take into account different vocational training demands revealing the need of HCP to improve professional quality. Our data suggest that future training programs should be shared and common, including not only technical contents but also the representations of HCP about their professional context.

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HIV-1 PRIMARY INFECTION: VIROLOGICAL FINDINGS IN 78 PATIENTS REFERRING TO THE AZIENDA OSPEDALIERO-UNIVERSITARIA PISANA (AOUP)

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During last fifteen years, 78 subjects, 64 male and 14 female (median age 36 years – range 18 to 70 years) were admitted to Infectious Disease Unit of AOUP with primary HIV infection, diagnosed on the basis of compatible clinical syndrome, the availability of a negative HIV antibody test result during the last 12 months and/or a restricted pattern of anti-HIV western blot reactivity (limited to three viral antigens). 74 subjects were Italians, 3 Africans and 1 French. Clinical, immunological and virological data were collected at the moment of admission and after three and six months of antiretroviral therapy. In 54 subjects (69%) the infection was acquired by sexual route (33 hetero), 5 patients were IDU, and in 19 patients the modality of infection was unknown.
Anti-retroviral treatment was administered only to 59% of patients, according to guidelines effective at the time of diagnosis.
Routine HIV antibody test was performed using a commercial anti-HIV assay (Dade-Behring) and an HIV-1 western blot (WB) (Genelabs blot HIV, vs 2,2). CD4+ T-lymphocyte counts were assessed by standard flow cytometry methods and HIV viral load was determined by Cobas AmpliPrep-Cobas Amplicor vs 1.5 and COBAS AmpliPrep/COBAS TaqMan HIV-1 assay vs 1 (Roche Molecular Systems).
Genotyping was carried out with the ViroSeq™ HIV-1 Genotyping System, vs2.0 (Abbott Diagnostics). Each sequence was submitted to Stanford University database (http://hivdb.stanford.edu) and mutations were defined as differences from the consensus B reference sequence. Subtype assignation in the *pol* region was inferred by comparison of sequences with those stored in the Stanford database and in the Los Alamos HIV database (BLAST search).
At the time of diagnosis, in one subject the WB resulted indeterminate, in 55.5 % of samples reactivity was limited to 2-4 HIV antigens, in 17.4% sera reacted with more than 4 antigens and 25.8% of patients showed a complete pattern. Median CD4+ count was 551 cells/mm^3, and HIV-1 viral load ranged from 10^2 $\log_{10}$ to 10^7 $\log_{10}$. Genotyping was performed in 67 subjects, and on the basis of *pol* region sequences, 71.6% of the patients were infected with subtype B virus, followed by subtype F (17.9%), unique recombinant forms (URFs) (5.9%), subtype C (2.9%) and CRF02_AG (1.5%). Baseline drug resistance was detected in 5 patients.
Our results show that: a) the sexual route of infection was the most frequent; b) 28.4% resulted HIV 1 non B subtype infected; c) among these, subtype F was the most prevalent; d) prevalence of URFs appear to be relevant and should be taken into account as a marker of genetic evolution of HIV 1 epidemic.

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A RELATIVELY SLOW RISK OF DISEASE PROGRESSION IN HIV-POSITIVE PATIENTS WITH INDOLENT INFECTION HAS BEEN FOUND IN THE ICONA COHORT

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Background: As HIV infection faces its third decade of epidemics, estimated life-expectancy for HIV-positive persons exceeds 30 years when considering patients aged 20-30 years and diagnosed between 1996-2005. However analyses including severe non-AIDS defining events as outcome and applied to the earliest patient population remain to be carried out.
Objective: To estimate the 20-year survival free of severe events (AIDS, death, severe cardiovascular events, cirrhosis and non-AIDS defining malignancies) in the ICoNA population with evidence of a history of ≥10 years with HIV.
Methods: All patients in the ICoNA cohort who, at the time of enrolment, were free of severe events, and date of their first HIV-positive test ≥10 years before enrolment were included in the analysis. The K-M estimates of remaining free of severe events over time was calculated. A multivariable Cox regression model was used to identify predictors of remaining event-free. Factors included in the analysis were: gender, age, mode of HIV infection, year of HIV/enrolment as time-fixed, and HCV co-infection, CD4 count, viral load and current use of ART as time-dependent covariates.
Results: We studied 1,009 patients, 24% females, 85% IDU with a median age at enrolment of 37 years (range:29-71). The median year of first HIV+ test, year of enrolment, CD4 count and viral load were: 1986 (1981-1998), 1997 (1997-2008), 426 cells/mmc3 (5-1406), 4.2 (1.3-7.1) log copies/mL. 65% of participants (n=654) started ART at some point, the median year of starting was 1998 (1997-2008). By 20 years of patients' first HIV+ test, 22% (95% CI:17-27) had developed a severe event or had died. 129 events observed over a median of 4.5 years contributed to the calculation of this probability and were: 84 AIDS diagnosis (65%), 4 deaths (3%), 6 severe cardiovascular events (5%), 30 cirrhosis (23%) and 6 non-AIDS defining malignancies (5%). At multivariable analysis, the adjusted relative hazards of experiencing severe events or dying was associated with current CD4 cell count (RH per 100 cells higher 0.82; 95%CI 0.75-0.90), current viral load (RH per log copies higher 1.58; 95%CI 1.34-1.86), and current use of ART (RH 2.00; 95%CI 1.33-3.00). No association was found between the outcome and gender, age, mode of HIV transmission, HCV co-infection, year of HIV diagnosis, and year of enrolment.
Conclusions: In our selected population of patients who were living with HIV infection for ≥10 years without ART, the 20-year risk of experiencing a severe event or dying was relatively low at 22%. Classic disease markers were the strongest progression determinants, while to receive ART showed a protective effect. In light of the remarkable success of cART in achieving chronic viral suppression, the objective of curing HIV infection, remaining to date an elusive goal, may be challenged.

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CO = Oral communication; PP = Poster presentation; PO = Poster