Abstracts presented at the
10th International Workshop on Adverse Drug
Reactions and Lipodystrophy in HIV
London, UK, 6–8 November 2008
Organizing Committee and Plenary Speaker Disclosures

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Professor Weller is co-chair of an Oversight Committee which oversees a large programme of research on the side effects of HIV drugs. This effort was initiated by the EMEA in 1999. This programme is funded by all of the above companies and funds are handled by a contract research organisation (CRO), from which his honorarium is paid and then paid into a department fund and not kept personally. Travel, hotel accommodation and meals are also covered by the CRO.

Plenary Speakers:

Pierre Corvol
Nothing to disclose

William Evans
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Lewis Kuller
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Vamsi Mootha
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Kitt Petersen
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Stuart Ralston
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ORAL PRESENTATIONS
ABSTRACT O-01
Antiviral Therapy 13 Suppl 4:A3

Differential alterations of gene expression in visceral versus subcutaneous adipose tissue from HIV-1-infected, HAART-treated patients with lipodystrophy: a pilot study

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Aim: Opposite alterations (lipatrophy versus hypertrophy) are often observed in subcutaneous (SCA) versus visceral (VSA) adipose tissue in HIV type-1 (HIV-1)-infected, highly active antiretroviral therapy (HAART)-treated patients with lipodystrophy. Although the molecular alterations in SCA from these patients have been studied previously, no data is available on gene expression disturbances in VSA because of the difficult availability of such adipose samples. The present pilot study takes advantage of the availability of seven samples of VSA from HIV-1-infected, HAART-treated patients with lipodystrophy collected after minor surgery. The objective was to compare gene expression alterations in SCA and VSA depots to gain insight in their differential responsiveness to HIV-1 infection and antiretroviral treatment.

Methods: SCA from 10 and VSA from 7 HIV-1-infected, HAART-treated patients with lipodystrophy as well as SCA and VSA from 10 non-infected control individuals were analysed. Four samples from the patient groups corresponded to double biopsies of SCA and VSA from the same patient. Main patterns of sex and age distribution, cumulative antiretroviral treatment pattern (including zidovudine, as well as protease inhibitors) and systemic metabolic alterations (lipidemia and HOMA) were not significantly different between the patient groups.

Results: Mitochondrial DNA levels were decreased in SCA and VSA from patients with respect to their corresponding controls. A similar profile of decrease in both depots was observed for mitochondrial mRNA levels. The increase in mitochondrial protein amount already described in SCA from patients was equally observed in VSA from patients. The same occurred for CD68 mRNA, indicative of macrophage infiltration and for HLA-DQα2 mRNA. This was confirmed by immunoblot analysis of β2-microglobulin levels that was induced both in SCA and VSA from patients.

Conclusions: To our knowledge, this is the first study in which a gene expression analysis of VSA from HIV-1-infected, HAART-treated patients with lipodystrophy is reported. Similar alterations in markers of mitochondrial function and inflammation in SCA and VSA from patients suggest that these processes are unlikely to be the main determinants of the differential behaviour of the two adipose depots in patients. No impairment in gene expression for marker genes of adipogenesis in VSA is consistent with the lack of atrophy of this depot and highlights the relevance of the adipogenic differentiation processes in the outcome of adipose tissue depots in response to viral and drug-induced insults.

ABSTRACT O-02
Antiviral Therapy 13 Suppl 4:A3

HIV protease inhibitors differently affect human subcutaneous and visceral fat: they induce IL-6 production and alter lipid storage capacity in subcutaneous but not visceral adipose tissue explants

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Objectives: Antiretroviral therapy (ART)-related lipatrophy is associated with a chronic low grade adipose tissue inflammation and an increased local production of interleukin (IL)-6. ART is also associated with a chronic excess of circulating fatty acids, which could account for increased liver triglyceride production and promote the development of an insulin resistant state. We have previously identified in human adipose tissue a new adipocyte lipid metabolic pathway, glyceroneogenesis, that participates during lipolysis in the recycling of fatty acids towards triglycerides. Mice invalidated in adipose tissue for its key enzyme, phosphoenolpyruvatecarboxykinase (PEPCK-c), present smaller adipose tissue depots together with increased systemic concentration of fatty acids. Thus, we wondered whether ART could affect glyceroneogenesis in human adipose tissue and whether increased IL-6 production could be related to altered lipid metabolism. As the ART-related lipodystrophic syndrome differentially affects subcutaneous and visceral fat depots, we comparatively studied the effect of ART in both.
Methods: Human adipose tissue explants from abdominal subcutaneous (SCAT) and visceral depots (VAT) were recovered from non-HIV-infected lean women during gynaecologic surgery. They were treated ex vivo with 10 mM of stavudine, nelfinavir, lopinavir or ritonavir. Glycerol, fatty acids and cytokines secretion were quantified in the culture medium. Fatty acids re-esterification by glyceroneogenesis, PEPCK-c enzyme activity and gene expression (by real-time reverse transcriptase-PCR) were evaluated in the explants.

Results: We observed that the three protease inhibitors (PIs), but not stavudine, increased fatty acid efflux from SCAT in the lipolytic situation. This effect was related to a PI-induced increased fatty acid re-esterification by glyceroneogenesis. Importantly, this effect was observed in SCAT but was absent in VAT. Accordingly, the different PIs were able to increase IL-6 gene expression and secretion in SCAT while they had no effect on these parameters in VAT. We then evaluated whether IL-6 overproduction could be responsible for altered lipid storage. We observed that IL-6 was able to decrease PEPCK-C enzyme activity. To further confirm that glyceroneogenesis is affected by PI-induced inflammation of SCAT, we showed that the addition of an anti-inflammatory agent inhibiting the NF-kappaB pathway (parthenolide) to nelfinavir prevented both IL-6 gene activation and PEPCK-C gene inhibition induced by the PI.

Conclusions: Our results show, that some PIs induce an inflammatory profile in human SCAT as indicated by increased IL-6 production. This resulted in decreased fatty acid re-esterification through the glyceroneogenesis pathway and increased fatty acid release. These alterations could help to understand the ART-related SCAT lipoatrophy and systemic hyperlipidaemia. Under similar conditions, VAT was resistant to the deleterious actions of PIs. These data are in accordance with the clinical discordant effect of ART in the two fat depots observed in HIV-related lipodystrophies.

ABSTRACT O-03

Antiviral Therapy 13 Suppl 4:A4

Acute effects of ritonavir in GLUT4 and GLUT2 knockout mice

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Objectives: The ability of HIV protease inhibitors (PIs) to acutely block facilitative glucose transporter (GLUT) activity has been established in vitro and is believed to contribute to altered glucose homeostasis in vivo. However, several GLUT-independent mechanisms have been postulated to mediate both inhibition of peripheral glucose disposal and impairment of glucose-stimulated insulin secretion. To determine the specific contribution of GLUT blockade on PI-mediated insulin resistance, the acute effect of ritonavir on glucose homeostasis was investigated in previously established genetically modified mice lacking either the insulin-responsive transporter GLUT4 (G4KO) or the pancreatic transporter GLUT2 (G2KO).

Methods: G4KO and non-transgenic C57BL/6J control mice (n=11 per group) were given a single 10 mg/kg intraperitoneal injection of ritonavir or vehicle 15 min prior to the start of a standard 2 g/kg intraperitoneal glucose tolerance test. Pancreatic islets were isolated from G2KO mice, which have GLUT1 expressed under the control of the rat insulin promoter in order to circumvent the neonatal lethality associated with GLUT2 ablation. Islets were then exposed to 20 μM ritonavir or vehicle for 60 min in the presence of 1 and 16.7 mM glucose and total insulin secretion was assessed.

Results: Under control conditions, G4KO mice exhibited increased fasting blood glucose values when compared with wild-type C57BL/6J mice (340 ±47 and 116 ±10 mg/dl, respectively, P<0.001). Importantly, ritonavir produced a significant impairment in glucose disposal in wild-type mice (blood glucose at 30 min=322 ±32 mg/dl with PI versus 237 ±21 mg/dl without PI, P<0.001) but did not exacerbate glucose intolerance in G4KO mice (blood glucose at 30 min=427 ±40 mg/dl with PI versus 452 ±27 mg/dl without PI). In contrast to the differential effects of ritonavir on glucose tolerance in G4KO versus wild-type mice, relative glucose-stimulated insulin secretion (GSIS) was sensitive to inhibition by ritonavir in both wild-type and G2KO islets (51 ±13% and 69 ±13% reduction in GSIS, respectively).

Conclusions: These data confirm that the acute effect of ritonavir on peripheral glucose disposal is mediated through direct inhibition of GLUT4 activity in vivo. In contrast, the effect of ritonavir on insulin secretion does not appear to be mediated by GLUT2 blockade. The ability of GLUT4 blockade to contribute to derangements in the other molecular pathways that influence insulin sensitivity remains to be determined.
ABSTRACT O-04

Antiviral Therapy 13 Suppl 4:A5

Effects of IGF-1/IGFBP-3 treatment on glucose metabolism and fat distribution in HIV-infected patients with abdominal obesity and insulin resistance

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Objective: Growth hormone (GH) treatment decreased visceral fat and improved lipid profiles in HIV-positive patients with visceral adiposity. However, GH also worsened glucose metabolism. Insulin-like growth factor (IGF)-1, which mediates many of the effects of GH, improved insulin sensitivity and lipid profiles in HIV-negative individuals. We performed a pilot, open-label study to determine whether IGF-1, complexed to its major binding protein (IGFBP-3), would improve glucose metabolism and alter body fat distribution in HIV-positive patients with abdominal obesity and insulin resistance.

Methods: Ten HIV-positive men with waist circumference >100 cm and HOMA-IR >2.77 received IGF-1/IGFBP-3 (Insmed, Inc.) for 3 months; seven received 0.5 mg/kg/day and three received 1.0 mg/kg/day, given SQ. Glucose metabolism was assessed under fasting conditions, and during both an oral glucose tolerance test (OGTT) and hyperinsulinemic euglycaemic clamp. Endogenous glucose production (EGP) and gluconeogenesis (GNG) were measured with stable isotope infusions. Body composition was assessed by DEXA and single-slice computerized tomography scan. Data are means ±SE at baseline and month 3. Because the change in free IGF-1 levels achieved with the two doses were not significantly different (3.9 and 3.3 ng/ml, respectively), results were combined in this pilot study. Results were analysed by paired t-test.

Results: HOMA-IR decreased (5.45 ±0.69 to 3.69 ±0.54, P=0.04), reflecting a decrease in both fasting insulin (21 ±3 to 16 ±2 µIU/ml, P=0.039) and glucose (105 ±3 to 98 ±2 mg/dl, P=0.005) levels. During OGTT, both glucose AUC (481 ±24 to 433 ±23 mg·h/dl, P=0.04), and insulin AUC (391 ±74 to 233 ±39 µIU·h/ml, P=0.02) decreased. Insulin-mediated glucose uptake (clamp) increased (3.60 ±0.46 to 5.86 ±0.86 mg/kg·min·µIU/ml, P=0.02). Fasting EGP increased (2.03 ±0.26 to 2.21 ±0.28 mg/kg/min, P=0.007) and during hyperinsulinemic euglycaemic clamp, suppression of EGP was blunted with IGF-1/IGFBP-3 treatment (0.35 ±0.16 to 0.52 ±0.18 mg/kg·min, P=0.011). An increase in GNG (0.53 ±0.12 to 0.65 ±0.13 mg/kg/min, P=0.011) explained most of the observed increase in fasting EGP. Lean body mass increased (1.04 ±0.35 kg, P=0.015, and total body fat and truncal fat decreased (-1.72 ±0.74 kg, P=0.045 and -1.08 ±0.44 kg, P=0.04); changes in limb fat were small and not significant. Visceral adipose tissue and both fasting triglyceride and total cholesterol levels did not change significantly.

Conclusions: In this pilot study, treatment with IGF-1/IGFBP-3 was associated with improvement in whole body glucose uptake and oral glucose tolerance. However, an increase in fasting EGP and blunted suppression during hyperinsulinemic euglycaemic clamp were also observed. Although lean body mass increased and total body fat decreased, visceral fat and lipid profiles were unchanged.

ABSTRACT O-05

Antiviral Therapy 13 Suppl 4:A5

Association of C-reactive protein and HIV infection with acute myocardial infarction

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Objective: To investigate whether increased C-reactive protein (CRP) levels and HIV infection are independently associated with acute myocardial infarction (AMI) among patients receiving care in a large US healthcare system.

Methods: Analyses were restricted to patients receiving care in the system between January 1997 and December 2006, with a most recent CRP <3 years and >1 week prior to AMI. A total of 70,357 (487 HIV and 69,870 non-HIV) patients met these criteria from the background population of 1,648,687 patients followed in the system over this time period. Among patients with CRP data available prior to AMI, the percentage of patients with most recent CRP high or not was compared among HIV and non-HIV groups. Multivariate logistic regression analysis was used to test the association of increased CRP and HIV with AMI after adjustment for demographic and other cardiovascular covariates, including hypertension, diabetes and dyslipidaemia, which were more prevalent among the HIV population. Increased CRP was defined based on the normal range of the assay used. Both CRP and high-sensitivity CRP (hsCRP) were included. Sensitivity analyses were performed with CRP restricted to 2 and 1 years before AMI. ICD-9 codes for AMI and other cardiovascular risk factors were validated. Patients with multiple encounters were counted only once and, for those with an AMI event, only the first event was considered.
Results: Among 70,357 patients with CRP data available prior to AMI, the most recent CRP was high in 287 HIV patients (59%) and 26,992 non-HIV patients (39%; P<0.0001). The median time from most recent CRP to first AMI was not significantly different (199 versus 176 days for HIV versus non-HIV patients; P=0.5). In univariate analyses, increased CRP and HIV were each significantly associated with AMI (odds ratio [OR] 2.51; 95% confidence interval [CI] 2.27–2.78; P<0.0001 for increased CRP and OR 2.07; 95% CI 1.31–3.10; P=0.001 for HIV). In a combined model, including CRP category and HIV status, increased CRP (OR 2.50; 95% CI 2.26–2.77; P<0.0001) and HIV (OR 1.74; 95% CI 1.10–2.61; P=0.01) were both independently associated with HIV. In a fully adjusted model, both increased CRP (OR 2.13; 95% CI 1.92–2.37; P<0.0001) and HIV (OR 1.93; 95% CI 1.21–2.93; P=0.004) remained independently associated with AMI, controlling for age, gender, race, diabetes, hypertension and dyslipidaemia. Compared with patients with normal CRP and without HIV, the OR for AMI was increased more than fourfold among patients with HIV and increased CRP.

Conclusions: Increased CRP and HIV are independently associated with increased AMI risk, and HIV patients with increased CRP have a markedly increased risk of AMI compared with those with neither risk factor. Measurement of CRP may be useful in the cardiovascular risk assessment and prediction of AMI in HIV patients.

ABSTRACT O-06

Antiviral Therapy 13 Suppl 4:A6

Ritonavir 100 mg twice daily, but not 100 mg once daily, increases adipophilin expression: potential effect of ritonavir on cardiovascular disease (CVD)

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Background: We previously showed that, in healthy volunteers, ritonavir 100 mg twice daily, but not 100 mg once daily, increased triglyceride concentrations over 2 weeks; this increase was related to higher ritonavir exposure. Reduced HDL and CD36 expression were observed for both ritonavir doses. Several other markers are associated with atherogenesis and CVD. We aimed at investigating the role of ritonavir in altering proinflammatory marker concentrations (hs-CRP, sICAM-1 and CD40L) and adipophilin expression. Adipophilin is responsible for cellular lipid accumulation through the inhibition of cholesterol efflux.

Methods: Non-smoking male and female healthy volunteers were randomized to arm 1 (ritonavir 100 mg once daily, washout and ritonavir 100 mg twice daily) or arm 2 (ritonavir 100 mg twice daily, washout and ritonavir 100 mg once daily); all study phases lasted 14 days. Proinflammatory markers and adipophilin expression were measured before and after ritonavir 14-day intake by standard validated methods. Full steady-state ritonavir pharmacokinetics was assessed on days 14 and 43 by high performance liquid chromatography/mass spectrometry/mass spectrometry (HPLC-MS/MS). Paired t-test and Pearson’s correlation were used for statistical analysis.

Results: The study was completed by 20 individuals (10 females). Median (range) age and body mass index were 28 (19–45) years and 22 (18–26) kg/m², respectively. Significant increases were observed for plasma sCD40L following ritonavir once daily (12%, P=0.008) and twice daily (19%, P=0.003) 14-day intake. No changes in hs-CRP and sICAM-1 were observed. Ritonavir induced an increase (30%, P=0.044) in adipophilin mRNA quantity in peripheral blood mononuclear cells in individuals treated twice daily, whereas no significant effect on adipophilin expression was seen when ritonavir was administered 100 mg once daily. No difference was observed in adipophilin gene expression between males and females. A significant correlation was observed between ritonavir plasma exposure and adipophilin gene expression (r=0.4, P=0.012).

Conclusions: In healthy volunteers, 100 mg twice daily ritonavir, but not 100 mg once daily ritonavir, led to an increase in adipophilin gene expression over 2 weeks; the increase was related to higher ritonavir exposure. Increased CD40L concentrations were measured for both ritonavir dosages.

ABSTRACT O-07

Antiviral Therapy 13 Suppl 4:A6

Carotid intima-media thickness (cIMT) improves over time in HIV-infected children

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Background: cIMT is an established surrogate marker for subclinical atherosclerosis and cardiovascular disease (CVD) risk. HIV+ subjects have increased cIMT and HIV+ adults have more rapid IMT progression than HIV- controls. This is the first study reporting IMT progression in HIV+ children.
Methods: cIMT was measured in 39 HIV+ children and 39 healthy controls at baseline and yearly for 3 years, and reported as internal carotid artery (ICA) and common carotid artery (CCA) thicknesses. Fasting metabolic profile was measured concurrently. Diabetes and family history of premature CVD were exclusionary. Here, we present the 48-week results. Within- and between-group comparisons of cIMT changes from baseline to 48 weeks were made using two-sample tests appropriate to the distribution. Spearman correlation coefficients were used to assess correlations with changes in IMT. Regression analyses were performed first to determine baseline prognostic factors for change at 48 weeks in cIMT and secondly to determine which factors change relative to the changes in cIMT over 48 weeks.

Results: HIV was acquired by 89% of HIV+ children by vertical transmission; 63% were female, 74% AA, median age 10 years, and body mass index (BMI) 18.7 kg/m²; median baseline CD4 was 840 (32%); and 69% had HIV RNA <50 copies/ml. A total of 89% were on antiretroviral therapy (ART) with 46% on non-nucleoside reverse transcriptase inhibitors (NNRTI), 34% on protease inhibitors (PI) and 9% on NNRTI+PI. The median duration of ART and PI was 70 and 25 months, respectively. Mean CCA IMT was nominally higher in HIV+ than HIV- (P=0.07), whereas ICA thicknesses (mm) was significantly higher in HIV+ (mean ±SD 1.05 ±0.16) versus 0.95 ±0.15; P=0.006). There were no differences in age, BMI, waist circumference (WC), HOMA-IR, or high-sensitivity C-reactive protein (hsCRP) between groups, but fasting lipids and waist-to-hip ratio (WHR) were higher in the HIV+ group.

Four HIV+ patients and two controls were lost to follow-up. At 48 weeks, there was no change from baseline in HIV RNA, but CD4% increased (P=0.02), LDL decreased (P=0.009) and WC increased (P<0.001) in the HIV+ group; in controls, BMI (P=0.007) and WC (P<0.001) increased over time. At 48 weeks, mean (±sd) change in cIMT for HIV+ subjects was -0.13 (0.18) and -0.16 (0.23) mm for CCA and ICA, respectively (both P<0.001). In the HIV- group, cIMT did not change significantly, and cIMT changes were not significantly different between groups. CCA and ICA changes were correlated with antiretroviral duration (R=-0.44, P=0.009) and PI duration (R=-0.46, P=0.006), and ICA changes were correlated with baseline CD4 and CD4% (both R=-0.37, P=0.04). In multiple regression analyses, antiretroviral duration was predictive of CCA change, and baseline CD4, age, sex, total- and LDL-cholesterol were predictive of ICA change. Change in CCA was also significantly associated with CD4 change and change in ICA was associated with change in LDL-cholesterol.

Conclusions: At 48 weeks, cIMT improved in HIV-infected children. This might be due to the concurrent decrease in LDL-cholesterol and increase in cIMT counts.

ABSTRACT O-08

Antiviral Therapy 13 Suppl 4:A7

Metabolic profile of two fixed-dose nucleoside analogue combinations (tenofovir/emtricitabine versus abacavir/lamivudine): BICOMBO MET, a substudy of the BICOMBO study

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Background: Antiretroviral agents might be associated with unfavourable metabolic profiles that contribute to an increase in cardiovascular (CV) risk, although new agents with a lower metabolic impact have been developed. The objective of this study was to compare the metabolic profile and estimated CV risk of two fixed-dose nucleoside analogue combinations (tenofovir/emtricitabine [TDF/FTC] and abacavir/lamivudine [ABC/3TC]) in virologically suppressed patients.

Methods: BICOMBO is a multicentre trial comparing TDF/FTC- versus ABC/3TC-based regimens in patients with virological suppression. In a metabolic substudy, fasting total cholesterol (TC), very low density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, LDL subfractions, apolipoprotein A-I (apo A-1), apolipoprotein B (apo B), triglycerides (TG), glucose, insulin, C-peptide and HOMA index were measured at baseline (BL) and 12 months. CV risk was estimated by the Framingham equation. Unpaired t-test or Mann-Whitney U test were used for comparisons between arms and paired t-test or Wilcoxon signed rank test were used for comparisons between BL and follow-up.

Results: In total, 103 patients (TDF/FTC n=55 and ABC/3TC n=48) were evaluated. BL demographic and metabolic variables did not differ, except for insulin (TDF/FTC 46.3 versus 61.1 pmol/l, P=0.06). At week 48, a significant increase in TC, LDL cholesterol and apo B, but also in HDL cholesterol and apo A-I was observed in ABC/3TC compared with TDF/FTC (P<0.001, P<0.001, P<0.006, P<0.001 and P<0.001, respectively). Despite these changes, LDL/HDL cholesterol and apo A-I/apo B ratios remained stable in both arms. An increase in small, dense LDL cholesterol subfractions (4, 5 and 6) was observed in both arms (ABC/3TC 36.8%, P<0.001; TDF/FTC 22.2%, P=0.004), but only ABC/3TC use was associated with an increase in the more atherogenic B phenotype (P=0.028) and a decrease in LDL cholesterol size (P=0.001). No significant changes were found in TG levels or estimated CV risk.
risk. Insulin levels increased (P=0.018) but HOMA index did not change in the TDF/FTC arm.

Conclusions: Quantitative lipid profile modifications were associated with the use of TDF/FTC and ABC/3TC. ABC/3TC was associated with a more atherogenic LDL cholesterol profile although estimated CV risk remained stable with both therapies.

ABSTRACT O-09
Antiviral Therapy 13 Suppl 4:A8
Pathogenesis of lipoatrophy: analysis of tissue and plasma

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Objectives: The use of thymidine NRTI (tNRTI) drugs for treatment of HIV, specifically stavudine and zidovudine, increases the risk of developing lipoatrophy – a pathology of the adipose tissue involving reduction in mitochondrial (mt) DNA copy numbers per adipocyte, tissue fibrosis and increased adipocyte death. Adipose tissue pathology in other settings represents a significant risk for cardiovascular health.

Methods: To elucidate the pathogenesis of lipoatrophy, we have quantified proportional fat loss by DEXA-measured leg fat percentage normalized by body mass index (BMI), adipocyte tissue mtDNA by qPCR, adipose tissue macrophages by histological evaluation and adipokine expression (including IL-6, IL-8, TNF-α, MCP-1, HGF, resistin and adiponectin in fat and plasma samples) by lincoplex and luminex technology. Adipose tissue biopsies were obtained from consenting study participants from the West Australian observational HIV cohort, including samples from NRTI-treated patients (stavudine n=37, zidovudine n=65 and abacavir n=43) and ART-naive patients (n=50).

Results: Significant mtDNA depletion in subcutaneous fat was specifically associated with tNRTI treatment (P<0.0001), with a more pronounced effect of stavudine > zidovudine (P<0.05). Values for abacavir NRTI therapy were comparable with ART-naive samples (P=0.2). Adipocyte mtDNA depletion occurred relatively early (within 6 months) on tNRTI therapy and then equilibrated to a drug-specific level, whereas limb fat loss occurred more slowly over 1–3 years. During tNRTI therapy, nadir leg fat percentage/BMI correlated with increases in the number of adipose tissue macrophages (P<0.0001), as well as decreases in plasma adiponectin (P<0.05). Plasma adiponectin also correlated negatively with tissue protein expression of IL-6, IL-8, MCP-1 and HGF (P<0.05). Examining paired tissue samples from 15 individuals pre- and post-tNRTI switching, we found partial normalization of mtDNA, in that values were still significantly lower than ART-naive individuals (P=0.01 after 1–6 months and P=0.05 after 8 months), but were also significantly increased from pre-switch levels (P<0.01). Upon switching from thymidines, increases in adipocyte mtDNA correlated with decreases in adipose tissue inflammatory-related proteins leptin, MCP-1, HGF, resistin, PAI, IL-6 and IL-8 (P=0.005). We found poor correlations between the same analyte in plasma versus tissue measured at similar time points, with the exception of MCP-1 and IL-8 (r≥0.5 for both). Individuals with more severe lipoatrophy, as assessed by nadir leg fat percentage/BMI, showed less reduction in tissue expression of IL-6, IL-8, MCP-1 and HGF after switching from tNRTI treatment.

Conclusions: The study demonstrates that lipoatrophy shares a number of histopathological features with obesity, including adipose tissue inflammation and macrophage infiltration, although in this case adipocyte-specific mt toxicity appears to be a primary pathogenic mechanism. Those with most severe pathology appear to show the poorest recovery.

ABSTRACT O-10
Antiviral Therapy 13 Suppl 4:A8
Skeletal muscle mitochondrial proteins discordantly regulated by insulin in HIV+ with insulin resistance: a mass spectrometry-based muscle proteomics study

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Background: Insulin resistance (IR) and diabetes are common metabolic complications in HIV-infected people treated with antiretroviral therapy. Skeletal muscle is mitochondria (mt)-rich and the primary site for insulin-stimulated glucose storage. Impairments in human muscle mt protein expression patterns and activities might be involved in the pathogenesis of HIV+ IR. We aimed to identify and characterize human muscle mt protein expression patterns associated with HIV+ IR.

Methods: During a hyperinsulinaemic euglycaemic clamp, thigh muscle samples were obtained from six healthy normal men (35 ±5 years, body mass index [BMI]=27 ±2 kg/m² and fat =21 ±3%) and six HIV+ IR men (36 ±2 years, median CD4=544 ±120 copies/µl, VL=Und, HIV+ duration =7 ±3 years, BMI=27 ±1 kg/m² and fat=24 ±4%; all on nucleoside reverse transcriptase inhibitors, 5/6 on non-nucleoside reverse transcriptase inhibitors and 3/6 on protease inhibitors). Glucose disposal rate (M µmol/kg FFM/minute/µU/ml insulin) was lower in HIV+ IR at baseline (-36%) and during hyperinsulinemia (-14%). One muscle sample was obtained at baseline (insulin 6–10 µU/ml) and the second
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[34x6]lipoatrophy. We randomized HIV-infected patients with
Decreasing exposure to antiretroviral therapy
Background:
JM Miró and JM Gatell
M Martínez, M Calvo, JL Blanco, J Mallolas,
M Larrousse, S Vidal, A León, M Lonca, M Laguno,
E Martínez, A Milinkovic, F Garcia, E de Lazzari,
Supported by NIH.
Results:
Sixty-five protein spots were discordantly regulated by insulin; five were identified as mt proteins: aconitase 2, mitofilin, malate dehydrogenase, calmitine and 3-hydroxacyl-CoA dehydrogenase. Mitofilin (IMMT; MW=83626, Mascot score=441, 29 peptides matched and 36% protein coverage) is a unique inner mt membrane protein, not previously recognized to be insulin-regulated. In controls, insulin increased mitofilin expression 17-fold more than in HIV+ IR. Mitofilin is crucial for maintaining normal tubular mt cristae and cristae junction morphology. Mitofilin deficiency results in tightly packed cristae, which could impair ion and metabolite exchange between mt membranes.
Conclusions:
These mt proteins represent potential biomarkers and sites of pathogenesis in HIV+ IR. The structure and function of the muscle intramitochondrial membrane and mt cristae might be altered in HIV+ IR. This could impair mt metabolism and ion flux, oxidative phosphorylation and mt ATP production during insulin stimulation.

ABSTRACT O-11
Antiviral Therapy 13 Suppl 4:A9
Greater limb fat increase with intermittent (relative to continuous) thymidine-sparing antiretroviral therapy in HIV-infected patients with lipoatrophy
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Background: Decreasing exposure to antiretroviral therapy (ART) might have favourable effects on HIV-associated lipoatrophy. We randomized HIV-infected patients with

lipoatrophy receiving thymidine-containing ART to intermittent CD4- or HIV-1 RNA-guided thymidine-sparing ART or to continuous thymidine-sparing ART.
Methods: Participants with moderate/severe lipoatrophy receiving thymidine-containing ART with >45 000 copies/ml and HIV-1 RNA <200 copies/ml for ≥6 months were randomized to continue on ART switching from thymidine to non-thymidine nucleosides (control [C] group) or to stop ART until CD4 <350/mm³ (immune-guided [I] group) or HIV-1 RNA >30 000 copies/ml (viral-guided [V] group), then resuming ART for ≥3 months until CD4>450/mm³ and HIV-1 RNA<200 copies/ml and re-initiating the cycle again. Fasting metabolic parameters at least every 3 months and whole-body, femoral and lumbar spine DEXA scans at baseline, 12, and 24 months were assessed. Primary endpoint was limb fat change at 24 months. Treatment groups were compared by intention-to-treat for absolute and percent changes in fat, lipids and bone mineral density scores using linear and random-effects regression models.
Results: There were 147 patients (median 39 years, 65% male, 17% hepatitis C+, 43% stavudine, 34% protease inhibitor and median CD4 753/mm³) randomized to C (n=44), I (n=53) or V (n=50) groups. Median baseline values of absolute and percent limb fat, triglycerides, total-LDL- and HDL-cholesterol were 4.1 kg, 15.2%, 134 mg/dl, 219 mg/dl, 128 mg/dl and 51 mg/dl, respectively. By 24 months, 26% (I group) and 30% (V group) had re-initiated ART. Compared with C group, changes in absolute and percent limb fat in intermittent therapy groups at 24 months were +292 mg (I group, P=0.004) and +732 mg (V group, P=0.026) and +39% (I group, P=0.046) and +29% (V group, P=0.146), respectively. Factors independently associated with a greater (upper quartile) limb fat change were months off ART (per 3 months, adjusted odds ratio [OR] 1.07, 95% confidence interval [CI] 1.02–1.12, P=0.006) and baseline trunk fat (per 100 g, adjusted OR 1.01, 95% CI 1.00–1.02, P=0.01). Relative to the C group, all plasma lipids significantly decreased in the I group, but not in the V group. Bone mineral density scores in femur and lumbar spine remained stable or increased in both intermittent ART groups, whereas they decreased in the C group. Five (5%) patients assigned to intermittent ART-experienced events leading to ART re-initiation because of acute retroviral syndrome, thrombocytopenia, psoriasis, hepatitis C reactivation and pregnancy. All patients in both intermittent groups were able to reach HIV-1 RNA <200 copies/ml on resuming ART.
Conclusion: In HIV-infected patients with lipoatrophy receiving thymidine-containing ART, intermittent thymidine-sparing ART leads to significantly greater increases in limb fat at 24 months than continuous thymidine-sparing ART.
**ABSTRACT O-12**

*Antiviral Therapy* 13 Suppl 4:A10

Prolonged exposure to HIV protease inhibitors (PIs) induces pancreatic islet beta-cell death and dysfunction

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**Objectives:** We previously reported that prolonged exposure (7 weeks) to indinavir accelerated the diabetic state, exacerbated hyperglycaemia and oral glucose intolerance in Zucker diabetic/fatty (ZDF) and wild-type rats (ZWT). Indinavir and lopinavir/ritonavir were associated with increased tumour necrosis factor-α, suppressor of cytokine signalling-1 (SOCS-1), SREBP-1 protein levels and reduced IRS-2 protein levels in ZDF and ZWT adipose, skeletal muscle and liver tissues. Activation of the SOCS-1 signalling cascade is a recognized contributor to the development of insulin resistance and diabetes. Prolonged protease inhibitor (PI) exposure also promoted significant insulinopaenia in these ZDF rats, raising the possibility that prolonged exposure to current PIs impair beta-cell function and viability. This was examined in the present study.

**Methods:** Insulin secretion in response to glucose (0–20 mM) plus forskolin (2.5 μM) and cell viability by TUNEL analyses were examined in 832/13 insulinoma (INS-1) cells and human pancreatic islet cells following 48 or 96 h exposures, respectively, to 20 μM indinavir, ritonavir, lopinavir, atazanavir or tipranavir, and in pancreatic islets isolated from ZWT rats exposed to indinavir (170 mg/kg orally twice a day) or vehicle for 3 weeks. Immunoblotting analyses were used to examine induction of markers of ER stress (phospho-pancreatic ER kinase [PERK]) and of apoptosis (polyADP-ribose polymerase [PARP], caspases 3 and ER factor C/EBP homologous protein [CHOP]). Mitochondrial membrane potential (ΔΨ) was monitored by flow cytometry.

**Results:** We found increased apoptosis and reduced insulin secretory capacity in INS-1 and human pancreatic islet cells after exposure to these PIs. Administration of indinavir to ZWT rats resulted in dramatically lower islet yields and induction of greater islet cell death in comparison with vehicle-administered rats. The higher incidence of HIV PI-induced cell death was associated with activation of caspase 3 and cleavage of PARP, but not with activation of PERK or induction of CHOP. Exposure to the HIV PIs, however, caused a loss in Δ (and cytochrome c release from the mitochondria, suggesting that the HIV PIs currently in clinical use can induce beta-cell apoptosis by activating the mitochondrial apoptotic pathway.

**Conclusions:** Taken together, these findings reveal for the first time that prolonged in vivo or in vitro exposure to some newer HIV PIs, despite promoting better serum lipid profiles, can cause beta-cell secretory dysfunction and beta-cell death by activating the mitochondrial, but not the ER stress, apoptotic pathway. In summary, our studies identify novel affects of HIV PI on pancreatic islet beta-cells and highlight the importance of considering beta-cell viability and function when assessing glycaemic control and diabetes in HIV-positive patients receiving PIs.

**ABSTRACT O-13**

*Antiviral Therapy* 13 Suppl 4:A10

Involvement of the adipocyte renin-angiotensin system in HIV protease inhibitor in vitro toxicity. Beneficial effect of angiotensin II type 1 receptor blockers

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**Objectives:** Some HIV antiretrovirals can induce adipocyte dysfunction leading to insulin resistance in HIV-infected patients. In vitro, we have shown that some antihypertensive angiotensin II type 1 receptor (AT1R) blockers (ARBs) with PPARγ-activation properties (telmisartan and irbesartan) can prevent protease inhibitor-induced adipocyte dysfunction. Whether the specific adipocyte renin angiotensin (RAS) system is involved in these abnormalities remains to be determined.

**Methods:** 3T3-F442A murine adipocytes and primary human adipocytes were incubated with two frequently prescribed protease inhibitors (PIs) in HIV-infected patients: lopinavir (LPVr; 10 μM) and atazanavir (ATVr; 5 μM) associated with ritonavir (2 μM). AT1R, AT2R, renin protein expression, AT1R cellular localization and angiotensin II effect on MAP kinases were investigated. We also evaluated AT1R expression on subcutaneous adipose tissue biopsies of HIV-infected patients treated with indinavir and compared with HIV controls. Finally, we determined the potential benefit of two ARBs (irbesartan and telmisartan) and rosiglitazone on PI-induced adipocyte RAS dysfunction.

**Results:** In cultured murine and human adipocytes, PI combinations deregulated the protein expression of AT1R and AT2R (up and down-regulation, respectively), increased renin expression and accumulated AT1R at the plasma membrane. PI combinations also increased the effects of angiotensin II on MAP kinases resulting in constitutive activation of the adipocyte RAS. In subcutaneous biopsies,
AT1R protein level was also increased in HIV-positive as compared with HIV-negative controls. The two ARBs (partial PPARγ agonists) prevented the PI effects on adipocyte RAS along with rosiglitazone (full PPARγ agonist). However, this beneficial effect was totally abolished by a PPARγ antagonist (PD).

Conclusions: Our study demonstrates for the first time that, in vitro, the adipose RAS is upregulated and activated by PIs, probably via a PPARγ pathway. In vivo experiments are warranted to evaluate the potential beneficial effect of PPARγ-activating ARBs on the PI-induced lipodystrophic syndrome and insulin resistance.

ABSTRACT O-14
Antiviral Therapy 13 Suppl 4:A11
Effect of initiation of highly active antiretroviral therapy on insulin sensitivity, autonomic nervous system function and beta-adrenergic mediated lipolysis

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Objectives: HIV-associated metabolic syndrome is associated with insulin resistance, increased plasma norepinephrine concentration, increased sympathetic nervous system (SNS) activity and increased basal lipolytic rates. However, it is not known whether these abnormalities are caused by highly active antiretroviral therapy (HAART) itself or are related to treatment-related changes in body fat distribution, and whether the increase in lipolysis is due to an increase in sympathetic nervous system (SNS) activity. Accordingly, we evaluated the hypothesis that short-term treatment with HAART alters autonomic nervous system activity, insulin sensitivity and β-cell function, basal lipolytic rates and the contribution of β-adrenergic activity to lipolysis in treatment-naive people with HIV infection.

Methods: We measured body composition using DEXA, insulin sensitivity and disposition index (a measure of pancreatic β-cell function) using 5-h oral glucose tolerance testing with minimal modelling, lipolytic rate by infusing stable isotopically labelled [3H]palmitate and [3H]glycerol before and during 60 min of propranolol infusion and autonomic nervous system activity (plasma norepinephrine concentration [index of SNS activity], sympathetic skin response [index of SNS responsiveness] and heart-rate variability [index of cardiovagal parasympathetic tone]) in 10 asymptomatic, treatment-naive patients with HIV infection (8 men, 4 African-American, age 32 ± 3 years). Measurements were repeated after 4 months of HAART (six atazanavir/ritonavir, two lopinavir/ritonavir and two efavirenz-based).

Results: HAART increased CD4+ T-cell count (371 ± 24 versus 512 ± 62 cells/mm3, P<0.04), body mass index (26.3 ± 1.5 versus 27.2 ± 1.7 kg/m², P=0.02) and trunk fat (9.1 ± 2.0 versus 9.8 ± 2.2 kg, P=0.05). Insulin sensitivity declined (6.6 ± 1.9 to 4.8 ± 0.8 × 10−4 dl/kg/min, P<0.05), but disposition index remained unchanged (7.85 ± 1.3 versus 9.0 ± 0.5 × 10−4 dl/kg/min3/pmol/l). Plasma norepinephrine concentration (184 ± 27 versus 141 ± 12 pg/ml), palmitate rate of appearance (Rp; 1.7 ± 0.2 versus 1.6 ± 0.2 μmol/kgFFM/min), glycerol Rg (3.1 ± 0.3 versus 3.0 ± 0.3 μmol/kgFFM/min) and propranolol suppression of palmitate Rg (18.8 ± 4.7% versus HAART 17.7 ± 5.3%) or glycerol Rg (pre 17.6 ± 4.6% versus post 19.7 ± 4.7%) did not change with HAART. Basal heart rate variability was not affected by HAART (16 ± 3% versus 18 ± 2%). Sympathetic skin response amplitude declined markedly (3,127 ± 603 versus 495 ± 62 mA, P<0.02) with HAART, but latency was unchanged (1,182 ± 12 versus 1,152 ± 98 ms).

Conclusions: Short-term HAART causes insulin resistance, but does not affect basal lipolytic rates or the contribution of β-adrenergic activity to lipolysis. In addition, HAART does not affect sympathetic or parasympathetic nervous system activity, but impairs SNS responsiveness. These data demonstrate that HAART likely causes insulin resistance in skeletal muscle, but not adipose tissue. The mechanisms responsible for these metabolic effects are not known, but it does not involve changes in autonomic nervous system activity.

ABSTRACT O-15
Antiviral Therapy 13 Suppl 4:A11
Autonomous nervous system activity and glucose metabolism in HIV patients receiving antiretroviral therapy

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Background: Lipodystrophy has been described as a side effect of antiretroviral therapy and the autonomous nervous system (ANS) has been proposed to contribute peripheral fat loss and metabolic disturbances.

Methods: This was a prospective cross-sectional study including 38 HIV patients, with or without lipodystrophy, receiving antiretroviral therapy and 15 therapy-naive HIV patients. After an overnight fast, patients underwent an oral glucose tolerance test (OGGT), indirect calorimetry, assessment of autonomous nervous system activity (Finometer®), anthropometric measurements and DEXA. Constitutive individual differences in ANS activity were assessed by...
monitoring the SD of each indicator about its mean value of interbeat interval and systolic blood pressure during the final 60 s of a verbal serial subtraction task or metronome-paced respiration (6 respiration cycles/min⁻¹).

**Results:** Patients on therapy had dyslipidaemia with significantly higher total cholesterol, total triglycerides, apolipoprotein A-2, Apo E and lipoprotein(a), and lower high-density lipoprotein cholesterol (P<0.05). Therapy was associated with insulin resistance and signs of beta cell dysfunction indicated by higher 120 min glucose during OGTT (5.1 ±0.3 versus 6.3 ±0.3 mmol/l, P=0.007), 120 min insulin (30.8 ±5.1 versus 57.7 ±7.8 µU/ml, P=0.006) and 120 min proinsulin (2.9 ±0.6 versus 7.7 ±1.2 pmol/l, P=0.001). HOMA-IR index was higher in patients on therapy (1.1 ±0.1 versus 1.7 ±0.2 mmol/minU, P=0.075). Patients receiving antiretroviral therapy with low ANS activity had significantly higher 120 min glucose concentrations as compared with patients who had low ANS activity (6.9 ±0.5 versus 5.5 ±0.4 mmol/l, P=0.041) and a trend towards a higher area under the curve for insulin 6,195.8 ±718.0 versus 8,825.3 ±1470.3 µU/ml and C-peptide (1,060.3 ±64.2 versus 1,295.0 ±139.3 ng/ml, P=0.09). Basal resting energy consumption and during OGTT was significantly lower in patients with low ANS activity and these patients had a lower central-to-peripheral fat ratio (1.7 ±0.2 versus 2.2 ±0.2, P=0.078), although serum lipid was not different.

**Conclusions:** To our knowledge these data provide the first evidence that low ANS activity might be associated with impaired glucose homeostasis in HIV patients receiving antiretroviral therapy.

**ABSTRACT O-16**

_Antiviral Therapy 13 Suppl 4:A12_

**β2-Adrenergic receptor polymorphisms are linked to lipoaccumulation while a β3-adrenergic receptor polymorphism influences lipoatrophy**

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**Objectives:** Adrenergic receptors (AR) are essential components of the autonomic nervous system, which controls various physiological functions including metabolism of glucose and lipids. An association has been suggested between obesity phenotypes and some polymorphisms located in the functional regions of the β3- and the β2-AR. The aim of our study was the evaluation of the role of β3- and β2-AR polymorphisms in the onset of lipodystrophy in patients of the Italian Cohort of Antiretroviral-Naive patients (I.Co.Na).

**Methods:** We randomly selected for this study 255 patients included in LipolCoNa after excluding non-Caucasian patients. For the identification of the polymorphisms, we used a sequence selective hybridization followed by a sequence-dependent termination and a sequence-specific primer extension. A standard Poisson regression multivariable model was used to study whether the polymorphisms were predictors of lipoatrophy and fat accumulation.

**Results:** In a follow-up of 973 person-years, 70 patients developed lipoatrophy, 7.1 per 100 person-years of follow-up (PYFU; 95% confidence interval [CI] 5.6–9.1). β3-AR codon 64 TT genotype carriers tended to be at lower risk of lypoatrophy as compared with those with a TC/TT genotype (adjusted relative risk [ARR] 0.39, 95% CI 0.14–0.96 versus TC/CC, P=0.066). In a follow-up of 976 person-years, 63 patients developed at least one pathological characteristic typical of fat accumulation (IR 6.45, 95% CI 5.04–8.26 per 100 PYFU). The β2-AR codon 16 AA genotype was significantly associated with higher risk (ARR 3.72, 95% CI 1.58–8.76 versus AG/GG, P=0.0026), whereas the β2-AR codon 27 CC genotype was significantly associated with lower risk (ARR 0.21, 95% CI 0.08–0.51 versus CG/GG, P=0.0006).

**Discussion:** The ADRB3 protein is a G-coupled receptor expressed on adipocytes involved in lipolysis. The C mutation might determine a reduced function of the receptor and inhibit triglycerides accumulation in adipocytes favouring lipoatrophy. The β2-AR is the main lipolytic receptor in white human adipose tissue. The glutamic acid 27 allele is a risk factor for the accumulation of visceral fat. Our data supports the involvement of codon 27 CC/CC and codon 16 AA genotypes in fat accumulation and underlines the potential risk of long term cardiovascular disease in HIV-1-infected patients receiving antiretroviral therapy.

Given the high prevalence of the polymorphism analysed and the relative low cost and feasibility of gene testing, it might be useful to determine the genetic predisposition of each single HIV-1-positive patient starting antiretroviral therapy. It could be possible to design individual regimens for each patient in order to avoid the rapid emergence of side effects and take adequate measures to delay their appearance.
ABSTRACT O-17
Antiviral Therapy 13 Suppl 4:A13
High HIV viral load inhibits osteoblast function and signalling
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Introduction: The prevalence of osteoporosis in a HIV-positive cohort is more than three times higher than in matched HIV-negative controls. Although antiretroviral therapy (ART) treatment has been associated with increased odds of reduced bone density compared with ART-naive patients, the pathogenic mechanisms underlying the initiation and progression of osteoporosis in HIV patients remain to be elucidated. Recent studies have reported altered bone biology and function in response to ART exposure, including effects on osteoclasts and osteoblasts. However, the direct effect of HIV on bone cell biology has not been evaluated.

Hypothesis: We hypothesized that exposure to HIV alters human osteoblast function and activity, and ultimately leads to osteopenia/osteoporosis.

Methods: Primary human osteoblasts (hOB) were cultured in growth medium in vitro. Growth medium was supplemented with serum from three distinct patient groups (HIV-negative, HIV-positive low [viral load range 120–4,000] or high [viral load range 100,000–500,000] viral load serum [5% concentration, 72 h, n=5 per patient group, HIV serum obtained from ART-naive patients]). Cell proliferation (as a biological endpoint) and calcium deposition (as a functional endpoint) were determined using established methods. In addition, to identify the effect of HIV on transcriptional regulators of the bone phenotype, real-time PCR with gene-specific primers was used to quantify mRNA expression of RUNX-2, a pro-osteogenic transcription factor.

Results: Exposure of hOB to control low or high HIV viral load serum did not affect hOB cell proliferation, demonstrating that these exposures did not have a cytotoxic effect on osteoblasts in vitro. hOB calcium deposition reduced significantly (P<0.005) after treatment with high viral load serum compared with either low viral load or HIV-negative control serum. Osteoblast RUNX-2 mRNA expression declined by 25% (P<0.05) after exposure to high viral load serum compared with HIV-negative controls.

Conclusions: These data demonstrate bioactivity of HIV in the setting of osteoblast cell culture. Serum obtained from HIV patients with high viral load affected significant changes in the bone phenotype, as evidenced by reduced capacity for calcium deposition. Intriguingly, this functional effect was mirrored by changes in the expression of the osteogenic transcription factor RUNX-2. These findings support the hypothesis that HIV itself, in addition to the well described effect of ART, can modulate bone phenotype and, at least in part, drive the osteopenia and osteoporosis, which is increasingly seen in HIV patients.

ABSTRACT O-18
Antiviral Therapy 13 Suppl 4:A13
Ex vivo modulation of mesenchymal stem cell function in HIV-1 infection
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Introduction: An increased incidence of bone and metabolic toxicities are associated with HIV-1 infection and its treatment. However, the exact mechanisms of these toxicities and the relative contribution of virus and treatment remains to be elucidated. Mesenchymal stem cells (MSC) are multipotent bone marrow-derived cells that can differentiate into a number of cell lines, including osteoblasts (OB) and adipocytes (AC). Herein, we hypothesize that perturbation of MSC function and differentiation might underpin the bone and fat abnormalities associated with HIV-1 infection and treatment.

Methods: In this ex-vivo study, human MSCs were treated with media supplemented with either HIV-negative (n=5), HIV-positive low (LVL; viral load 120–4,000, n=5) or high (HVL; viral load 100,000–500,000, n=4) viral load serum (5% concentration, HIV serum obtained from highly active antiretroviral therapy-naive patients) and chemically induced to differentiate into either OBs or ACs. Calcium deposition and lipid levels, as measures of osteogenesis and adipogenesis, respectively, were assessed using established methods. To determine whether short-term exposure to serum induced changes in gene expression, non-differentiating cells were treated with serum from each group (5% serum, 24 h) and levels of mRNA for the differentiation markers RUNX-2, PPARγ and β-catenin, as well as tumour necrosis factor (TNF)-α and CD4, were determined using real-time PCR with gene-specific primers. Finally, in order to determine if long-term exposure affected cell phenotype and function, non-differentiating MSCs were exposed to serum (5% serum) from each group over a 72 h time course. Cell activity and number were determined using MTS assay and ponceau red staining, respectively, and the levels of LPL protein and ALP activity were determined using whole cell ELISA and BCIP/NBT staining, respectively.

Results: Serum from either high or low viral groups increased the degree of adipogenesis, an induction that

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was significant following exposure to HVL serum. Moreover, the degree of adipogenesis in HVL serum-treated cells was significantly greater than that observed in LVL serum-treated cells (P≤0.01), suggesting the effect was dependent on viral concentration. Expression of PPARγ mRNA expression in non-differentiating cells was significantly upregulated by HVL serum (5%, 24h), whereas RUNX-2 and β-catenin expression was unchanged. Treatment with serum from both groups also downregulated CD4 and TNF-α expression. Finally treatment of non-differentiating cells with HVL serum for 72 h, significantly increased cell activity, decreased cell number, decreased ALP activity and increased LPL protein levels.

**Conclusions:** Serum from HIV-1 patients both increased the degree of chemically induced adipogenesis from MSCs and drove the presentation of a pro-adipogenic phenotype in non-differentiating MSCs in a viral load-dependent manner. These findings underscore the hypothesis that perturbations in MSC cell differentiation are responsible, at least in part, for the observed toxicities seen in HIV patients in vivo.

**ABSTRACT O-19**

*Antiviral Therapy 13 Suppl 4:A14*

**Continuous antiretroviral therapy decreases bone mineral density: results from the SMART study**

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**Background:** HIV-infected adults have lower bone mineral density (BMD) than the general population and might experience more fractures. We evaluated the role of antiretroviral therapy (ART) on BMD and fracture risk.

**Methods:** In the SMART trial, HIV-positive patients with CD4 counts >350 cells/mm³ were randomly allocated to continuous ART (viral suppression [VS] group) or CD4-guided intermittent ART (drug conservation [DC] group). In 214 participants, hip and spine BMD were measured annually by dual-energy X-ray absorptiometry (DEXA) and trabecular BMD of the spine by quantitative computed tomography (qCT). We compared treatment groups for change in BMD using longitudinal models and, in the full SMART study (n=5,472), for incidence of fractures using Cox regression. In the VS cohort, we prospectively evaluated associations of BMD decline with cumulative ART use and other factors.

**Results:** Participants (median 44 years; 19% female; 73% on ART; 12% with osteoporosis; median T-scores -0.5 [femur], -0.9 [spine qCT], and -0.7 [spine DXA]; 98 randomized to the VS group and 116 to the DC group) were followed for a mean of 2.4 years. In the VS group, participants received ART for 93% of follow-up time, compared with 37% in the DC group. BMD declined by 0.9% per year (femur), 2.9% (spine qCT) and 0.4% (spine DXA) in the VS group, and significantly less in the DC group. Estimated DC versus VS group differences in mean BMD change from baseline through follow-up were 1.4% (95% confidence interval [CI] 0.5–2.3, P=0.002) at the femur, 2.9% (95% CI 0.7–5.1, P=0.01) for spine by qCT and 1.2% (95% CI 0.02–2.3, P=0.05) for spine by DEXA. No consistent drug-specific association with BMD decline was found. In the parent study, 10 of 2,753 participants in the VS group (0.13 per 100 person-years of follow-up) and 2 of 2,720 participants in the DC group (0.03 per 100 person-years of follow-up) reported fractures as grade 4 adverse events (hazard ratio 4.9 [95% CI 1.1–22.5], P=0.04).

**Conclusions:** Continuous ART is associated with progressive decline in BMD and possibly more fractures relative to intermittent, CD4-guided ART.
ABSTRACT 0-20

Antiviral Therapy 13 Suppl 4: A15

Total body and spine bone mineral density across Tanner stages in vertically HIV-infected compared with uninfected children and youth: preliminary results of PACTG1045

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Aim: To characterize differences in total body bone mineral content (BMC) and total body and spinal bone mineral density (BMD) between perinatally HIV-infected (HIV-pos) and uninfected (HIV-neg) children and youths across stages of pubertal development.

Methods: HIV-pos youths, aged 7–24 years, were randomly selected for cross-sectional study from six strata based on Tanner stage (1, 2–3 and 4–5) and protease inhibitor (PI) use (PI 12 months versus non-PI-containing ART) across 37 PACTG sites. From these clinics, HIV-pos youths of similar age were selected from the same three Tanner strata to reflect overall gender and race distribution of the first 100 HIV-pos youths (group-matching). BMC and BMD were measured by DXA and results were standardized in a central laboratory. Tanner stage was re-categorized (1–2, 3–4 and 5) because growth velocity is greatest at Tanner 3 and 4. Using linear regression models for each outcome, differences between HIV-pos and HIV-neg were evaluated across Tanner stage, adjusted for DXA type, race/ethnicity, gender, height, age and potential risk factors for low BMD (CD4% and viral load [current and worst], Centers of Disease Control and Prevention class, vitamin D and calcium intake, exercise and TV hours). Models were tested for two- and three-way interactions of HIV status, Tanner stage and height. Separate models were fit for males and females. We calculated the predicted mean BMD/BMC at each median height of HIV-pos and at the median height of HIV-neg within each Tanner group.

Results: Adequate DXA measurements were obtained in 236 HIV-pos (median age 12.6 years) and 143 HIV-neg (median age 11.9 years) youths. The two groups were comparable for gender (52.5% versus 58.0% male) and race/ethnicity (White/other 13.1% versus 14.0%, Black 54.7% versus 54.5% and Hispanic 32.2% versus 31.5%). Among females, there were no significant differences between HIV-neg and HIV-pos for total body BMC (P=0.524), total BMD (P=0.784) or spinal BMD (P=0.967) at any Tanner stage. In contrast, among males, there were statistically significant three-way interactions between HIV status, Tanner stage and height on all three outcomes (total body BMC P=0.028; spinal BMD P=0.039; total BMD P=0.045). At Tanner stage 1–2, predicted BMD and BMC were similar between HIV-pos and HIV-neg males, but HIV-pos had lower BMD/BMC than HIV-neg males at Tanner stages 3–4 and 5. Non-Hispanic African-Americans had significantly higher BMC (males and females), total BMD (males and females) and spine (females only) followed by Hispanics and then Whites.

Conclusion: In this random sample of youth, HIV-pos males showed evidence of delayed bone density compared with HIV-neg males. The difference between the groups was most pronounced at the final stage of pubertal development. In contrast, there was no effect of HIV status on BMC or BMD among females. These data suggest that perinatally infected males might be at increased risk for bone disease during adulthood.

ABSTRACT 0-21

Antiviral Therapy 13 Suppl 4: A15

Efficacy of a computerised physician reminder system to control cardiovascular risk factors in HIV-infected patients receiving antiretroviral therapy (cART): a randomised controlled cluster trial nested into the Swiss HIV Cohort Study (SHCS)

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Background: Exposure to cART might lead to marked metabolic changes and increased risk of coronary heart disease (CHD) events. Computerized clinical decision support systems have been advocated to improve the management of patients at risk for CHD, but there is insufficient evidence whether such systems improve CHD risk factors in HIV-infected and uninfected patients.
Methods: In total, 165 clinicians at the seven study SHCS centres, associated hospitals and private practices were randomised in June 2006 to the provision of CHD risk profiles plus guidelines for cART-treated patients versus the provision of evidence-based guidelines for CHD risk factor management alone. CHD risk profiles, which included CHD risk factors, Framingham risk score, CHD drug prescriptions and CHD events, were generated on flow charts by the SHCS data centre based on a computerized program and data from biannual assessments at baseline and during the 12 month intervention period. CHD risk profiles were filed in patient charts by study nurses. Clinicians were randomised in strata of centre and patient volume and instructed about the trial by the responsible clinician of the centre (guardian). The primary outcome was the reduction in total cholesterol; secondary outcomes were systolic and diastolic blood pressure and Framingham risk score. Patients eligible for analysis had to be on cART for >90 days, aged 18 or older, not pregnant and with complete CHD risk factor data at baseline. We used linear regression with outcome measured at baseline and concomitant lipid lowering or antihypertensive medication as covariates and, to adjust for missing outcomes, weighted each patient's outcome by the inverse probability of the patient being included in the analysis.

Results: Of the 5,782 screened patients, 26 women were pregnant, 1,421 patients were not on cART over the full 90 days prior to baseline and 377 patients had at least some missing CHD risk information, leaving an intention-to-treat population of 4,089 patients. Mean differences in some missing CHD risk information, leaving an intention-to-treat population of 4,089 patients. Mean differences in some missing CHD risk information, leaving an intention-to-treat population of 4,089 patients. Mean differences in some missing CHD risk information, leaving an intention-to-treat population of 4,089 patients. Mean differences in some missing CHD risk information, leaving an intention-to-treat population of 4,089 patients. Mean differences in...
HIV-infection, CG best reflected measured GFR and might be preferred over other estimates to monitor glomerular function in antiretroviral-treated patients.

**ABSTRACT O-23**

*Antiviral Therapy* 13 Suppl 4:A17

AIDS and non–AIDS defining malignancies in HIV-infected patients: the 2006 ONCOVIH French study

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Objectives: The aim of the ONCOVIH study was to describe the distribution of malignancies in HIV-infected patients in France and the 1-year prognosis following this diagnosis.

Methods: ONCOVIH was a national cross-sectional study with a prospective reporting of all new cases of malignancies diagnosed in HIV-infected patients in 2006 in over 300 care centres involved in the management of patients with HIV and/or malignancies. Characteristics of HIV infection and malignancies, occurrence and cause of death were collected using a standardized questionnaire at the diagnosis of malignancy and every 3 months during 1 year. Histological results and causes of death were reviewed by a panel of clinicians and epidemiologists. Data from HIV patients followed in hospital in France in 2006 were extracted from ANRS CO4-FHDH.

Results: Overall, 116 clinical centres reported 694 new malignancies in 690 patients, of whom 669 patients (533 men and 136 women) were evaluable (Table 1). Most common malignancies were NHL (n=145, 21.5%), Kaposi’s sarcoma (n=107, 15.9%), lung cancer (n=63, 9.4%), anal cancer (n=55, 8.2%), Hodgkin’s lymphoma (n=51, 7.6%), cutaneous non-melanoma (n=46, 6.8%) and liver cancers (n=38, 5.6%). Cervix cancer was diagnosed in 10 women. Conclusion: In 2006, almost two thirds of diagnosed malignancies in HIV-infected patients were non-AIDS defining. Malignancies were diagnosed in patients with a lower CD4+ T-cell count than the whole population of HIV-infected patients, even for non-AIDS malignancies. Patients with AIDS malignancies also more often had detectable plasma HIV RNA. This suggests that a better control of HIV and its associated immunodeficiency is required to prevent malignancies in HIV-infected patients.

**Table 1. The mean mGFRs, eGFRs and change from baseline (Abstract O-22)**

<table>
<thead>
<tr>
<th>GFR Assessment</th>
<th>ZDV/3TC continue</th>
<th>TDF/FTC switch</th>
<th>Mean change from baseline (s d), ml/min/1.73 m²</th>
<th>Difference between changes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (s d), ml/min/1.73 m²</td>
<td>Mean (s d), ml/min/1.73 m²</td>
<td>Mean (s d), ml/min/1.73 m²</td>
<td>Continue</td>
<td>switch</td>
</tr>
<tr>
<td>mGFR*</td>
<td>143 (31)</td>
<td>150 (33)</td>
<td>125 (39)</td>
<td>+7 (10)</td>
<td>-11 (16)*</td>
</tr>
<tr>
<td>CG*</td>
<td>133 (35)</td>
<td>137 (33)</td>
<td>134 (58)</td>
<td>+4 (9)</td>
<td>-16 (17)*</td>
</tr>
<tr>
<td>CrCl*</td>
<td>142 (39)</td>
<td>147 (66)‡</td>
<td>123 (41)</td>
<td>-4 (49)</td>
<td>-7 (24)</td>
</tr>
<tr>
<td>MDRD-4</td>
<td>88 (9)</td>
<td>92 (9)</td>
<td>96 (23)</td>
<td>+3 (5)</td>
<td>-8 (7)*</td>
</tr>
<tr>
<td>MDRD-6</td>
<td>111 (13)</td>
<td>115 (13)</td>
<td>125 (29)</td>
<td>+4 (7)</td>
<td>-13 (12)*</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>93 (26)</td>
<td>89 (18)</td>
<td>91 (20)</td>
<td>-4 (19)</td>
<td>-9 (11)</td>
</tr>
</tbody>
</table>

*Corrected for body surface area. †P <0.05 change within arm. ±n=8. §n=9. CG, Cockcroft–Gault; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, gold-standard glomerular filtration rate; TDF, tenofovir; ZDV, zidovudine; 3TC, lamivudine.

**ABSTRACT O-24**

*Antiviral Therapy* 13 Suppl 4:A17

Impaired myocardial glucose metabolism in men with HIV-associated metabolic syndrome

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Objective: To quantify myocardial glucose and fatty acid (FA) metabolism in HIV-positive men with and without the ATP-III-defined metabolic syndrome (MS).

Background: Whole-body abnormalities in glucose and FA metabolism and risk of myocardial ischaemia in HIV-associated MS are established; however, HIV-associated MS effects on myocardial substrate metabolism are unknown.

Methods: In 18 HIV-positive men with MS (HIV+/MS+, 40 ±7 years) and 13 HIV-positive men without MS (HIV+/MS-, 41 ±6 years) myocardial perfusion (MBF), oxygen consumption (MVO2), glucose extraction fraction (GLUEF),...
glucose utilization (GLUT), glucose utilization/serum insulin (GLUT/INS), FA extraction fraction (FAEF) and FA oxidation (FAO) were quantified using 11C- and 17O-tracers and positron emission tomography (PET) imaging.

Results: As expected, waist circumference \((P<0.0001)\), BMI \((P<0.0004)\) and fasting HOMA \((P<0.0001)\) were greater in HIV+/MS+ than HIV+/MS-. Blood lactate levels were higher in HIV+/MS+ during the PET \((P<0.004; \text{Table 1})\).

Whole body insulin resistance (fasting HOMA) predicted lower myocardial GLUEF \((r=-0.46, P<0.01)\) and HDL predicted higher GLUEF \((r=0.45, P<0.01)\) and GLUT/INS \((r=-0.39, P<0.04)\). Higher blood lactate level during the PET study tended to correlate with lower myocardial GLUEF, \((r=-0.35, P<0.10)\), GLUT/INS \((r=-0.37, P<0.08)\) and lower FAEAF \((r=-0.36, P<0.10)\).

Conclusions: The myocardium in HIV+/MS+ appears insulin resistant compared with HIV+/MS-. FA extraction and metabolism were also impaired in HIV+/MS+. These findings imply greater myocardial lactate use in HIV+/MS+, but this requires further study. In HIV+/MS+, the heart’s ability to adapt to conditions requiring increased glucose or FA metabolism could be impaired.

Table 1. Characteristics (at diagnosis for ONCOVIH or in 2006 for FHDH) of patients (Abstract O-23)

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>AIDS-defining malignancies</th>
<th>Non-AIDS-defining malignancies</th>
<th>ANRS CO4-FHDH 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>669</td>
<td>258</td>
<td>411</td>
<td>–</td>
</tr>
<tr>
<td>Proportion of women, %</td>
<td>20</td>
<td>19</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>Median age, years (interquartile range)</td>
<td>47 (41–55)</td>
<td>44 (38–51)</td>
<td>49 (42–57)</td>
<td>43 (37–49)</td>
</tr>
<tr>
<td>Proportion of patients diagnosed with HIV infection &lt;6 month previously, %</td>
<td>14</td>
<td>28</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Median nadir CD4+ T-cell count, cells/mm³ (interquartile range)</td>
<td>144 (49–260)</td>
<td>134 (44–263)</td>
<td>147 (52–259)</td>
<td>193 (86–307)</td>
</tr>
<tr>
<td>CD4+ T-cell count, cells/mm³ (interquartile range)</td>
<td>275 (144–446)</td>
<td>193 (67–357)</td>
<td>329 (193–500)</td>
<td>454 (312–634)</td>
</tr>
<tr>
<td>Proportion of patients receiving ART and with plasma HIV RNA &lt;500 copies/ml, %</td>
<td>47</td>
<td>23</td>
<td>51</td>
<td>67</td>
</tr>
</tbody>
</table>

With 185 deaths, the overall 1-year survival rate was 72% (95% confidence interval 68–75) and much lower after a diagnosis of lung cancer (35%), hepatocarcinoma (47%) or NHL (65%).

Table 1. (Abstract 0-24)

<table>
<thead>
<tr>
<th></th>
<th>MBF, ml/g/min</th>
<th>MVO₂, j/g/min</th>
<th>GLUEF, %</th>
<th>GLUT, nmol/g/min</th>
<th>GLUT/INS, nmol/g/min/µU</th>
<th>FAEAF, %</th>
<th>FAO, nmol/g/min</th>
<th>FAUT, nmol/g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+/MS+</td>
<td>1.01 ±0.35</td>
<td>4.3 ±1.1</td>
<td>2.6 ±1.5</td>
<td>132 ±76</td>
<td>16 ±21</td>
<td>37 ±6</td>
<td>101 ±35</td>
<td>129 ±38</td>
</tr>
<tr>
<td>HIV+/MS-</td>
<td>0.93 ±0.28</td>
<td>3.9 ±1.1</td>
<td>4.4 ±3.2</td>
<td>176 ±134</td>
<td>51 ±48</td>
<td>51 ±20</td>
<td>117 ±50</td>
<td>150 ±59</td>
</tr>
<tr>
<td>P-value</td>
<td>NS</td>
<td>0.19</td>
<td>0.02</td>
<td>0.13</td>
<td>0.01</td>
<td>0.01</td>
<td>0.31</td>
<td>0.23</td>
</tr>
</tbody>
</table>

FAEAF, fatty acid extraction fraction; FAO, fatty acid oxidation; GLUEF, glucose extraction fraction; GLUT, glucose utilization; INS, serum insulin; MBF, myocardial perfusion; MVO₂, oxygen consumption.

ABSTRACT O-25

**Antiviral Therapy 13 Suppl 4:A18**

The impact of raltegravir and lopinavir/ritonavir on peripheral glucose disposal in HIV-negative subjects

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Objectives: This study investigated the impact of raltegravir and lopinavir/ritonavir on the peripheral glucose disposal rate (M), assessed using the hyperinsulinaemic euglycaemic clamp, in HIV-negative male subjects.

Methods: An open-label, two phase crossover study design was used. Important exclusion criteria were body mass index >28 kg/m², waist-to-hip ratio >0.97 and any medication or disease process likely to cause marked disturbances on lipid and glucose homeostasis. Fasting glucose, cholesterol and triglycerides all had to be within normal limits. Subjects were randomized 1:1 to receive 2 weeks of lopinavir/ritonavir 400/100 mg twice daily followed by a 2-week washout period then 2 weeks of raltegravir 400 mg twice daily or raltegravir initially followed by lopinavir/ritonavir. A clamp was performed prior to and following each 2-week phase of study medication.

Results: In total, 16 subjects completed all four clamps. Data from the lopinavir/ritonavir phase was not included.
in the analysis for one subject because of poor compliance with dosing during these 2 weeks. The mean (SEM) percentage change from baseline was -16.10 (3.84) after 2 weeks of lopinavir/ritonavir and -0.43 (4.83) after 2 weeks of raltegravir (See Table 1).

Conclusions: In HIV-negative male subjects, 2 weeks of raltegravir was not associated with a significant impact on the M assessed during the euglycaemic clamp. In contrast, 2 weeks of lopinavir/ritonavir resulted in a significant reduction in the M, which is consistent with previously published findings.

Table 1. (Abstract O-25)

<table>
<thead>
<tr>
<th>Study medication</th>
<th>Mean baseline M, mg/kg/min (SEM)</th>
<th>Mean 2-week change in M, mg/kg/min (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir (n=15)</td>
<td>7.97 (0.33)</td>
<td>-1.30* (-1.94 – -0.66)</td>
</tr>
<tr>
<td>Raltegravir (n=16)</td>
<td>8.30 (0.31)</td>
<td>-0.13 (-0.86–0.60)</td>
</tr>
</tbody>
</table>

*P<0.001 for the difference from baseline to week 2 (paired t-test). CI, confidence interval; M, peripheral glucose disposal rate.
ABSTRACT P-01

Antiviral Therapy 13 Suppl 4:A23

Comparison of the effects of lopinavir/ritonavir and efavirenz on gene expression and differentiation of human adipocytes

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Aim: Lopinavir/ritonavir and efavirenz are drugs of choice for initial antiretroviral therapy. Several reports indicate deleterious effects of these drugs on adipocytes in vitro as well as their potential contribution to lipodystrophy and metabolic alterations in HIV type-1-infected, highly active antiretroviral therapy (HAART)-treated patients. Our objective was to perform a parallel comparative assessment of the effects of the lopinavir/ritonavir (4:1) combination commonly used in antiretroviral treatment with respect to efavirenz on differentiation and expression of marker genes of adipogenesis, inflammation, mitochondrial toxicity and endoplasmic reticulum (ER) stress in human adipocytes in culture.

Methods: Human adipocytes were differentiated in primary culture from precursor cells obtained from liposuction from healthy individuals. We determined the effects of exposure to equivalent concentrations of lopinavir/ritonavir (4:1) and efavirenz of pre-adipocytes during their 10-day process of differentiation into adipocytes. The same comparison was performed by studying the effects of 24 h exposure of already differentiated human adipocytes to these drugs. Acquisition of adipocyte morphology, lactate release to the medium (Roche) and changes in mRNA levels for selected genes (TaqMan; Applied Biosystems) were determined.

Results: Lopinavir/ritonavir (4:1) caused a dose–response impairment of morphological human adipocyte differentiation that was, however, less pronounced than that caused by equivalent concentrations of efavirenz. This was paralleled by a dose–response reduction in transcripts of marker genes of adipogenesis (PPARγ, adiponectin and lipoprotein lipase), but always to a lesser extent for lopinavir/ritonavir (4:1) than for equivalent concentrations of efavirenz. Conversely, MCP-1 mRNA levels were induced both by lopinavir/ritonavir (4:1) and efavirenz, but to a higher extent for efavirenz. Neither the levels of transcripts encoding mitochondrial proteins (COII mRNA and COIV mRNA) nor mitochondrial proteins (COII mRNA and COIV mRNA) nor lactate release to the medium were altered by the drugs. In differentiated adipocytes, lopinavir/ritonavir (4:1) caused a dose-dependent reduction of adipogenesis-related gene expression (that is, 47% reduction of adiponectin mRNA at 4 µM lopinavir/ritonavir (4:1) that was milder than that elicited by efavirenz (85% reduction in adiponectin mRNA at 4 µM efavirenz). In this experimental setting, analysis of GRP78 mRNA levels, the marker of ER stress, was performed. Exposure of adipocytes to lopinavir/ritonavir (4:1) and to efavirenz caused an increase of GRP78 mRNA levels, which was more intense for equivalent concentrations of lopinavir/ritonavir (4:1).

Conclusions: Exposure of adipocytes to the lopinavir/ritonavir combination used in HAART impairs adipogenesis and increases inflammation-related gene expression, but to a lesser extent than equivalent amounts of efavirenz. Mitochondrial toxicity is not involved in these effects. Preferential induction of ER stress by lopinavir/ritonavir (4:1) does not appear to be associated with worsening the effects of this drugs combination on adipocyte biology with respect to efavirenz.

ABSTRACT P-02

Antiviral Therapy 13 Suppl 4:A23

Clinical concentrations of efavirenz (EFV) reduce cellular proliferation and viability in several human cell lines

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Efavirenz (EFV)-containing therapies have been related to several side effects including hepatotoxic events and chronic disorders in lipid metabolism, but the possible mechanisms underlying these effects have received very little study. We evaluated the cytotoxic effects of clinical (10–25 µM) and supraclinical (50 µM) concentrations of EFV in various human cellular models. MTT assays after 24 h of culture in the presence of the drug revealed reduced viability in the human hepatoma cell line Hep3B (significant for all three concentrations and calculated as 84.59 ±8.82% decrease for 50 µM EFV), human cervix carcinoma cell line HeLa (71.92 ±5.49% reduction for 50 µM EFV) and primary human umbilical vein endothelial cells (HUVEC; 96.76 ±0.27% decrease for 50 µM EFV).
was measured with a Clark-type electrode. Following incubation (1 h) with EFV (10, 25 or 50 µM), intracellular ATP was measured by fluorescence, mitochondrial membrane potential (∆Ψm), which is indicative of mitochondrial function, was analysed by static cytometry and AMPK was evaluated by western blotting. In order to further study the implication of this enzyme, selected experiments were performed in cells pretreated (30 min) with the AMPK inhibitor compound C (20 µM). The expression of the fatty acid transporter CD36 was analysed using PCR and the intracellular lipid content was determined by nuclear magnetic resonance after 4 h of incubation with EFV.

EFV produced an immediate reduction of mitochondrial function, evident by the significant and dose-dependent inhibition of mitochondrial oxygen consumption and the decrease of intracellular ATP and ∆Ψm. This metabolic stress promoted the activation of AMPK, triggering several of its signalling pathways, as EFV induced an increment in CD36 messenger RNA expression and in intracellular lipid content that could have been a result of the formation of lipid droplets. This intracellular lipid increase was not present in cells treated with compound C, which points to a key role for AMPK in these mechanisms.

Given that EFV treatment is usually prolonged, these mechanisms might affect the general regulation of lipid metabolism and could cause the alterations that are characteristic of lipodystrophy.

ABSTRACT P-03
Antiviral Therapy 13 Suppl 4:A24
Efavirenz induces alterations in lipid metabolism through AMPK activation

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Recent evidence suggests that the non-nucleoside reverse transcriptase inhibitor efavirenz (EFV) contributes to changes in lipid and body fat composition that are implicated in lipodystrophy. As the liver is an important organ in lipid metabolism, we have evaluated the effects of clinically used concentrations of EFV on mitochondrial function and cellular lipid metabolism in vitro and the implication of AMP-activated protein kinase (AMPK), the master switch for regulation of cellular bioenergetics, in these processes. Oxygen consumption in non-HIV-infected Hep3B cells was measured with a Clark-type electrode. Following incubation (1 h) with EFV (10, 25 or 30 µM), intracellular ATP reduction for 50 µM EFV). This result was corroborated with 3-day proliferation experiments in which Hep3B were exposed to different concentrations of EFV. A significant reduction (60.1 ±6.54% after 3 days) was detected with 25 µM EFV, whereas cytotoxicity (97.01 ±1.13% reduction) was observed with 50 µM; however, no changes were detected with 10 µM EFV. With the aim of analysing the mechanisms responsible for this diminished cellular viability, we performed bivariate annexin V/propidium iodide analysis of HeLa cells using static cytometry, and found that EFV-treated cells (4 and 8 h) presented features of late or advanced apoptosis. We also observed a dose-dependent translocation of two mitochondrial proapoptotic proteins, cytochrome c and AIF, in Hep3B cells after EFV treatment (4 h), which was accompanied by a significant reduction in the mitochondrial membrane potential (∆Ψm), as measured by TMRM fluorescence. Confocal fluorescence microscopy experiments revealed dose-dependent activation of caspase-3 and -9 and an absence of activation of caspase-8, pointing to EFV induction of the intrinsic (mitochondrial) apoptotic pathway. In conclusion, clinical concentrations of EFV can be cytotoxic and lead to activation of apoptotic programmes in common cellular models. This suggests that the therapeutic range of EFV is rather narrow and also that prolonged administration of this drug could result in highly active antiretroviral therapy-related mitochondrial dysfunction.

ABSTRACT P-04
Antiviral Therapy 13 Suppl 4:A24
Opposite effects of nevirapine and efavirenz on differentiation and gene expression of human adipocytes in culture

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Aim: Efavirenz has been reported to have negative effects on mouse 3T3L1 adipocytes in culture and similar effects have been suggested for human adipocytes. Nevirapine has been less studied and slight positive effects have been reported for mouse brown adipocyte differentiation. Recent data indicating some extent of lipoatrophic disturbances associated with the presence of efavirenz in antiretroviral treatment regimes highlight the importance of the direct assessment of the action of these two non-nucleoside reverse transcriptase inhibitors on human adipose cells. The objective of this study was to compare the action of these two drugs on human adipocyte differentiation and gene expression.

Methods: Human adipocytes were differentiated in primary culture from precursor cells obtained from liposuction
from healthy individuals. Firstly, human pre-adipocytes were exposed to distinct concentrations of the drugs throughout the process of differentiation of pre-adipocytes into adipocytes (10 days). In a second experimental setting, already differentiated adipocytes were exposed to the drugs during 24 h. The extent of morphological adipocyte differentiation was measured by optical microscopy and by counting the cells accumulating lipid droplets. Molecular analysis was performed by RNA isolation (RNAsasy; Qiagen) and quantitative determination of transcripts using real-time PCR (TaqMan; Applied Biosystems).

**Results:** Efavirenz caused pre-adipocyte cell death at concentrations higher than 10 µM, whereas no signs of toxicity of nevirapine were observed at this range of concentration. Lower doses of efavirenz (0.5, 2 and 4 µM) caused a dose-dependent reduction in adipocyte differentiation evidenced by the impairment in the acquisition of adipocyte morphology and the reduction in the mRNA expression of master genes of adipogenesis (PPARγ) and adipocyte phenotype (that is, adiponectin and lipoprotein lipase). No changes in mitochondrial DNA abundance or in the expression of mitochondrial DNA-encoded (COII) or nuclear DNA-encoded (COIV) transcripts for mitochondrial proteins were observed. Nevirapine treatment did not cause any impairment in adipogenic differentiation on the basis of adipocyte morphology or expression of marker genes. In fact, 20 µM nevirapine resulted in a mild positive induction of adipogenesis (upregulation of PPARγ, adiponectin and lipoprotein lipase mRNAs). Treatment of already differentiated adipocytes with efavirenz (0.5, 4 and 10 µM) also caused a reduction in the mRNAs of PPARγ and adiponectin, whereas no changes occurred for these transcripts in adipocytes treated with the same concentrations of nevirapine. Again, 20 µM nevirapine induced significantly PPARγ and adiponectin mRNA levels.

**Conclusions:** Efavirenz impairs morphological adipogenic differentiation and adipogenic gene expression without causing mitochondrial toxicity. In contrast, nevirapine did not impair and even induced slight adipogenesis. Considering the evidence that alterations in the adipogenic processes take place in lipoatrophic adipose tissue from patients, inclusion of non-nucleoside reverse transcriptase inhibitors in antiretroviral regimes design should take into account the anti-adipogenic properties of efavirenz with respect to nevirapine.

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**ABSTRACT P-05**

**Antiviral Therapy 13 Suppl 4:A25**

**Genome-wide transcriptomic analysis reveals distinct patterns of altered gene expression in subcutaneous adipose tissue associated with HIV-1 infection, antiretroviral treatment and lipodystrophy**


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**Aim:** The relative contribution of the distinct pathogenic events leading to lipoatrophy in HIV type-1 (HIV-1)-infected, antiretroviral-treated patients is poorly known. To ascertain the major molecular events associated with the appearance of lipoatrophy, we performed whole-genome transcriptomic analysis of subcutaneous fat from distinct sets of patients in comparison with healthy controls.

**Methods:** We obtained RNA from subcutaneous adipose tissue biopsies from four groups of individuals: HIV-1-uninfected healthy controls, HIV-1-infected patients naive to antiretroviral treatment and HIV-1-infected patients under treatment without or with lipodystrophy, including peripheral lipodystrophy. Microarray analysis was performed using eight distinct individual RNA samples for every group and chemoluminescence-based Applied Biosystems Human-Genome Survey arrays. Differential gene expression in relation to biological processes was analysed using the PANTHER ontology tool. Validation of results was performed by quantitative TaqMan reverse transcriptase-PCR of selected transcripts representative of functional categories of genes.

**Results:** Adipose tissue from untreated HIV-1-infected patients had altered expression of genes of ‘inflammation mediated by chemokines and cytokines’, ‘complement-mediated immunity’ and ‘interferon-mediated immunity’ as well as of ‘T-cell activation’. Several of these alterations remained in treated patients with and without lipodystrophy. Macrophage-mediated immunity was altered in treated patients only, and more deeply in those with lipodystrophy. MHC-I-mediated immunity and MHC-II-mediated immunity were altered only in patients with lipodystrophy. Lipid metabolism and tricarboxylic acid cycle-related gene expression were also modified in fat from all the HIV-1-infected patient groups, although alterations were more profound in treated patients and in those with lipodystrophy. Mitochondrial oxidative phosphorylation and electron transfer-related gene expression were altered only in adipose tissue from treated patients, and more deeply in those showing lipodystrophy. Only adipose tissue from patients...
with lipodystrophy showed a modification in apoptosis-related gene expression. Another pathway in which gene expression was altered was detoxification-related (only in treated patients).

Discussion: Alterations of gene expression in relation to immunity, inflammation and metabolism appear in adipose tissue from non-treated HIV-1-infected patients. Treated patients, in addition to disturbances in gene expression for those processes, show modifications in gene expression for metabolic pathways related to mitochondrial oxidation, macrophage activation and detoxification. Apoptosis-related gene expression is specifically altered in association with full-blown lipoatrophy. Present results highlight a role for HIV-1 infection in addition to antiretroviral treatment in eliciting adipose tissue alterations. Establishment of direct or indirect actions of HIV-1 on adipose tissue, identification of cellular actors other than macrophages as involved in the proinflammatory response of adipose tissue to HIV-1 infection and knowledge of the molecular basis for the specific alterations in energy metabolism appear as novel directions for research in HIV-1 lipodystrophy in the light of present findings.

ABSTRACT P-06

Antiviral Therapy 13 Suppl 4:A26

Leptin, a marker of evolution to lipodystrophy? Results of a 1-year follow-up in HIV-infected patients

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Introduction: Adipocyte-derived hormones (ADH) might help to explain the relationship between the distribution of adipose tissue and the progressive metabolic changes associated to HIV-related lipodystrophy, namely insulin resistance.

Aims: We aimed to evaluate ADH in HIV-infected patients undergoing antiretroviral therapy (ART) and to measure their evolution over a 1-year follow-up in the total of patients and in patients with and without clinically defined lipodystrophy.

Methods: A total of 131 HIV-infected patients undergoing ART were evaluated for the presence of CL and ADH (adiponectin, leptin, resistin and tumour necrosis factor-α [TNF-α]), ghrelin and insulin resistance (HOMA and Quicki) were measured. The results are presented as mean ± SD. Means were compared using Student’s t-test or non-parametric Mann–Whitney U test.

Results: After a 1-year follow-up, we found that in the total of patients, a decrease in adiponectin (6,117.9 ± 6,757.9 versus 1,407.6 ± 0.19.6 ng/ml, P < 0.001), TNF-α (55.4 ± 40.3 versus 27.6 ± 21.2 pg/ml, P < 0.001), ghrelin (133.8 ± 135.2 versus 94.8 ± 122.1 pg/ml, P = 0.006), an increase in resistin (1.06 ± 0.48 versus 1.45 ± 0.99 ng/ml, P = 0.001) and no differences in leptin levels. In those without CL, a decrease in adiponectin (5,221.9 ± 6,398.1 versus 1,434.1 ± 1,732.34 ng/ml, P = 0.002), TNF-α (61.0 ± 55.5 versus 29.5 ± 22.8 pg/ml, P = 0.004), an increase in resistin (1.11 ± 0.83 versus 1.67 ± 1.52 ng/ml, P = 0.032) and no differences in leptin and ghrelin levels. In those with CL, a decrease in adiponectin (5,587.0 ± 7,000 versus 1,681.7 ± 1,732.1 ng/ml, P < 0.001), TNF-α (56.1 ± 40.6 versus 25.9 ± 19.2 pg/ml, P < 0.001), ghrelin (122.8 ± 117.6 versus 82.1 ± 108.3 pg/ml, P = 0.003), an increase in resistin (1.29 ± 1.24 versus 1.37 ± 0.65 ng/ml, P = 0.014) and no differences in leptin levels. No differences were found in the progression over a year of resistin, adiponectin, TNF-α and ghrelin between patients without and with clinical lipodystrophy. On the contrary, we found statistically significant differences for the evolution of leptin (Table 1).

Conclusions: ADH and ghrelin, except leptin, showed a similar evolution on 1-year follow-up in HIV-infected patients with or without lipodystrophy. The decrease of leptin in patients without lipodystrophy seems to indicate a decrease in subcutaneous fat in these patients and could be a marker of progression to lipodystrophy.

Table 1. (Abstract P-06)

<table>
<thead>
<tr>
<th></th>
<th>Without clinical lipodystrophy (difference after 1 year)</th>
<th>With clinical lipodystrophy (difference after 1 year)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistin, ng/ml</td>
<td>0.58 ±1.52</td>
<td>0.30 ±0.78</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin, ng/ml</td>
<td>-5,204.2 ±7,382.7</td>
<td>-4,542.9 ±16,173</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-α, pg/ml</td>
<td>-36.6 ±65.0</td>
<td>-24.3 ±35.1</td>
<td>NS</td>
</tr>
<tr>
<td>Ghrelin, pg/ml</td>
<td>-8.36 ±208.6</td>
<td>-53.2 ±140.8</td>
<td>NS</td>
</tr>
<tr>
<td>Leptin, ng/ml</td>
<td>-1.1 ±4.1</td>
<td>0.79 ±3.39</td>
<td>0.028</td>
</tr>
</tbody>
</table>

NS, not significant; TNF-α, tumour necrosis factor-α.
Antiviral Therapy 13 Suppl 4:A27

ABSTRACT P-07

BMI and lipodystrophy: a complex interplay on adipocyte-derived hormones on HIV-infected patients

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Introduction: Adipocyte-derived hormones (ADH) could be the link between the distribution of adipose tissue and the metabolic changes, namely insulin resistance (IR), related to HIV lipodystrophy.

Aims: To evaluate ADH (adiponectin, leptin, resistin and TNF-α), ghrelin and IR in HIV patients undergoing antiretroviral therapy with and without clinically defined lipodystrophy, with and without lipodystrophy defined by fat mass ratio (FMR) by DEXA, according to different types of fat distribution (without clinical lipodystrophy [CL] and without abdominal prominence [AP], without CL and with PA, with CL and without AP, and with CL and with AP). AP was defined by waist circumference (WC) by IDF-2005.

Methods: A total of 163 patients were evaluated for the presence of CL, lipodystrophy defined by FMR and abdominal fat according to CT.

Results: When lipodystrophy was clinically defined, no statistically significant differences were found in resistin, adiponectin, TNF-α, ghrelin, HOMA and Quicki, between patients with and without CL. Leptin was significantly lower in patients with CL (without CL 9.42 ±10.27 versus 4.25 ±4.08 ng/ml, P<0.001). All the former results were similar when patients were divided by gender. When lipodystrophy was defined by FMR, the results were similar in the total of patients. When divided by gender, the results were similar, except for adiponectin (without CL 8,682.6 ±9,476.9 versus L 4,282.3 ±4,153.5 ng/ml, P=0.029), leptin (no statistically significant differences), HOMA (increase) and Quicki (decrease) in males with lipodystrophy. According to the types of fat distribution no differences were found for resistin, TNF-α and ghrelin; adiponectin was lower in patients with AP and leptin was higher in those without AP. In patients without CL, those with AP had lower adiponectin (without AP 8,856.0 ±8,849.7 versus with AP 3,808.7 ±4,569.8 ng/ml, P=0.004), higher leptin (without AP 4.50 ±4.26 versus with AP 11.74 ±11.44 ng/ml, P=0.001) and higher insulin resistance (HOMA without AP 1.4 ±0.7 versus with AP 3.4 ±3.4, P=0.005). In the patients with CL, those with AP had higher leptin (without AP 2.46 ±1.79 versus with AP 6.13 ±4.93 ng/ml, P<0.001); no differences were found in HOMA and Quicki in those with and without AP. In the total of patients, we found correlations between leptin and body mass index (BMI; r=0.493, P<0.001), WC (r=0.440, P<0.001), total fat (r=0.803, P<0.001), trunk fat (r=0.774, P<0.001), lower limb fat (r=0.734, P<0.001), visceral/subcutaneous fat mass by CT (r=0.451, P<0.001) and FMR (r=0.265, P=0.001); between adiponectin and total fat (r=–0.209, P=0.013), trunk fat (r=–0.195, P=0.020) and lower limb fat (r=–0.168, P=0.047); between resistin and BMI (r=–0.177, P=0.024); and between ghrelin and HOMA (r=0.205, P=0.013) and Quicki (r=0.211, P=0.011). We found the same correlations formerly described for leptin, independently of the presence of CL.

Conclusions: The lipodystrophy of HIV-infected patients is a complex model with an interplay of adiposity and fat redistribution on ADH.
ABSTRACT P-08

Antiviral Therapy 13 Suppl 4:A29

Inhibition of the insulin receptor kinase by antiretroviral protease inhibitors

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Background: HIV protease inhibitors (HPIs) are potent antiretroviral agents. Unfortunately, prolonged use of these drugs causes many complications among patients, including insulin resistance, lipodystrophy, hyperglycaemia and type 2 diabetes mellitus. The incidence of these complications is increasing as patients with HIV infection who are on treatment experience prolonged lifespans. The molecular basis for these drug-induced metabolic syndromes is still unknown and few studies have attempted to address this.

Objectives: In this study we have sought to elucidate how HPIs may affect the insulin signalling pathway in Chinese hamster ovary cells transfected with high levels of human insulin receptor and in differentiated 3T3-L1 murine adipocytes. We have also examined the effects of these drugs on lipoprotein lipase (LPL) in the adipocytes, as LPL levels have been found altered in patients treated with HPIs who later develop lipodystrophy.

Methods: We investigated the effects of HPIs on cells treated with saquinavir and indinavir for 16 h and then stimulated with insulin. Insulin-stimulated tyrosine phosphorylation was analysed by immunoblotting with antiphosphotyrosine antibody.

Results: We found that saquinavir (30–40 \( \mu \text{M} \)) displayed potent inhibition of the tyrosine phosphorylation of the insulin receptor \( \beta \)-subunit and insulin receptor substrate proteins in both cell types. Indinavir (50 \( \mu \text{M} \)) had similar effects on insulin signalling, but with a different dose-response profile. Thus, both drugs displayed potency differences in their effects on insulin signalling, which may influence the propensity to cause the side effect of insulin resistance seen in patients. The inhibition of insulin signalling appears to be at a proximal level and involves a direct effect on the insulin receptor. We postulated that the inhibition of the insulin receptor kinase may occur because of changes in the level or activity of tyrosine phosphatases and suppressor of cytokine signaling 1 (SOCS-1). However, we found that protein tyrosine phosphatase-1B (PTP1B) and anti-SOCS-1 levels were not altered.

Conclusions: We conclude that the effects of HPIs to cause insulin resistance does not involve PTP1B or SOCS-1 protein, but may involve other regulatory proteins.

ABSTRACT P-09

Antiviral Therapy 13 Suppl 4:A29

The impact of tenofovir disoproxil fumarate on insulin sensitivity, adipocytokines and markers of endothelial function

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Objectives: This study aimed to assess the impact of tenofovir disoproxil fumarate (TDF) on insulin sensitivity, selected adipocytokines and markers of endothelial function.

Methods: This was a single-centre, randomized, double-blind, placebo-controlled study that used a two-sequence, two-period crossover design. HIV-negative males were recruited to the study and randomized 1:1 to receive either 2 weeks of TDF 300 mg once daily followed by 2 weeks of placebo or placebo initially followed by TDF. A hyperinsulinaemic euglycaemic clamp was performed at baseline, after 2 weeks and after 4 weeks (2 weeks after treatment switch).

Results: In total, 16 participants completed all three clamps. Mean (±SD) insulin sensitivity (peripheral glucose

<table>
<thead>
<tr>
<th>Table 1. (Abstract P-09)</th>
<th>Baseline (day 1 clamp)</th>
<th>After 2 weeks of TDF</th>
<th>After 2 weeks of placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (ng/ml)</td>
<td>4,647 (3,193–6,692)</td>
<td>5,603 (2,314–7,453.5)</td>
<td>5,521 (3,548.5–8,939)</td>
</tr>
<tr>
<td>Leptin (µg/ml)</td>
<td>3,398 (1,456–6,862)</td>
<td>4,497 (1,592–5,457)</td>
<td>3,312.5 (1,915–8,474)</td>
</tr>
<tr>
<td>PAI-1 (ng/ml)</td>
<td>4.25 (2.98–5.87)</td>
<td>4.68 (1.37–8.04)</td>
<td>4.35 (3.067–7.48)</td>
</tr>
<tr>
<td>Selectin P (ng/ml)</td>
<td>122.42 (103.05–163.46)</td>
<td>123.73 (104.50–161.28)</td>
<td>133.58 (125.14–162.98)</td>
</tr>
<tr>
<td>Selectin E (ng/ml)</td>
<td>35.67 (20.53–49.05)</td>
<td>34.19 (21.01–46.98)</td>
<td>33.77 (18.38–45.93)</td>
</tr>
</tbody>
</table>

Data are medians (interquartile range). n=16. PAI-1, plasminogen activator inhibitor-1; TDF, tenofovir disoproxil fumarate.
disposal rate/mean insulin concentration [M/I] during the last hour of the clamp) was 15.4 (±4.64) at baseline, 16.2 (±4.32) after 2 weeks of TDF and 18.8 (±7.72) mg/kg/min per mU/l insulin x100 after 2 weeks of placebo. There was no significant difference in M/I between groups or from baseline. In addition levels of adiponectin, leptin, plasminogen activator inhibitor-1, selectin P and selectin E were not significantly altered. No significant correlation between changes in adiponectin and leptin and changes in M/I was found. See Table 1.

Conclusions: Two weeks of TDF did not have any significant impact on insulin sensitivity, assessed by the M/I ratio during euglycaemic clamp, adipocytokines or markers of endothelial function. These results support the view that TDF has minimal metabolic impact and would be suitable as backbone treatment in metabolic studies in HIV-positive patients.

### Table 1. (Abstract P-10)

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>25(OH) VitD, ng/ml</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 DM</td>
<td>106</td>
<td>14.78</td>
</tr>
<tr>
<td>No type 2 DM</td>
<td>1,704</td>
<td>19.24</td>
</tr>
</tbody>
</table>

CI, confidence interval; DM, diabetes mellitus; 25(OH) VitD, 25-OH vitamin D.

25(OH) VitD level and type 2 DM while controlling for traditional risk factors for DM.

Results: There were 1,811 patients aged 14–76 years with available 25(OH) VitD and fasting glucose values. The mean 25(OH) VitD level was 18.98 ng/ml with 65.5% of patients having vitamin D deficiency (25(OH) VitD<20 ng/ml). In total, 6% of the patients had type 2 DM (see Table 1). Patients with adequate vitamin D levels (>20 ng/ml) were less likely to have type 2 DM (adjusted odds ratio 0.59 [95% CI 0.36–0.97]) after adjusting for age, body mass index and triglyceride levels.

Conclusions: Individuals with HIV and type 2 DM had significantly lower vitamin D levels in comparison with HIV infected individuals without type 2 DM. Patients with vitamin D deficiency were more likely to have type 2 DM in comparison with those with adequate vitamin D levels. Although causality cannot be inferred, vitamin D deficiency might be a modifiable risk factor for the development of type 2 DM among HIV-infected patients.

### ABSTRACT P-11

Antiviral Therapy 13 Suppl 4: A30

The impact of switching double-boosted protease inhibitors to darunavir/ritonavir on insulin sensitivity

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Background: Double-boosted protease inhibitors (DBPIs) are used in the treatment of experienced patients who have resistance to or intolerance of drugs from other available classes. There is insufficient data available to support this approach and there is concern that long-term side effects of PIs may be potentiated. The advent of newer drugs has opened the possibility of rationalizing the treatment of these patients, potentially reducing toxicity.

Methods: This open-label, prospective, cohort study investigated the effect of substituting ritonavir-boosted darunavir (DRV/r) for DBPIs on insulin sensitivity. Ten HIV-positive male patients were enrolled. They were stable on a DBPI regimen with no prior evidence of DRV resistance-associated mutations. A hyperinsulinemic euglycaemic clamp was performed at baseline and repeated after
4 weeks of twice daily DRV 600 mg and ritonavir 100 mg. All other drugs in the initial regimen were continued.

Results: Five patients were switched to DRV/r monotherapy and five received DRV/r in addition to their nucleoside reverse transcriptase inhibitors. All patients maintained an undetectable viral load after 4 weeks of treatment. There was a mean (±SEM) percentage increase of 16.2% (±9.1) from baseline for the peripheral glucose disposal rate (GDR; P=0.160). Subjects were divided according to their baseline GDR; the five patients with a GDR less than the median (5.05 mg/kg/min) had a mean (±SEM) increase of 31.3% (±14.5). In contrast, the five patients whose GDR was above the median only demonstrated an increase of 1.1% (±6.85). There was no significant change in CD4+ T-cell counts and lipid parameters after 4 weeks of switching treatment.

Conclusions: In patients switching from a DBPI regimen to DRV/r, virological control was maintained after 4 weeks. Overall, there was no deleterious impact on insulin sensitivity at baseline there was evidence of an improvement. Overall, there was no deleterious impact on insulin sensitivity at baseline there was evidence of an improvement.

ABSTRACT P-12

Antiviral Therapy 13 Suppl 4:A31

Low physical function is associated with diabetes mellitus among HIV-infected and HIV-negative men

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Objectives: Low physical activity is a contributing factor to both diabetes mellitus (DM) and insulin resistance (IR) has been overlooked in most studies of HIV-infected populations despite a known association in the general population. The objective of this study was to investigate low physical function (a surrogate for physical activity) as a contributor to DM and IR among HIV-infected and HIV-negative men.

Methods: In total, 384 HIV-negative and 274 HIV-infected men (n=658) from the Pittsburgh centre of the Multicenter AIDS Cohort Study contributed clinical and physical function data. DM was defined by a fasting serum glucose ≥126 mg/dl. IR was calculated using the homeostasis model assessment (HOMA). The Physical Functioning Ten Scale from the Short Form-36 Health Survey assessed baseline physical function with a lower score indicating lower physical function. Baseline covariates included age, race, HIV, AIDS, body mass index (BMI) and CD4+ T-cell count. Multivariate logistic regression analysis was used to assess the independent association between physical function and DM as well as physical function and IR.

Results: HIV-negative men with normoglycaemia had the highest physical function scores. HIV-negative men had better physical function scores than HIV-infected men regardless of glucose level. In both HIV-negative and HIV-infected men, lower physical function scores were observed among individuals with DM compared with those with normoglycaemia. Men with both diabetes and AIDS had the lowest mean physical function score among all groups. In both HIV-negative and HIV-infected men, physical function scores were lower in men with hyperinsulinemia and in men with higher HOMA scores. In multivariate analysis, lower physical function score (odds ratio [OR]=1.5 per 25 unit decrease, P=0.02), older age (OR=1.5 per 5 years, P=0.0001) and Black race (OR=2.8, P=0.002) were associated with DM. In addition, older age (OR=1.3 per 5 years, P=0.0001), higher BMI (OR=2.8 per 5 units, P=0.0001), HIV infection (OR=11.3, P=0.01), black race (OR=2.0, P=0.004) and the interaction between HIV and physical function (OR=2.1, P=0.003) were associated with IR.

Conclusions: This study suggests that low physical function (as a surrogate for physical activity) is associated with DM and IR in both HIV-infected and HIV-negative men. Future research using objective physical activity measures is warranted to further understand the contribution of low physical activity to DM and IR among HIV-infected populations. Ongoing HIV cohort studies should address the role of physical activity as an important contributor to impaired glucose metabolism.

ABSTRACT P-13

Antiviral Therapy 13 Suppl 4:A31

Effects of diet and exercise and/or rosiglitazone on body composition and glucose metabolism in HIV-positive and HIV-negative subjects

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Aims: We previously reported lack of improvement in glucose metabolism in obese, HIV-infected women, despite 7.3% weight loss through diet and exercise. This study compared responses to 16 weeks of diet and exercise and/or rosiglitazone in HIV-infected and uninfected men and women.

Methods: This was a 16-week, prospective, randomized, placebo-controlled (for rosiglitazone) trial. Participants...
were overweight or obese and insulin resistant (fasting insulin $\geq 16 \mu U/ml$) at screening. They were stratified by HIV status and gender to randomly receive 8 mg/day rosiglitazone (ROSI), hypocaloric diet and exercise training plus placebo (DEAP) or diet and exercise plus rosiglitazone (DEAR). Body composition was measured by whole body MRI and DEXA. Glucose metabolism was measured by euglycaemic hyperinsulinaemic clamp at baseline and week 16. Data are presented as mean $\pm SD$. Statistical comparisons between baseline and follow-up were done by paired $t$-test, between HIV groups by Student’s $t$-test and between interventions by ANOVA with Bonferroni post hoc comparisons.

**Results:** Baseline and follow-up data are currently available for 15 subjects (4 HIV-positive and 4 HIV-negative men, 3 HIV-positive and 4 HIV-negative women). At baseline, subjects weighed an average of 97.5 kg (body mass index 33.2 $\pm 4.9$ kg/m$^2$). Weight change was significantly different between treatment groups ($P=0.0006$), with weight loss in DEAP (-7.4 $\pm 3.1$ kg, -7.9%, $P=0.006$) and DEAR (-6.4 $\pm 4.1$ kg, -6.5%, $P=0.02$) and gain in ROSI (2.2 $\pm 1.5$ kg, $P=0.03$). Skeletal muscle and visceral adipose tissue changes did not differ significantly by intervention, whereas subcutaneous adipose tissue (overall $P=0.008$) decreased in DEAP (-4.0 $\pm 2.0$ l, $P=0.01$) and DEAR (-3.5 $\pm 1.8$ l, $P=0.01$) but not in ROSI ($P=0.50$). Changes in body weight and composition were not significantly different by HIV status. For all subjects, fasting insulin at baseline was 25.4 $\pm 10.5$ U/ml and did not differ by HIV status. Glucose disposal rate (GDR) per kg fat free mass (FFM) increased in response to all interventions ($P<0.03$) but was greater in DEAR than in DEAP ($P=0.03$); DEAR and DEAP were not different from ROSI and GDR change did not differ by HIV status ($P=0.3$). GDR adjusted for insulin levels at steady state during the clamp ($M/I$) improved in all treatment groups ($P<0.05$) and did not differ by group ($P=0.3$), but less improvement was seen with HIV infection (28.3 $\pm 22.8$ versus 10.3 $\pm 9.4$, $P=0.07$). Suppression of endogenous glucose production (SEGP)/FFM did not change in response to any intervention ($P=0.57$) nor within either HIV group ($P=0.35$). Changes in weight and body composition did not correlate with changes in glucose metabolism except that a 0.65 $\pm 0.62$ l visceral adipose tissue decrease in DEAP correlated with $M/I$ and SEGP/FFM improvements ($P=0.03$ for both).

**Conclusions:** Weight loss and rosiglitazone are equally effective in improving glucose metabolism. HIV status did not affect treatment responses in obese, insulin resistant individuals in this study.
ABSTRACT P-14

*Antiviral Therapy* 13 Suppl 4:A33

Bone mineral mass loss risk in HIV-infected patients on HAART: a longitudinal study

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**Aim:** To perform a longitudinal study on bone mineral density (BMD) in a cohort of HIV-infected patients exposed to highly active antiretroviral therapy (HAART).

**Methods:** In each patient, BMD (g/cm²) was measured to highly active antiretroviral therapy (HAART). Methods: In each patient, BMD (g/cm²) was measured by DEXA in the lumbar spine and femur; patients were classified according to World Health Organization criteria as normal (T-score >-1.0), osteopenic (T-score ≤-1.0 and ≥-2.5) and osteoporotic (T-score < -2.5). Serum bone alkaline phosphatase (BAP, ng/ml), as a marker of bone formation, was assayed by IRMA, and urine pyridinoline and deoxypyridinoline (PYD & DPD, nM/mM creatinine), as markers of bone resorption, was assayed by EIA. These parameters were evaluated at baseline and rechecked after 48–60 months. Patients receiving drugs affecting bone metabolism were excluded.

**Results:** In a series of 172 adult HIV patients, 51 (27 males and 24 females) were followed in a longitudinal study. At baseline, 25/51 (49.0%) patients were heterosexuals, 21/51 (41.2%) previous intravenous drug users, 5/51 (9.8%) homosexuals, mean age was 39.3 ±6.7 years and 16/51 (33.3%) patients had previous AIDS diagnosis. Furthermore, 46/51 (90.1%) patients were HAART experienced, mean CD4+ T-cell count was 597 ±287 cells/µl and mean HIV RNA was 4.88 ±5.48 log₁₀ copies/ml. At baseline, 8/51 (15.7%) patients were osteoporotic and 16/51 (31.4%) osteopenic in spine and/or femur, whereas 27/51 (52.9%) had normal BMD. No statistical difference was observed between the two groups in age, HAART duration, weight, femur and spine BMD, BAP and PYD & DPD. During follow-up, 27 (52.9%) patients (group 1) received protease inhibitors (PI) plus nucleoside reverse transcriptase inhibitors (NRTI) and 24 (47.1%) patients (group 2) received non-nucleoside reverse transcriptase inhibitors (NNRTI) plus NRTI or triple NRTI. No significant change in BMD values was ascertained in lumbar spine in group 1 patients, whereas BMD values had a significant (P<0.011) reduction in femur than basal values (0.86 ±0.13 versus 0.83 ±0.16 g/cm²). In group 2, mean BMD values remained unmodified in both spine and femur. In particular, 2/16 (12.5%) patients osteopenic at baseline underwent osteoporosis in the follow-up and 11/27 (40.7%) with basal normal BMD developed osteopenia in spine and/or femur. BAP levels increased in both group 1 and 2, and PYD & DPD levels increased only in group 1, but not significantly. There was no significant CD4+ T-cell count increase and HIV RNA decrease in both groups.

**Conclusions:** This longitudinal study demonstrates that in HIV patients on HAART a decrease of BMD, even osteoporosis, can occur. Bone mass loss, when continuing treatment, persisted over time and further worsened in some of our cases, in particular when receiving PI. Thus, a correct bone metabolism follow-up is suggested in patients on HAART, even more when other risk factors are present, to early identify those cases to be submitted to appropriate preventive treatments to reduce fracture risk.

ABSTRACT P-15

*Antiviral Therapy* 13 Suppl 4:A33

Association between peripheral lipoatrophy and bone demineralization in treated HIV-positive males

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**Introduction:** Bone demineralization is increasingly recognized as an important component of the metabolic complications affecting HIV-positive patients. In the general population, multiple factors influence bone mineral density (BMD) including both regional lean and fat mass. In treated HIV patients, body composition changes still include peripheral lipoatrophy, relative stability of lean mass and variable changes in central fat mass. We investigated factors associated with regional bone demineralization in HIV-positive males.

**Methods:** A cohort of treated, clinically stable males who underwent DXA scans between 2001 and 2007 were characterized with regards to clinical (highly active antiretroviral therapy [HAART] usage, CD4s, HIV viral load [VL], body mass index, cigarette use and serum testosterone levels), metabolic (fasting lipid and glucose homeostasis), DXA-derived regional body composition (limb fat mass/total body fat mass ratio [%L/TBFM]) and DXA-derived BMD parameters (femoral neck [FN], total hip [TH] and lumbo-sacral [LS] spine T-scores). Differences between medians of variables were compared using the Mann–Whitney U
Background: Osteonecrosis of the hip (OTNH) in HIV-infected patients has been related to corticosteroids, dyslipidaemia, alcoholism, lipodystrophy and the HIV infection itself. Some cases of OTNH have been also related to antiretroviral drugs (ARV). The aim of this study was to evaluate the prevalence of silent OTNH in HIV-infected patients and its association with risk factors.

Methods: Adults outpatients (<70-years-old) with HIV infection diagnosis before January 2006 were prospectively evaluated between March and May 2008. Patients diagnosed with OTNH and those with current symptoms were excluded. A magnetic resonance study (MR) of the hips was performed. According to ARV treatment, patients were classified group I: patients without previous ARV treatment; group II: those who have received only one scheme of ARV treatment; and group III: patients with multiple ARV treatments.

Results: MR was performed in 97 white patients (group I: 23, group II: 24 and group III: 50), 68 were men with a mean age of 44.8 years (range 24–67). OTNH was detected in four patients (4.1%), two of them were bilateral. The four patients with OTNH were males, with a mean age of 46 years (range: 40–55). The current average of total CD4 lymphocyte count was 506 cells/µl (range 205–807) and the mean CD4 lymphocyte nadir was 27 cells/µl (range 12–43). All the patients except one have undetectable levels of HIV viral load (<40 copies/ml). Three patients were in group III and the other in group II. The mean duration of the ARV treatment was 11 years (range: 5–15). Multiple risk factors for OTNH were recorded in every patient: three with lipodystrophy, one with corticosteroids therapy, one with hypertyglyceridaemia, two with alcoholism and one with pancreatitis. CD4 lymphocyte nadir (P=0.034), proportion of patients with CDC stage C (P=0.039) and patients with previous treatment with corticosteroids (P=0.042) were significantly different between patients with OTNH and those with normal MR.

Conclusions: The prevalence of asymptomatic OTNH in HIV-infected patients was 4.1%. The most important risk factors for OTNH were corticosteroid treatment, a lower CD4 lymphocyte nadir and AIDS-defining disease. In this group of patients, ARV treatment was not associated with the presence of osteonecrosis.
Long-term changes in body fat and bone mass density after switching from nucleoside reverse transcriptase inhibitors to fixed-dose tenofovir/emtricitabine or abacavir/lamivudine

Background: Whether switching to fixed-dose tenofovir/emtricitabine (TE) or abacavir/lamivudine (AL) has a different impact on body fat and bone mineral density (BMD) is unknown. The BICOMBO study randomized patients to switch their nucleoside reverse transcriptase inhibitors (NRTI) to TE or AL.

Methods: Participants at three sites were co-enrolled in the BICOMBO Body Composition substudy. Dual-energy X-ray absorptiometry scans were performed at baseline and annually. Regional fat and BMD changes from baseline in both groups were compared with non-parametrical tests. Changes in limb and total fat were assessed both as absolute and percent changes relative to baseline. The sample size was calculated to detect an increase in limb fat of 500 g from baseline with 80% power at a 5% significance level.

Results: There were 45 patients (median 42 years, 73% male, 11% on protease inhibitor and 89% on non-nucleoside reverse transcriptase inhibitor) randomized to TE (n=25) or AL (n=20). Previous antiretroviral regimens and baseline characteristics were equivalent between groups. At baseline, limb and total fat (median, interquartile range) in the pooled group was 5,082 g (3,386–6,434 g) and 14,619 g (10,498–19,071 g), respectively. There was an absolute gain of fat and BMD in both groups. Limb fat gain at 96 weeks was 337 g (7.6%, P=0.039 within group) in the TE group and 756 g (12.1%, P=0.023 within group) in the AL group (P=0.126 between groups). Total fat changes at 96 weeks were a decrease of 130 g (0.69%, P=0.757 within group) in the TE group and an increase of 1,779 g (12.1%, P=0.044 within group) in the AL group (P=0.087 between groups). BMD increased from 0.93 to 1.14 g/cm² (P<0.001 within group) in the TE group and from 1.06 to 1.18 g/cm² (P=0.001 within group) in the AL group (P=0.217 between groups).

Objective: To compare changes in total limb fat, by dual energy X-ray absorptiometry (DEXA) scan assessment, after switching from an AZT/3TC backbone to FTC/TDF versus maintaining AZT/3TC.

Methods: A 72 week, open-label, randomized, controlled study. Virologically-suppressed (<50 copies/ml) HIV-infected patients on highly active antiretroviral therapy (HAART) containing AZT/3TC (plus either a non-nucleoside reverse transcriptase inhibitor [NNRTI] or a protease inhibitor [PI]) were assigned to either switch their AZT/3TC backbone to FTC/TDF or continue on AZT/3TC. Stratification was performed by third agent of HAART (either NNRTI or PI). Post-hoc subanalyses were performed for total limb fat changes in patients by baseline (BL) limb fat, BL body mass index and prior duration of AZT/3TC therapy.

Results: Eighty patients were included (39 FTC/TDF and 41 AZT/3TC). Mean age was 44 years. Patients were predominantly male (81%). Median baseline CD4 count was higher in the FTC/TDF versus AZT/3TC arm (653 versus 504 cells/mm³, P=0.037). In the FTC/TDF arm, one patient discontinued because of an adverse event (abdominal pain) and four patients in AZT/3TC group discontinued because...
of an adverse event (two cases of renal colic, one anaemia and one lactic acidosis). Mean change from BL to week 48 in estimated glomerular filtration rate (creatinine clearance by C-G) was -11.8 ml/min for FTC/TDF and -3.6 ml/min for AZT/3TC. See Table 1 and 2 for further results.

Conclusions: Through 48 weeks, switching from AZT/3TC to FTC/TDF was well tolerated, efficacy was maintained and significant improvements in overall limb fat content were observed. Switching to FTC/TDF significantly increased limb fat at week 48 compared with AZT/3TC for patients with BL limb fat content $\leq$ 7.2 kg, those with prolonged exposure to AZT and patients with BL body mass index $\leq$ 25 kg/m$^2$.

**ABSTRACT P-19**

*Antiviral Therapy* 13 Suppl 4:A36

**Effects of Tesamorelin (TH9507), a growth hormone-releasing factor (GRF) analogue, on visceral adipose tissue (VAT) in HIV-infected patients with excess abdominal fat: impact of antiretroviral therapy regimen**

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**Background:** HIV-infected patients on antiretroviral therapy (ART) often show increased visceral adipose tissue (VAT), a known cardiovascular risk factor. Previous data showed that administration of daily 2 mg tesamorelin, a growth hormone-releasing factor analogue, to HIV-infected patients with excess abdominal fat for 26 weeks resulted in a significant decrease in visceral adipose tissue (VAT) over placebo and improvements in lipids as well as patient-reported outcomes related to body image. Here we report the percent change from baseline to week 26 in VAT per type of ART regimen for the combined Phase III studies of tesamorelin in HIV-infected patients with lipohypertrophy.

**Methods:** A total of 816 HIV-infected patients with abdominal fat accumulation in the context of HIV treatment were randomized in two independent Phase III studies to receive daily subcutaneous injection of either tesamorelin 2 mg ($n=550$) or placebo ($n=266$) for 26 weeks. The primary endpoint of these studies was the percent change from baseline to week 26 in VAT, as assessed by computerized tomography (CT) scan, using the intent-to-treat population with the last observation carried forward for patients not completing the study.

**Results:** Mean ($\pm$ s d) age was 48 $\pm$ 7 years, waist circumference 105 $\pm$ 9 cm, body mass index 29 $\pm$ 4 kg/m$^2$, CD4 cell count 599 $\pm$ 290 cells/mm$^3$ and 76% of patients had undetectable HIV viral load at baseline. Mean time since initial diagnosis of HIV infection was 13.2 years. Mean duration on ART was 4.5 years, whereas mean time since initial diagnosis of lipodystrophy syndrome was 3.9 years. Patients received the following types of ART regimen during the studies: nucleoside reverse transcriptase inhibitors/non-nucleoside reverse transcriptase inhibitors (‘NRTI/NNRTI’; 33%), ‘NRTI/protease inhibitors (PI)’ (45%), ‘NRTI/NNRTI/PI’ (10%), ‘NRTIs alone’ (5%) and ‘Other’ (7%). At baseline, VAT values were 190, 175, 189, 199 and 171 cm$^2$ for the ‘NRTI/NNRTI’, ‘NRTI/PI’, ‘NRTI/NNRTI/PI’, ‘NRTIs alone’ and ‘Other’ groups, respectively. Overall, VAT decreased from baseline by

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>FTC/TDF</th>
<th>AZT/3TC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HIV RNA $&lt;$50 copies/ml, % (ITT M=F)</td>
<td>92</td>
<td>78</td>
<td>0.12</td>
</tr>
<tr>
<td>Median CD4 cell count change from BL, cells/mm$^3$</td>
<td>60</td>
<td>9</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 1. Efficacy outcomes at week 48 (Abstract P-18)**

| BL, baseline; M=F denotes missing=failure analysis; NS, not significant. |

<table>
<thead>
<tr>
<th>FTC/TDF</th>
<th>AZT/3TC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3,565</td>
<td>3,946</td>
</tr>
<tr>
<td>Patients with BL limb fat $\leq$7.2 kg</td>
<td>3,138</td>
<td>2,918</td>
</tr>
<tr>
<td>Patients with &gt;5 years of prior AZT/3TC</td>
<td>2,964</td>
<td>3,939</td>
</tr>
<tr>
<td>Patients with BL BMI $\leq$25 kg/m$^2$</td>
<td>3,311</td>
<td>2,533</td>
</tr>
</tbody>
</table>

| Last observation carried forward for dual energy X-ray absorptiometry. BL, baseline; BMI, body mass index. |

**Table 2. Median change from BL in total limb fat (g) at week 48 by dual energy X-ray absorptiometry (Abstract P-18)**
13% in tesamorelin-treated patients after 26 weeks of treatment \((P<0.001 \text{ versus placebo})\). The mean percent changes from baseline to Week 26 in VAT were -12.3, -14.5, -10.9, -16.0 and -8.2% for tesamorelin-treated patients in the groups ‘NRTI/NNRTI’, ‘NRTI/PI’, ‘NRTI/NNRTI/PI’, ‘NRTIs alone’ and ‘Other’, respectively, whereas the mean percent changes from baseline in VAT were 0.6, 2.9, 1.4, 1.6, and 6.6% for placebo-treated patients in the same groups \((P<0.05 \text{ for tesamorelin versus placebo for each type of ART regimen})\).

**Conclusions:** The results of this study indicate that daily administration of 2 mg tesamorelin is useful for reducing VAT in HIV-infected patients with excess abdominal fat on ART, regardless of type of ART regimen.

**ABSTRACT P-20**

*Antiviral Therapy 13 Suppl 4:A37*

A pathogenesis proposal of lipoatrophy reversibility after switching from thymidine analogues to tenofovir

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**Background:** Multiple clinical trials have demonstrated that switching from thymidine analogues (TA) to tenofovir disoproxil fumarate (TDF)-containing regimens can benefit patients with lipid abnormalities or lipoatrophy. However, no pathogenical explanation has been given.

**Methods:** A total of 29 HIV-infected patients with moderate to severe lipoatrophy, receiving stable antiretroviral therapy including TA (15 zidovudine and 14 stavudine) were prospectively switched to TDF, whereas the rest of their therapy remained unchanged. At baseline and 6 months after the switch, the biochemical markers (fasting plasma glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein cholesterol and venous lactate), leptin, adiponectin, insulin and resistin were measured. Furthermore, single-slice abdominal computed tomography (CT) scanning, dual energy X-ray absorptiometry (DEXA) body composition measurements and proton magnetic resonance spectroscopy \((1H-MRS)\) of the soleus and tibialis anterior were performed.

**Results:** As expected, 6 months after switching to TDF, a significant decrease was observed in triglycerides and total cholesterol values. Although peripheral and total fat content increased when measured by DEXA, peripheral and total lean mass decreased significantly \((P=0.0007 \text{ and } P=0.0004\), respectively). Furthermore, these findings correlated with a significant increase in extramiocellular lipid (EMCL) content in the soleus \((P=0.0289)\) and with an increase in EMCL and a decrease in intramiocellular lipid (IMCL) content in the tibialis anterior, although not significant, measured by \(1H-MRS\). The decrease in IMCL in the tibialis anterior at 6 months correlated significantly with an increase in HDL cholesterol \((P=0.034)\) and adiponectin \((P=0.042)\). The decrease of the IMCL values in the soleus correlated positively with triglyceride levels \((P=0.047)\). All changes were observed irrespective of choice of TA at baseline.

**Conclusions:** Switching from thymidine analogues to TDF leads to significant reversal of peripheral lipoatrophy and lipid values improvement, whereas lean mass decreased when measured by DEXA. Correlations were observed between peripheral fat gain, loss of peripheral lean mass and decrease of IMCL and increase of EMCL lipid content.

Pathogenic mechanism of lipoatrophy reversal due to a switching to TDF might be explained by ‘migration’ of lipid content from IMCL to EMCL and to periphery, which may appear as a lean mass decrease when measured by DEXA.

**ABSTRACT P-21**

*Antiviral Therapy 13 Suppl 4:A37*

The relation between duration of zidovudine (ZDV) use and limb fat content is dependent on whether used in combination with a boosted protease inhibitor (PI) or with a non-nucleoside reverse transcriptase inhibitor (NNRTI)

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**Objectives:** Recent results from a randomized trial in treatment-naive patients have suggested dual nucleoside reverse transcriptase inhibitor (NRTI) treatment plus lopinavir/ritonavir plus ritonavir to be associated with less limb fat loss than when used with the non-NRTI (NNRTI) efavirenz. We assessed body fat distribution in relation to duration of zidovudine use and in conjunction with either a protease inhibitor (PI) or NNRTI, using baseline body composition
Results: Of 135 patients, 117 were men, mean (SD) age 45.6 (10.0) years and body mass index was BMI 24.3 (3.2) kg/m². Mean duration of ART was 6.2 (2.6) years and baseline CD4 count was 557 (271) cells/mm³. Plasma HIV-1 RNA <50 copies/ml was recorded in 132 patients (97.8%). At present, 101 patients, 21 of whom had used PIs previously, used an NNRTI-containing regimen (59 efavirenz and 42 nevirapine). At present, 34 patients, 8 of whom had used NNRTIs previously, were on a PI-containing regimen, mostly lopinavir/ritonavir (n=18) or atazanavir/ritonavir (n=9). Limb fat amount was lower with longer zidovudine exposure, 200 g less per additional year of ART (P=0.017). Comparing the third drugs, PI-treated patients had 408 g less limb fat per additional year of ART (P=0.008), compared with 96 g less per year in those on NNRTI (P=0.266). In those on NNRTI, 194 g (P=0.154) and 28 g (P=0.844) less limb fat per year was seen for efavirenz and nevirapine, respectively. A sensitivity analysis (PI n=26 and NNRTI n=80) limited to patients who consistently had either used PI, efavirenz or nevirapine found similar results (540, 108, and 83 g less limb fat per additional year of ART, respectively) with a significant difference between PI and NNRTI as a class (P=0.021). Subcutaneous adipose tissue was also significantly related to ART exposure (P=0.007) and most pronounced in PI-treated patients (12.2 cm² less per year of ART compared with -2.2 cm² in NNRTI-treated). A trend towards more (+12.2 cm², P=0.060) visceral adipose tissue per year of ART was seen in PI-treated patients (sensitivity analysis +13.6 cm², P=0.030) but not in NNRTI-treated patients (+1.5 cm², P=0.640).

Conclusions: Longer duration of zidovudine exposure increases the likelihood of subcutaneous fat loss and possibly visceral adipose tissue gain. This association is most pronounced when combined with a PI and less with either efavirenz or nevirapine.

Background: Cardiovascular disease (CVD) is an important non-AIDS-related outcome in HIV-infected persons. Traditional cardiovascular risk factors may underestimate risk in antiretroviral therapy (ART)-treated individuals. Eicosanoids are arachidonic acid metabolites produced from membrane phospholipids by cyclo-oxygenase-dependent and -independent pathways. Because these products are mediators and markers of oxidant stress, inflammation and endothelial function, they are attractive as potential cardiovascular biomarkers, but studies are limited. One eicosanoid, urinary F2-isoprostane-metabolite (IsoP-M), correlated with the number of traditional CVD risk factors and angiographic coronary disease in the general population. We previously showed that IsoP-M was lower in HIV-infected patients on protease inhibitor (PI)-containing ART and positively correlated with high sensitivity C-reactive protein (hsCRP), Thromboxane-metabolite (TxB2) and prostacyclin-metabolite (PGI-M) were positively correlated with hsCRP and lipids, with sex-specific differences. We compared urinary eicosanoid metabolites and body fat by dual energy X-ray absorptiometry (DEXA) in these HIV-infected, ART-treated subjects.

Methods: Data are from a cross-sectional analysis of a prospective clinic-based cohort of HIV-infected adults with stable ART (including two or more nucleoside reverse transcriptase inhibitors [NRTIs]), HIV-1 RNA <10,000 copies/ml, no known CVD or diabetes and no current aspirin or tobacco use. Urine IsoP-M, TxB2, PGI-M and prostaglandin E-metabolite (PGE-M) were measured by mass spectrometry/gas chromatography. Anthropometric data included body mass index (BMI), waist-to-hip ratio, and DEXA-determined regional body fat content. Univariate analyses included Spearman correlation and Wilcoxon rank-sum test.

Results: Twenty-six subjects (19 men and 7 women) met inclusion criteria with DEXA and eicosanoid data available. Median age was 46 years, 15 (57%) were of non-white race, and 11 (42%) were on PI-containing ART. Median CD4 count and HIV-1 RNA were 592 cells/mm³ and <50 copies/ml, respectively. Median serum lipids were...
non-high-density lipoprotein (HDL) cholesterol 131 mg/dl, HDL cholesterol 47 mg/dl and triglycerides 170 mg/dl. Median (interquartile range [IQR]) hsCRP was 3.6 (1.1–7.8) mg/dl, indicating high CVD risk, and median (IQR) Framingham risk score was 3 (2–5) indicating low CVD risk. Median (IQR) BMI and waist-to-hip ratio were 25.5 (23.6–28.1) and 0.89 (0.86–0.93), respectively. IsoP-M correlated positively with absolute (Spearman’s rho 0.41, \( P=0.04 \)) and percent (0.47, \( P=0.02 \)) trunk fat, and percent body fat (0.38, \( P=0.05 \)) by DEXA. These correlations were driven by persons receiving PIs: Spearman’s rho 0.67 (\( P=0.02 \)) for absolute trunk fat, 0.68 (\( P=0.02 \)) for percent trunk fat, 0.61 (\( P=0.05 \)) for absolute body fat and 0.58 (\( P=0.06 \)) for percent total body fat. Other eicosanoids were not statistically associated with anthropometric measures (including limb fat) in this small sample.

**Conclusions:** In this pilot study of non-smoking, non-diabetic ART-treated patients, urine IsoP-M, a marker of systemic oxidant stress associated with CVD risk, correlated with DEXA-derived measures of trunk and total body fat, and these correlations were strongest in persons receiving PI-based ART. Future studies should assess eicosanoids and other measures of lipodystrophy, other metabolic complications and CVD outcomes.

**ABSTRACT P-23**

_Antiviral Therapy_ 13 Suppl 4:A39

**Objective amount of limb fat in HIV-infected subjects with subjective diagnosis of lipodystrophy**

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**Background:** The relationship between the subjective diagnosis of lipodystrophy and the objective amount of limb fat loss in HIV-infected adults is unclear.

**Methods:** We identified published articles through Medline reporting the amount of arm, leg or limb fat measured by dual X-absorptiometry in HIV-infected patients with moderate–severe lipoatrophy and in healthy non-HIV-infected adults. We calculated the relative content of fat in the limbs, arms and legs of lipoatrophic patients with regard to the weighted arithmetic means of those fat values in healthy controls.

**Results:** We found 799 patients from 10 articles, and 73 healthy controls from 2 articles. Limb fat ranged from 2.6 to 4.4 kg in patients and from 7.1 to 7.2 kg in controls. Both patients and controls were almost exclusively men, of white race and between 40 and 50 years old. Weighted arithmetic means of arm, leg and limb fat in HIV-infected patients with clinically evident lipoatrophy were 1.0, 2.1 and 3.1 kg (48%, 41%, and 43% of healthy non-HIV-infected males, respectively).

**Conclusions:** The diagnosis of lipoatrophy was highly coincidental with the amount of limb fat irrespectively of the investigators. HIV-infected males with clinically evident lipoatrophy had more than 50% of their limb fat lost compared with non-HIV-infected healthy males.

**ABSTRACT P-24**

_Antiviral Therapy_ 13 Suppl 4:A39

Resting energy expenditure and substrate utilization in AIDS patients with lipodystrophy syndrome

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**Aim:** AIDS patients with lipodystrophy syndrome (LS) may have increased resting energy expenditure and altered macronutrient metabolism. The objective of this study was to describe substrate utilization and the resting energy expenditure (REE) in AIDS patients with and without LS and in health-control men.

**Methods:** It was a cross-sectional study with 44 male patients, who were divided into three groups: 10 AIDS patients receiving highly active antiretroviral therapy (HAART) and with LS (HIV+LIP+), 22 AIDS patients receiving HAART and without LS (HIV+LIP-) and 12 health-control men (HC). Body composition was evaluated by dual-energy X-ray absorptiometry. REE was measured by indirect calorimetry after 12 h overnight fast and macronutrient utilization was also determined by respiratory quocient. Statistical analyses were performed using ANOVA and Tukey post test.

**Results:** AIDS patients were clinically stable and had similar CD4 cell count, age and body mass index (BMI). The duration of HIV infection and the duration of HAART (Table 1) were similar among the patients. The HIV+LIP+ group showed less total body fat when compared with controls. Leg lipoatrophy was most evident in HIV+LIP+ patients. Although REE was similar among groups, when we adjusted for lean body mass (LBM; ratios of REE per kg LBM), which is known to be the major determinant of energy expenditure, we noticed that this ratio was significantly greater in HIV+LIP+ than the other two groups (HIV+LIP+ 37 ±1.2, HIV+LIP- 34 ±0.79 and HC 32 ±1.2 kcal/kg LBM, \( P=0.02 \)). In addition to higher REE, we also found a significantly higher respiratory quotient.
(RQ) in HIV+LIP+ and HIV+LIP- when compared with HC (HIV+LIP+ 0.90 ±0.03, HIV+LIP- 0.89 ±0.08 and HC 0.82 ±0.08, P=0.001).

Conclusions: Lipodystrophy syndrome could, independently, be a determinant of high energy expenditure in HIV patients. Also HIV patients with or without LS have a higher carbohydrate utilization.

Table 1. Demographic and nutritional data of AIDS patients with lipodystrophy (HIV+LIP+), without lipodystrophy (HIV+LIP-) and health control men (HC; Abstract P-24)

<table>
<thead>
<tr>
<th></th>
<th>HIV+LIP+</th>
<th>HIV+LIP-</th>
<th>HC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46 ±5</td>
<td>43 ±6</td>
<td>45 ±5</td>
<td>0.246</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24 ±3</td>
<td>24±3</td>
<td>26 ±3</td>
<td>0.112</td>
</tr>
<tr>
<td>Duration of HIV infection, months</td>
<td>114 ±27</td>
<td>96 ±64</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of HAART, months</td>
<td>110 ±23</td>
<td>78 ±52</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>CD4 cell count, ×10⁹</td>
<td>574 ±300</td>
<td>445 ±186</td>
<td>0</td>
<td>0.18</td>
</tr>
<tr>
<td>Total body fat mass, %</td>
<td>17 ±5</td>
<td>20 ±6</td>
<td>24 ±4</td>
<td>0.014</td>
</tr>
<tr>
<td>Total leg fat mass, %</td>
<td>10 ±5</td>
<td>17 ±7</td>
<td>22 ±7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Statistically different from HC. †HIV+LIP+ is statistically different from HIV+LIP- and HC. HAART, highly active antiretroviral therapy.

ABSTRACT P-25

Antiviral Therapy 13 Suppl 4:A40

Bone marrow magnetic resonance imaging changes in HIV-infected subjects with lipodystrophy

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Background: We have noted unusual serous-like bone marrow pattern in the legs on magnetic resonance (MR) studies of HIV-infected patients with lipodystrophy, probably related to a decrease in the bone marrow fat. Our aim is to present these imaging findings, to determine correlation with clinical parameters, and to show the evolution of the lesions after switching from thymidine analogues (TA) to tenofovir disoproxil fumarate (TDF).

Methods: Two radiologists in consensus determined three bone marrow patterns (serous-like, less intensity yellow marrow or normal fat marrow) in T1-W SE axial MR images in 28 HIV-infected patients with lipodystrophy syndrome on TA and 13 HIV-negative volunteers. We confirmed a serous-like pattern with T2-W fat-suppressed and T1-W fat-suppressed images without and with gadolinium, including whole-body MR study (T1-W and STIR images) to evaluate the distribution, and whole-body SPECT bone scans with Tc-99m sulfur colloid and skeletal X-ray exam to exclude other pathologies. MR images and clinical evaluation were performed at 6 months to assess changes after switching from TA to TDF.

We correlated patterns with demographic characteristics of the patients, metabolic profile, body composition measurements (fat, lean mass and bone meneral density–dual energy X-ray absorptiometry, visceral and subcutaneous fat-CT image at L4).

Results: Four patients (14.28%) presented foci of serous-like pattern, four (14.28%) a focal or diffuse less intensity, and the rest of patients (71.42%) and volunteers a normal bone marrow fat-signal. Serous-like lesions were in tibias, fibulas and distal femurs, and scattered in ankles (one case) and humerus (two cases). Non-malignancy, infection, haematological disorders or bone pain was observed. Serous-like group at the baseline showed lower fat and higher lean mass than no serous-like group, although only peripheral and total fat were significantly lower statistically (P<0.05). There were no significant differences between serous-like and less-intensity, and less-intensity and normal pattern group.

No changes in MR images at 6 months were observed, and the serous-like group showed higher recovery of the peripheral fat than the no serous-like group, although not significantly (P>0.005).

Conclusions: HIV-infected patients with lipodystrophy syndrome may present no malignant bone marrow MR changes in the peripheral skeletal, especially legs, in correlation with the peripheral lipatrophy. These findings may be related to a decrease in the fat bone marrow component, which probably needs more time to recover after switching from TA to TDF. It is important to be aware of these findings to avoid diagnostic mistakes.
**ABSTRACT P-26**

*Antiviral Therapy 13 Suppl 4:A41*

Metabolic and anthropometric characteristics of TVD, CBV or KVX associated with nevirapine. Results from the ‘NEVIRAPINE COMPANION’ prospective cohort

G Guaraldi¹, S Zona¹, C Sconiamilio², N Squillace¹, G Orlando¹, C Stentarelli¹ and R Esposito¹

¹Clinic of Infectious Diseases, Department of Medicine and Medical Specialities, University of Modena and Reggio Emilia, Modena, Italy; ²Medical Direction, Boehringer Ingelheim, Milan, Italy

Objectives: To assess anthropometric and metabolic profile of a prospective cohort undergoing stable nevirapine therapy associated with TDF+FTC (TVD), AZT+3TC (CBV) or ABC+3TC (KVX).

Methods: Prospective observational study that included repeated measures of all consecutive HIV-infected patients seen at a metabolic clinic undergoing stable nevirapine therapy for >6 months associated with TVD, CBV or KVX. Inclusion criteria for follow-up analysis were more than two antropometric evaluation with waist circumference (Wcrf) and DXA and more than two metabolic evaluations with fasting Apolipoprotein (Apo)-B/ApoA1 and HOMA-IR. Patients were censored if they changed or stop therapy in the follow-up period. Multilevel model was used to investigate independent predictors of change of antropometric measure (leg fat mass or Wcrf) or predictors of change in metabolic measure (ApoB/ApoA1 or HOMA-IR).

Results: A total of 101 patients were included in the study: 61 TVD arm, 20 CBV arm and 20 KVX arm. Median follow-up time of observation was 118 weeks. One hundred and ninety-one observations were analysed. Four multilevel models were generated with TDV arm as reference and using the following covariates: CBV arm, KVX arm, age, gender, CD4 current, Log₁₀ HIV-VL, ApoB/ApoA1, HOMA-IR and leg fat mass. Significant predictor of leg fat mass (g) decrease was male gender (B=-1.307; 95% confidence interval [CI] -1.903–-1.307; P<0.001). Significant predictors of leg fat mass increase were body mass index (BMI; B=184, 95% CI 126–243; P<0.001) and age (B=38.77, 95% CI 4.87–72.67; P=0.025)

Significant predictors of Wcrf (cm) increase were leg fat mass (×100 g; B=0.40, 95% CI 0.28–0.52; P<0.001) and male gender (B=7.91, 95% CI 3.78–12.04; P<0.001)

Significant predictor of ApoB/ApoA1 (×10) decrease was leg fat mass (×100 g; B=-0.05, 95% CI -0.08--.01; P=0.011). Significant predictor of ApoB/ApoA1 increase was BMI (B=0.20, 95% CI 0.05–0.35; P=0.008)

Significant predictor of HOMA-IR increase was BMI (B=0.19, 95% CI 0.03–0.35; P=0.0017)

Discussion: The change of metabolic and anthropometric variables were not predicted by TVD, CBV or KVX arms associated with nevirapine. We confirmed traditional risk factors for anthropometric and metabolic variables: male gender for both lipoatrophy and central fat accumulation and BMI for lipids and glucose abnormalities. KVX arm, in which was documented a poor metabolic profile at cross-section evaluation, does not display a disadvantage in the evolution of metabolic and anthropometric variables.

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**ABSTRACT P-27**

*Antiviral Therapy 13 Suppl 4:A41*

Different metabolic and anthropometric characteristics of TVD, CBV or KVX associated with nevirapine. Results from the ‘NEVIRAPINE COMPANION’ cross-sectional cohort

G Guaraldi¹, F Adorni², C Sconiamilio¹, S Zona¹, N Squillace¹, G Orlando¹, C Stentarelli¹ and R Esposito¹

¹Clinic of Infectious Diseases, Department of Medicine and Medical Specialties, University of Modena and Reggio Emilia, Modena, Italy; ²CNR Milan, Italy; ³Medical Direction, Boehringer Ingelheim, Milan, Italy

Introduction: To assess metabolic, anthropometric and cardiovascular risk profile of a cohort undergoing stable nevirapine therapy associated with TDF+FTC (TVD), AZT+3TC (CBV) or ABC+3TC (KVX)

Methods: Cross-sectional observational study that included all consecutive HIV-infected patients seen at a metabolic clinic undergoing nevirapine therapy for >6 months associated with TVD, CBV or KVX.

Results: A total of 244 patients were included (characteristics can be found in Table 1). Spearman’s rho did not find any correlation between NVP exposure and the surrogate toxicity endpoints (all P-values were not significant).

Discussion: KVX arm displayed a grater pro-atherogenic risk profile not withstanding lower body mass index in respect to CBV and TVD. This non-randomized cohort cannot discriminate if patients with a higher underlying risk of cardiovascular disease might be initially placed on KVX or if KVX associated with NVP per se had a poorer metabolic profile compared with the TVD and CBV arms. Careful assessment of metabolic parameters should be evaluated in people undergoing the association KVX+NEV even beyond initial 6 months of therapy and appropriated lipid-lowering therapy started if needed.
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>TVD (n=142)</th>
<th>CBV (n=62)</th>
<th>KVX (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>440</td>
<td>445</td>
<td>420</td>
<td>440</td>
<td>0.173</td>
</tr>
<tr>
<td>CDC Group C†</td>
<td>258</td>
<td>254</td>
<td>18</td>
<td>9</td>
<td>0.793</td>
</tr>
<tr>
<td>Nadir CD4, copies/µl*</td>
<td>156</td>
<td>141</td>
<td>166</td>
<td>188</td>
<td>0.457</td>
</tr>
<tr>
<td>NRTI cum exp, months*</td>
<td>119</td>
<td>132</td>
<td>112</td>
<td>126</td>
<td>0.073</td>
</tr>
<tr>
<td>Current NRTI Tx, months*</td>
<td>181</td>
<td>123</td>
<td>249</td>
<td>217</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PI cum exp, months*</td>
<td>42</td>
<td>47</td>
<td>36</td>
<td>38</td>
<td>0.100</td>
</tr>
<tr>
<td>NNRTI cum exp, months*</td>
<td>45</td>
<td>40</td>
<td>52</td>
<td>55</td>
<td>0.038</td>
</tr>
<tr>
<td>Current NEV Tx, months*</td>
<td>20</td>
<td>134</td>
<td>249</td>
<td>218</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI</td>
<td>225</td>
<td>225</td>
<td>2,355</td>
<td>2,154</td>
<td>0.020</td>
</tr>
<tr>
<td>Waist, cm*</td>
<td>83</td>
<td>83</td>
<td>87</td>
<td>80</td>
<td>0.009</td>
</tr>
<tr>
<td>Total fat mass, g*</td>
<td>9,905</td>
<td>9,538</td>
<td>11,926</td>
<td>8,656</td>
<td>0.012</td>
</tr>
<tr>
<td>Total lean mass, g*</td>
<td>50,754</td>
<td>51,590</td>
<td>50,754</td>
<td>45,940</td>
<td>0.257</td>
</tr>
<tr>
<td>Fat in legs, %*</td>
<td>914</td>
<td>910</td>
<td>1,201</td>
<td>743</td>
<td>0.080</td>
</tr>
<tr>
<td>Fat in legs(BMI, %)*</td>
<td>40</td>
<td>41</td>
<td>48</td>
<td>35</td>
<td>0.239</td>
</tr>
<tr>
<td>HOMA</td>
<td>279</td>
<td>278</td>
<td>278</td>
<td>282</td>
<td>0.993</td>
</tr>
<tr>
<td>TG, mg/dl*</td>
<td>130</td>
<td>120</td>
<td>133</td>
<td>142</td>
<td>0.200</td>
</tr>
<tr>
<td>TC, mg/dl*</td>
<td>199</td>
<td>194</td>
<td>196</td>
<td>215</td>
<td>0.040</td>
</tr>
<tr>
<td>HDL, mg/dl*</td>
<td>49</td>
<td>49</td>
<td>51</td>
<td>48</td>
<td>0.120</td>
</tr>
<tr>
<td>LDL, mg/dl*</td>
<td>123</td>
<td>122</td>
<td>113</td>
<td>137</td>
<td>0.028</td>
</tr>
<tr>
<td>ApoB, mg/dl*</td>
<td>102</td>
<td>99</td>
<td>945</td>
<td>1,155</td>
<td>0.009</td>
</tr>
<tr>
<td>ApoA1, mg/dl*</td>
<td>151</td>
<td>146</td>
<td>1,635</td>
<td>157</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Median or †percentage. Apo, apolipoprotein; BMI, body mass index; CDC, Centers of Disease Control and Prevention; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TC, total cholesterol; TG, triglyceride
ABSTRACT P-28
Antiviral Therapy 13 Suppl 4:A43

Friedewald’s equation underestimates LDL elevations for patients with high triglyceride levels in the ARTEMIS and TITAN trials

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Background: Low density lipoprotein (LDL) is normally calculated indirectly, using Friedewald’s equation (LDL=total cholesterol (TCHOL) - high density lipoprotein - triglyceride (TG)/5). This equation is not valid if TG levels are >4.52 mmol/l (400 mg/dl). Therefore, if drugs raise TG levels, use of the Friedewald equation may lead to underestimation of LDL elevations. The ARTEMIS trial (TMC114-C211) evaluated lopinavir (LPV)/ritonavir (r) versus darunavir (DRV)/ritonavir 800/100 mg once daily in treatment-naive patients, evaluated lopinavir (LPV)/ritonavir (r) versus darunavir (DRV)/ritonavir 800/100 mg once daily in treatment-naive patients, in combination with tenofovir/emtricitabine. The TITAN trial (TMC114-C214) evaluated LPV/r versus DRV/r 600/100 mg twice daily in treatment-experienced patients with HIV type-1 RNA >1,000 copies/ml, in combination with optimized NRTI/non-NRTI combinations.

Methods: In both trials, fasting lipid data were collected at baseline and through 48–96 weeks of randomized treatment. LDL elevations were analysed by mean levels or setting TG at 4.52 mmol/l for those with available LDL levels. In ARTEMIS, the DRV/r arm led to significantly lower mean TG levels at week 48 (1.6 mmol/l) versus LPV/r (2.2 mmol/l). In the TITAN trial, the DRV/r arm also led to significantly lower mean TG levels at week 48 (2.5 mmol/l) versus LPV/r (3.2 mmol/l). Use of Friedewald’s equation in the LPV/r arm of TITAN identified 36% fewer Grade 2–3 elevations of LDL in the LPV/r arm and 59% fewer Grade 3 LDL elevations, compared with Method 2. In both the TITAN and ARTEMIS trials, the Friedewald equation missed fewer LDL elevations in the DRV/r arm, which raised TG less.

Conclusions: The Friedewald equation underestimated the incidence of calculated LDL elevations in the LPV arms of the ARTEMIS and TITAN trials. Setting a TG value of 4.52 mmol/l (400 mg/dl) for samples with high TG levels detects more elevations of calculated LDL.

ABSTRACT P-29
Antiviral Therapy 13 Suppl 4:A43

Metabolic changes and cardiovascular risk after switching from lopinavir/r to atazanavir/r: metATAZIP, a substudy of the ATAZIP study

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Background: Metabolic disturbances are observed with several antiretroviral therapies, raising concern of a deleterious effect on cardiovascular (CV) risk. The objective of this study was to evaluate changes in metabolic profile and in CV risk in patients who switched from lopinavir/r (LPV/r) to atazanavir/r (ATV/r). ATAZIP is a multicentre trial in which patients receiving LPV/r-containing regimens with sustained viral suppression were randomized to continue or switch to ATV/r for 48 weeks. In a metabolic substudy performed in five centres, total cholesterol (TC), triglycerides (TG), very low density lipoprotein cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol, LDL subfractions, apolipoprotein A-I (apo A-1), apolipoprotein B (apo B), glucose, insulin, C-peptide and HOMA index were evaluated in fasting state at baseline (BL) and at 12 months (12 m). CV risk was estimated by the Framingham equation. Independent t-test or Mann–Whitney U test were used for comparisons between arms, t-test was used for repeated measurements and Wilcoxon signed-rank test was used for comparisons between follow-up and BL.

Results: In total 122 patients (61 LPV/r and 61 ATV/r) were enrolled in this substudy. At BL, both groups were comparable, except with regard to AIDS (LPV/r 60.7 versus 39.3%, P=0.019) and TC (LPV/r 5.56 versus 5.06 mmol/l, P=0.07). More patients in the LPV/r arm received lipid-lowering agents during the study period (24.6 versus 19.1%, P=0.04).
6.6%, \( P=0.006 \)). After 12 months, TC decreased in both arms. ATV/r patients presented a significant reduction in TG (versus LPV/r, \( P=0.028 \)) and in TC/HDL ratio (12 months versus BL, \( P=0.079 \)). Although LDL decreased in the LPV/r arm, LDL size also decreased in this group (\( P=0.012 \)) and the proportion of patients with the more atherogenic LDL B phenotype increased (\( P=0.022 \)); these unfavourable changes were not observed in ATV/r patients. Regarding glucose metabolism, a significant increase in C-peptide with no changes in insulin or HOMA index was observed in both arms. Estimated CV risk decreased in the ATV/r arm (median \(-17\%\), \( P=0.014 \)), but remained unchanged in LPV/r (\( P=0.76 \)).

Conclusions: Switching from LPV/r to ATV/r was associated with a favourable lipid profile and a decrease in estimated CV risk.

**ABSTRACT P-30**

*Antiviral Therapy 13 Suppl 4:A44*

**Early improvement of triglycerides and LDL-cholesterol levels in dyslipidaemic HIV-infected patients after switching NRTI backbone to tenofovir plus emtricitabine: the TOTEM randomized trial**

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1Pitié-Salpêtrière Hospital, Paris, France; 2Raymond-Poincaré Hospital, Garches, France; 3Saint-Antoine Hospital, Paris, France; 4Tenon Hospital, Paris, France; 5Hôtel-Dieu CHU, Lyon, France; 6Gilead Sciences France; 7Pierre et Marie Curie University, INSERM U720, Paris, France

**Objectives:** To prevent cardiovascular risk, current guidelines recommend changes in lifestyle for dyslipidaemic patients and modifying antiretroviral regimen before use of lipid-lowering treatments. This study was designed to evaluate the early (week 12) impact of switching two NRTIs of a combined antiretroviral therapy (cART) regimen to tenofovir/emtricitabine on serum triglycerides (TG) and LDL-cholesterol (LDL-C) in dyslipidaemic HIV-infected patients with undetectable plasma viral load (pVL).

**Methods:** TOTEM was an open-label, prospective, randomized multicenter trial conducted over 12 weeks in virologically suppressed (pVL<400 copies/ml) HIV-infected patients with fasting TG 2.3–11.4 mmol/l and/or LDL-C>4.1mmol/l, randomized (1:1) to tenofovir/emtricitabine group with the third agent unchanged or to a control group (baseline regimen maintenance). Primary endpoints were between-group comparisons of the changes in serum LDL-C and TG between baseline and week 12. All lipid parameters were measured in a lipid-dedicated central laboratory.

**Results:** Between September 2005 and April 2007, 91 patients were enrolled. Baseline characteristics (median [IQR]) were: age 48 years, TG 2.4 mmol/l (1.9–3.8), LDL-C 4.0 mmol/l (3.4–4.7), cART duration 8 years (2–11). NRTIs were zidovudine (59%), abacavir (19%) and stavudine (8%). The third agent was a non-NRTI in 41% of patients (efavirenz, \( n=18 \)) or a protease inhibitor (PI) in 59% (fosamprenavir, \( n=16 \); lopinavir, \( n=15 \); atazanavir, \( n=13 \); others, \( n=10 \)) including a boosted PI for 53%; 26% of patients were on lipid-lowering treatment. At week 12, the proportion of patients with LDL-C>4.1 mmol/l decreased from 48% at baseline to 26% in the tenofovir/emtricitabine group; no change was observed in the control group (49%). No virological failure was reported through week 12 (see Table 1).

**Conclusions:** In dyslipidaemic HIV-1-infected controlled patients, switching the NRTI backbone to tenofovir/emtricitabine significantly improved TG and LDL-C levels over 12 weeks, with a significant improvement noted as early as 4 weeks and more patients normalizing LDL-C by week 12.

<table>
<thead>
<tr>
<th>Tenofovir/emtricitabine group (n=46)</th>
<th>Control group (n=45)</th>
<th>Difference of change between groups (95% CI)*</th>
<th>( P)-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TG change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4, mmol/l</td>
<td>-0.6</td>
<td>0.0</td>
<td>(-0.57 (−1.26–-0.23))</td>
</tr>
<tr>
<td>Week 12, mmol/l (%)</td>
<td>-0.5 (-25%)</td>
<td>-0.1 (-6%)</td>
<td>(-0.42 (−0.86–-0.03))</td>
</tr>
<tr>
<td><strong>LDL-C change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4, mmol/l</td>
<td>-0.3</td>
<td>0.2</td>
<td>(-0.36 (−0.77–-0.17))</td>
</tr>
<tr>
<td>Week 12, mmol/l (%)</td>
<td>-0.4 (-9%)</td>
<td>-0.1 (-1%)</td>
<td>(-0.36 (−0.67–-0.03))</td>
</tr>
</tbody>
</table>

*Hodges–Lehmann estimate of the difference between groups and its 95% confidence interval (CI; Moses). †Mann–Whitney rank sum test for comparison between treatment groups. LDL-C, low density lipoprotein cholesterol; TG, triglycerides.
ABSTRACT P-31

Antiviral Therapy 13 Suppl 4:A45

HIV infection significantly reduces lipoprotein lipase which remains low after 6 months of antiretroviral therapy

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Objectives: Fractional clearance rate of apoliporotein B100-containing lipoproteins is reduced in HIV infection before and after antiretroviral (ARV) therapy. We compared lipoprotein lipase (LPL) activity and gene expression in HIV-positive subjects before and 6 months after ARV therapy with HIV-negative controls.

Methods: Total fasting blood post-heparin and hepatic lipase activity, adiponectin, leptin, insulin, glucose and lipid measurements were made in 32 HIV-infected and 15 HIV-negative controls. LPL was estimated by subtracting hepatic lipase from total lipase. Adiponectin, LPL, hormone sensitive lipase, fatty acid synthase and fatty acid binding protein gene expression were measured from iliac crest subcutaneous fat biopsies. Patients were tested before and 6 months after randomization to zidovudine (AZT)/lamivudine (n=15) or tenofovir (TDF)/emtricitabine (n=17) with efavirenz.

Results: There were no differences in gender, ethnicity, baseline body mass index (BMI), regional fat distribution (whole body DEXA) and visceral (VAT) and subcutaneous (SAT) fat measured by abdominal computer tomography scans between controls and patients. Trunk fat/BMI ratio, VAT and VAT/SAT ratio significantly increased after 6 months of ARV therapy (P<0.01). There were no differences between groups in serum non-esterified fatty acids, HOMA, leptin levels or adiponectin genes. Other selected results are shown in Table 1.

Conclusions: Post-heparin LPL activity is reduced in HIV and does not return to control levels after 6 months of ARV therapy. Regimens containing AZT are associated with a greater increase in LPL, LPL gene expression and plasma adiponectin than TDF.

Table 1. (Abstract P-31)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HIV (naive)</th>
<th>HIV (AZT 6 months)</th>
<th>HIV (TDF 6 months)</th>
<th>P-value (all HIV 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin, µg/ml</td>
<td>8.2 [4.9]</td>
<td>10.3 [4.1]</td>
<td>13.3 [6.8]</td>
<td>9.4 [3.3]</td>
<td>*0.04, *0.01</td>
</tr>
<tr>
<td>LPL, nmol/ml/h</td>
<td>528 [151]</td>
<td>297 [107]; 382 [212];</td>
<td>341 [167];</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*P&lt;0.0001</td>
<td>*P&lt;0.05, *P&lt;0.05;</td>
<td>*P&lt;0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPL, mRNA</td>
<td>173 [106]</td>
<td>188 [97]</td>
<td>386 [180];</td>
<td>293 [190];</td>
<td>*0.004, *0.007</td>
</tr>
<tr>
<td></td>
<td>*P&lt;0.05</td>
<td>*P&lt;0.05</td>
<td>*P&lt;0.05</td>
<td>*P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>HSL, mRNA</td>
<td>0.38 [0.29]</td>
<td>0.38 [0.29]</td>
<td>1.2 [1.5];</td>
<td>1.3 [1.6];</td>
<td>*0.02</td>
</tr>
<tr>
<td></td>
<td>*P&lt;0.05</td>
<td>*P&lt;0.05</td>
<td>*P&lt;0.02</td>
<td>*P&lt;0.015</td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td>66 [43]</td>
<td>139 [124]</td>
<td>321 [315];</td>
<td>220 [180];</td>
<td>*0.0001</td>
</tr>
<tr>
<td></td>
<td>*P&lt;0.0001</td>
<td>*P&lt;0.016</td>
<td>*P&lt;0.002, NS</td>
<td>*P&lt;0.002, NS</td>
<td></td>
</tr>
<tr>
<td>FABP4</td>
<td>468 [231]</td>
<td>562 [384]</td>
<td>143 [561];</td>
<td>986 [668];</td>
<td>*0.001</td>
</tr>
<tr>
<td></td>
<td>*P&lt;0.001</td>
<td>*P&lt;0.004</td>
<td>*P&lt;0.001, NS</td>
<td>*P&lt;0.001, NS</td>
<td></td>
</tr>
</tbody>
</table>

Measurements are means (±sd). RNA expressions are in arbitrary units. *Control versus HIV (naive). †Control versus HIV (6 months therapy). ‡HIV (naive) versus HIV (6 months therapy). AZT, zidovudine; FABP4, fatty acid binding protein; FAS, fatty acid synthase; HSL, hormone sensitive lipase; LPL, lipoprotein lipase, TDF, tenofovir.
ABSTRACT P-32

*Antiviral Therapy* 13 Suppl 4:A46

**Saquinavir versus atazanavir once daily, each boosted with 100 mg ritonavir and combined with tenofovir/emtricitabine, result in comparable lipid changes after 24 weeks in treatment-naive HIV-infected patients**

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1 Academic Medical Center, Amsterdam, the Netherlands; 2 IATEC, Amsterdam, the Netherlands; 3 Chelsea and Westminster Hospital, London, UK; 4 CHU Hôpital Dieu, Nantes, France; 5 University of Miami School of Medicine, Miami, FL, USA; 6 Hôpital Pitié-Salpêtrière, Paris, France; 7 Royal Sussex County Hospital, Brighton, UK; 8 Hôpital Tenon, Paris, France; 9 Cedars-Sinai Medical Centre, Los Angeles, CA, USA; 10 Gemeinschaftspraxis Mauss, Düsseldorf, Germany; 11 Orlando Immunology Center, Orlando, FL, USA; 12 St MC Jan van Goyen, Amsterdam, the Netherlands; 13 Central West Clinical Research, St Louis, MO, USA

**Objectives:** Atazanavir (ATV) and saquinavir (SQV) have minor, and ritonavir pronounced but dose-dependent, effects on lipids. We compared changes in lipids between SQV and ATV, each used once daily with 100 mg ritonavir (r).

**Methods:** BASIC is an investigator-initiated randomized multicentre multinational trial comparing SQV/r 2,000/100 mg and ATV/r 300/100 mg each once daily with 100 mg ritonavir and combined with tenofovir, lamivudine and either fosamprenavir/r or lopinavir/r. Participants were included if their body mass index was <28, their waist-to-hip ratio was <0.97, fasting glucose, lipids and triglycerides were normal and there was no evidence of any metabolic disturbance. Insulin sensitivity (by hyperinsulinaemic euglycaemic clamp) and lipoprotein subfractions (by nuclear magnetic resonance spectroscopy) were assessed at baseline and at 2 weeks after commencing treatment. A pharmacokinetic profile was performed at 2 weeks.

**Results:** There was no significant difference between the two groups in their effect on the lipoprotein profile. Within the low density lipoprotein (LDL) particles there were significant increases in the small (109.28 nmol/l, P=0.044) and medium-small (28.36 nmol/l, P=0.015) particles and a decrease in large LDL (-18.61 nmol/l, P=0.443) particles. Amongst the high density lipoprotein (HDL) particles there was an increase in the medium-sized HDL particles whilst large and small HDL were significantly reduced. There was no significant correlation between these changes and baseline CD4+ T-cell count, protease inhibitor drug levels or changes in viral load and insulin sensitivity (see Table 1).

**Conclusions:** When combined with tenofovir/emtricitabine, SQV/r 2,000/100 mg once daily and ATV/r 300/100 mg once daily have similar modest effects on lipids over 24W, with comparable virological and immunologic efficacy in treatment-naive patients.

ABSTRACT P-33

*Antiviral Therapy* 13 Suppl 4:A46

**A randomized comparative study of the impact of tenofovir, lamivudine plus lopinavir/r or fosamprenavir/r twice daily on lipoprotein subfractions in persons initiating antiretroviral therapy**

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Chelsea & Westminster Hospital, London, UK

**Objectives:** This study investigated the impact of commencing a protease inhibitor-based regimen on lipoprotein subfractions in HIV-1-positive patients.

**Methods:** In total, 27 HIV-1-positive, antiretroviral-naive male patients were enrolled and randomized 1:1 to receive tenofovir, lamivudine and either fosamprenavir/ritonavir (r) or lopinavir/r. Participants were included if their body mass index was <28, their waist-to-hip ratio was <0.97, fasting glucose, lipids and triglycerides were normal and there was no evidence of any metabolic disturbance. Insulin sensitivity (by hyperinsulinaemic euglycaemic clamp) and lipoprotein subfractions (by nuclear magnetic resonance spectroscopy) were assessed at baseline and at 2 weeks after commencing treatment. A pharmacokinetic profile was performed at 2 weeks.

**Results:** There was no significant difference between the two groups in their effect on the lipoprotein profile. Within the low density lipoprotein (LDL) particles there were significant increases in the small (109.28 nmol/l, P=0.044) and medium-small (28.36 nmol/l, P=0.015) particles and a decrease in large LDL (-18.61 nmol/l, P=0.443) particles. Amongst the high density lipoprotein (HDL) particles there was an increase in the medium-sized HDL particles whilst large and small HDL were significantly reduced. There was no significant correlation between these changes and baseline CD4+ T-cell count, protease inhibitor drug levels or changes in viral load and insulin sensitivity (see Table 1).

**Conclusions:** Commencing tenofovir, lamivudine plus either lopinavir/r twice daily or fosamprenavir/r twice daily in HIV-1 patients is associated with a shift towards an ‘atherogenic lipoprotein pattern’ typified by an increase in small LDL particles, a decrease in large LDL particles and accompanied by an increase in triglycerides and a decrease in HDL cholesterol. This was not associated with changes in insulin sensitivity.
**Table 1. (Abstract P-32)**

<table>
<thead>
<tr>
<th></th>
<th>SQV (mean ±sd)</th>
<th>ATV (mean ±sd)</th>
<th>Between-arm difference in mean percent (95% CI) lipid change from baseline to W24</th>
<th>P-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4^+ T-cell count, cells/mm^3</td>
<td>240 ±89</td>
<td>234 ±105</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HIV-1 RNA,</td>
<td>4.7 ±0.7</td>
<td>4.7 ±0.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>log_{10} copies/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>3.99 ±0.93</td>
<td>3.94 ±0.95</td>
<td>-5.1 (-14.1–3.9, 0.27</td>
<td></td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>0.97 ±0.26</td>
<td>0.95 ±0.26</td>
<td>-3.4 (-15.4–8.6, 0.57</td>
<td></td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>4.32 ±1.27</td>
<td>4.35 ±1.21</td>
<td>-2.1 (-11.3–7.1, 0.66</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>2.47 ±0.78</td>
<td>2.35 ±0.84</td>
<td>1.3 (-15.2–17.8, 0.88</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>1.30 ±0.15</td>
<td>1.47 ±0.96</td>
<td>-14.4 (-56.1–27.3, 0.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.20 ±0.24</td>
<td>1.17 ±0.21</td>
<td>-1.5 (-9.1–5.9, 0.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.86 ±0.21</td>
<td>0.86 ±0.21</td>
<td>-4.7 (-17.8–8.3, 0.48</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 change within arm. ATV, atazanavir; CI, confidence interval; HDL, high density lipoprotein cholesterol; HIV-1, HIV type-1; LDL, low density lipoprotein cholesterol; NA, not available; SQV saquinavir; TC, total cholesterol; TG, triglycerides; W, weeks.

**Table 1. (Abstract P-33)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline mean [±sd]</th>
<th>Mean (95% CI) change at 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VLDL/chylomicron</td>
<td>51.64 (17.51)</td>
<td>13.70 (6.79–20.61)</td>
</tr>
<tr>
<td>particles, nmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total LDL particles, nmol/l</td>
<td>895.77 (240.92)</td>
<td>95.85 (10.43–181.28)</td>
</tr>
<tr>
<td>Total HDL particles, μmol/l</td>
<td>24,948 (4.69)</td>
<td>-0.63 (-2.03–0.76)</td>
</tr>
<tr>
<td>Total triglyceride, mg/dl</td>
<td>75.44 (25.83)</td>
<td>22.77 (13.73–31.82)</td>
</tr>
<tr>
<td>Total HDL cholesterol, mg/dl</td>
<td>35.83 (9.68)</td>
<td>-1.50 (-2.03–0.43)</td>
</tr>
</tbody>
</table>

n=27. CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

**ABSTRACT P-34**

*Antiviral Therapy 13 Suppl 4:A47*

**Effect of specific antiretroviral therapy (ART) drugs on lipid changes amongst HIV-infected children in two clinics in London**

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**Background:** Much research has investigated the impact of specific antiretrovirals on cardiovascular disease (CVD) risk and associated surrogate markers in HIV-infected adults. However, this association is less well defined in children. We investigated the association between total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and triglycerides (TG) with specific antiretrovirals in children attending two large paediatric HIV clinics.

**Methods:** All children from St George’s and Great Ormond Street Hospitals, London, with routine lipid measurements from 1995–2007 were included. Additional demographic, laboratory and ART data were obtained from the Collaborative HIV Paediatric Study (CHIPS). The most commonly prescribed non-NRTIs and protease inhibitors (nevirapine [NVP], efavirenz [EFV], nelfinavir [NFV] and lopinavir [LPV]) were considered. Mixed effects models, including all measurements for each child, were used. Analyses were adjusted for gender, ethnicity (fixed), age, calendar year, body mass index and CD4^+ T-cell percent (time-updated). All lipid measurements are in mM/L.

**Results:** In total, 449 children (75% Black African, 50% female) were included with a median of 4 years follow-up. At first lipid measurement, median age was 7 years and 53% were currently receiving ART for a median of 2.1 years. Initial exposure to NVP was associated with a 0.28 higher TC (95% confidence interval [CI] 0.18–0.37, P<0.0001), which then declined slightly (but remained increased) with time. Initial EFV exposure was associated with 0.27 (0.18–0.35, P<0.0001) higher TC, although this declined by 0.09 in years 1–2, and by a further 0.13 in years 2–3. In contrast, those receiving NFV had 0.41 (0.28–0.54, P<0.0001) higher TC when initially starting the drug, with a further increase of 0.13 (-0.01–0.27, P=0.08) after exposure for >1 year. Initial LPV exposure was associated with 0.51 higher TC (0.43–0.58, P<0.0001), although this declined by 0.13 (-0.23–0.03, P=0.0009) in year 1–2 before stabilizing. Initial NVP receipt was associated with 0.17 (0.13–0.21, P<0.0001) higher HDL, which continued to increase.
Lipid changes in patients receiving nevirapine (NVP) in combination with tenofovir/emtricitabine: results from the CCIAT trial

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Objectives: Highly effective antiretroviral (ARV) therapy has resulted in improved patient longevity, but many ARV regimens are associated with increases in blood lipid markers, raising concern with the potential for premature atherosclerosis and coronary artery disease. Prior studies in treatment-naive patients using an NVP-based regimen noted an increase in low-density lipoprotein cholesterol (LDL-c) and triglycerides (TGs), although these increases were not as great as those seen with high-density lipoprotein cholesterol (HDL-c). The contribution of the NRTI backbone to this effect was unclear. To address this, we evaluated the effects of a regimen of NVP plus tenofovir/emtricitabine (TDF/FTC) on serum lipids in a subgroup of patients from the Cell Cycle Independent ARV Therapy (CCIAT) trial.

Methods: The CCIAT trial was an open-label, single-arm trial designed to investigate the efficacy and safety of NVP 200 mg twice daily in combination with TDF/FTC 300/200 mg once daily in treatment-naive HIV-positive patients. In total, 39 patients from the CCIAT trial (67% men, 95% African-American) were randomly chosen to participate in the lipid substudy. Total cholesterol (TC), TGs, HDL-c and LDL-c levels were measured at the screening visit (baseline) and at weeks 24, 48, 72 and 96 (study end).

Results: At baseline, mean TC, HDL-c, LDL-c and TGs were 168 mg/dl, 41 mg/dl, 94 mg/dl and 165 mg/dl, respectively. Patients had statistically significant increases from baseline in mean HDL-c levels (19.6 mg/dl, n=27; P<0.0001) and statistically significant decreases in mean TG levels from baseline (-84.4 mg/dl, n=27; P<0.05) at week 96 (see Table 1). The increases in mean HDL-c were statistically significant regardless of baseline level (20–30 mg/dl, P=0.01; 31–40 mg/dl, P=0.0007; >40 mg/dl, P=0.004). For example, 10 patients with HDL-c >40 mg/dl, who reached week 96 experienced a mean increase from 48 to 75 mg/dl. There were no clinically meaningful changes in the LDL-c and TC levels observed in this study.

Conclusions: The combination of NVP plus TDF/FTC resulted in favourable effects on serum lipids, with a significant increase in HDL-c, a significant decrease in TGs and non-significant change in LDL-c and TC. This regimen appears to improve the cardiovascular risk profile of patients taking ARV therapy.

<table>
<thead>
<tr>
<th>Change from baseline in lipid levels, mg/dl</th>
<th>Week 24</th>
<th>Week 48</th>
<th>Week 72</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (sd)</td>
<td>n</td>
<td>Mean (sd)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>39</td>
<td>8.2 (38.3)</td>
<td>37</td>
<td>2.7 (34.2)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>39</td>
<td>-46.7 (99.7)*</td>
<td>37</td>
<td>-70.6 (81.6)*</td>
</tr>
<tr>
<td>HDL-c</td>
<td>39</td>
<td>17.7 (20.8)*</td>
<td>37</td>
<td>16.1 (18.1)*</td>
</tr>
<tr>
<td>LDL-c</td>
<td>36</td>
<td>-2.2 (20.4)</td>
<td>36</td>
<td>1.3 (27.4)</td>
</tr>
</tbody>
</table>

*P<0.05. HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol.
ABSTRACT P-36

Antiviral Therapy 13 Suppl 4:A49

Micronutrient supplementation increases apolipoprotein A1 levels in persons living with HIV

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Objectives: Apolipoprotein A1 (ApoA1), the primary protein moiety of the high density lipoprotein (HDL) particle, has attracted recent attention as a marker of cardiovascular risk and as a pharmacological target in the treatment of atherosclerosis and other inflammatory disorders. In addition, both HDL and ApoA1 have been shown to have anti-HIV properties in vitro; longitudinal studies of patients on highly active antiretroviral therapy (HAART) have shown a direct correlation between serum HDL and maintenance of viral suppression. Thus, ApoA1 may play a role both in the inhibition of HIV replication and maintenance of viral suppression, and in improving lipid profile and cardiac risk. We examined the use of micronutrient supplementation with riboflavin, thiamine and l-carnitine as a means of increasing ApoA1 levels in persons living with HIV.

Methods: As part of an ongoing study of the effects of micronutrient supplementation on lactate metabolism in persons living with HIV, 22 subjects were given thiamine 50 mg once daily, riboflavin 100 mg once daily and l-carnitine 1,000 mg twice daily. Various lipid profile values including serum levels of ApoA1 and HDL cholesterol (HDL-C) were measured before and after 4–6 weeks of supplementation and were compared in treated HIV-infected participants, untreated HIV-infected participants and a group of seronegative control participants.

Results: At baseline, all HIV-infected participants showed lower levels of ApoA1 ($P<0.01$) and HDL-C ($P<0.05$) than control subjects. Treated HIV-infected subjects displayed higher ApoA1 levels than those who were untreated ($P<0.01$); there was no significant difference in HDL-C. After 4–6 weeks of supplementation, all HIV-infected subjects showed a significant increase in serum ApoA1 (0.145 ±0.057 g/l increase on HAART, 0.112 ±0.049 g/l untreated, $P<0.03$). No change was seen in serum HDL-C, low density lipoprotein cholesterol, total cholesterol or triglycerides.

Discussion: As demonstrated in previous studies, HIV infection is associated with decreased serum HDL-C levels, as well as lower levels of ApoA1. Our results suggest that supplementation with specific micronutrients may increase levels of ApoA1 in persons living with HIV. This increase was comparable to levels associated with decreased cardiac risk in population studies. While further research is needed to determine the clinical significance of these changes, the indirect evidence for an antiatherogenic, immunomodulatory and antiviral effects of HDL-C mediated by ApoA1 is intriguing and understudied. Micronutrient supplementation may represent a relatively safe and non-resistance-inducing adjunct to both increase the efficacy and help alleviate the adverse effects of HIV treatment.

ABSTRACT P-37

Antiviral Therapy 13 Suppl 4:A49

Switching HIV-infected, suppressed patients from ABC/3TC to FTC/TDF improves lipids – the SETTLE study

JC Gathe, Jr

Therapeutic Concepts, Houston, TX, USA

Background: Current antiretroviral therapies for HIV infection are associated with metabolic side effects, including lipid abnormalities and insulin resistance. Highly active antiretroviral therapy (HAART) with fewer metabolic side effects may decrease cardiovascular risk. Two prospective, controlled-switch studies have shown improvements in lipids with tenofovir (TDF) over abacavir (ABC; RAVE [UK] and BICOMBO [Spain]), but to date no studies have demonstrated lipids benefits when patients are switched from ABC to TDF.

Methods: SETTLE is a prospective, single arm, open-label, 48-week trial examining impact on fasting lipids of switching from ABC/lamivudine (3TC) fixed-dose combination tablets (Epzicom®; EPZ) to emtricitabine (FTC)/TDF fixed-dose combination tablets (Truvada®). Antiretroviral-experienced patients receiving ABC/3TC with HIV RNA<400 copies/ml and no resistance to TDF/FTC were eligible. Those receiving lipid-lowering agents either prior to ABC/3TC or at enrolment, if not at a stable dose, were excluded. Patients were counselled to maintain consistent dietary and exercise habits throughout study participation. Data are presented as median (range).

Results: In total, 24 patients were enrolled. The majority were male ($n=22$) and African-American ($n=15$), with a median age of 42 years (23–58). Coadministered HAART included fosamprenavir plus ritonavir ($n=20$), lopinavir plus ritonavir ($n=3$) and unboosted fosamprenavir ($n=1$). None received lipid lowering agents prior to or during the study. Three patients discontinued (lost to follow-up) after week 24 but prior to week 48 – none for AE. Median fasting total cholesterol (TC) at baseline was 230 mg/dl (146–317). At week 4, median TC was significantly decreased from baseline (205 mg/dl [103–251], $P<0.001$) to week 12 (206 mg/dl [144–271], $P=0.007$). By week 48, median TC was 220 mg/dl (140–322; $P<0.05$). However, the proportion of patients with TC>240 was reduced from 43% at baseline to 33% at week 48. The ratio of TC to high density lipoprotein was unchanged from baseline through 48 weeks. Triglycerides demonstrated reductions...
from a median of 224 mg/dl (74–605) at baseline to 156 mg/dl (43–321) at week 4 and 150 mg/dl (57–685) at week 12. At week 48, median TG remained lower at 154 mg/dl (64–685, P > 0.05). Similarly, the proportion exceeding NCEP recommendations with TG > 200 mg/dl decreased from 54% at baseline to 29% at week 48. No significant changes were noted in CD4+ T-cell count and 20 of 24 patients (83%) maintained HIV RNA < 400 copies/ml at 48 weeks (ITT M=F). FTC/TDF was well tolerated with no toxicity > grade 2 reported.

**Conclusions:** Switching to FTC/TDF demonstrated significant lipid reductions evident through week 12 and the proportion of patients meeting NCEP guidelines remained improved by week 48. This suggests switching to FTC/TDF therapy may play a role in minimizing metabolic side effects related to HAART. The ongoing SWIFT study is examining patients switching from EPZ to TVD versus continued EPZ. Results from SWIFT should further elucidate potential benefits.
ABSTRACT P-38

Antiviral Therapy 13 Suppl 4:A51

Some protease inhibitors induce human endothelial cell dysfunction and prelamin A accumulation

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Objectives: Clinical studies have underlined the associations between HIV antiretroviral therapy (ART), lipid alterations and the increased risk of cardiovascular disease. Endothelial cell dysfunction has been consistently reported in HIV-infected patients and the contribution of ART in that setting has been questioned. Some HIV protease inhibitors (PI) have been shown to inhibit the protease responsible for the maturation of prelamin A to lamin A, leading to the accumulation of farnesylated prelamin A. This phenotype is associated with premature aging in patients with progeria and related syndromes. The aim of this study was to investigate the effects of some PIs on vascular human endothelial cell function and their ability to induce prelamin A accumulation.

Methods: Human umbilical vein endothelial cells (HUVEC) were treated for 2 weeks with either ritonavir (10 µM) or atazanavir (5 µM) associated with ritonavir (2 µM). Oxidative stress was evaluated by the reduction of the reactive oxygen species (ROS) indicator CM-H2DCFDA. Nitric oxide (NO) production by endothelial cells was measured by the fluorescence of DAF-DM diacetate and the protein expression of the NO synthase, NOS3, on western blot. The protein expression of prelamin A was evaluated by western blot using CD31 (PECAM-1) as an endothelial cell marker and the percentage of dysmorphic nuclei was measured in DAPI-labelled cells.

Results: A 15-day treatment of human endothelial cells with PIs induced impaired NO production by endothelial cells. This was shown by the decreased protein expression of NOS3. Accordingly, NO production was decreased, as indicated, by the decreased fluorescence of the NO indicator, DAF-DM diacetate. PIs also induced an oxidative stress in cultured endothelial cells, as evaluated by the increased fluorescence of the ROS indicator, CM-H2DCFDA. A 15-day treatment with PIs also triggers prelamin dysfunction as indicated by the increased percentage of dysmorphic nuclei and by prelamin A accumulation suggesting a cellular premature senescence phenotype.

Conclusions: Our results show that a chronic incubation of human endothelial cells with ritonavir or the combination atazanavir/ritonavir could alter endothelial cell function by decreasing NO bioavailability and increasing ROS production. These PIs also trigger prelamin accumulation, a phenotype associated with premature senescence. These results indicate that some PIs could have a direct effect on the endothelial cell system, ultimately leading to endothelial dysfunction and premature senescence. These alterations are probably involved in increased cardiovascular risk.

ABSTRACT P-39

Antiviral Therapy 13 Suppl 4:A51

Protease inhibitors lopinavir and indinavir do not induce leukocyte–endothelial cell interactions in the microvasculature

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Aim: Combined antiretroviral therapy is associated with atherosclerosis and cardiovascular complications. As patients receive various drugs simultaneously, it has been difficult to determine the role of each particular antiretroviral group or specific agent in these side effects. Although clinical studies suggested protease inhibitors (PIs) as the agents responsible for these complications, this issue remains unclear. The present study was designed to analyse the acute effects of PIs on one of the first steps in the pathogenesis of atherosclerosis, that is, leukocyte recruitment.

Methods: Leukocyte rolling, adhesion and emigration were monitored in the mesenteric postcapillary venules of anaesthetized rats by using intravitral video microscopy. We compared the effects of the PIs lopinavir and indinavir (boosted with ritonavir) administered orally 5 h before the measurements. Doses were chosen according to the literature in order to generate plasma levels in animals similar to those clinically present in humans. Data were compared using a one-way ANOVA followed by a Newman–Keuls post hoc test. All experiments were performed in groups of n=3 animals.

Results: Acute administration of the PIs lopinavir (53 or 106 mg/kg), boosted with ritonavir (13 or 26 mg/kg, respectively) or indinavir (20 or 40 mg/kg), boosted with
Table 1. (Abstract P-39)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage, mg/kg</th>
<th>Rolling flux, cells/min</th>
<th>Adhesion, cells/100 µm</th>
<th>Emigration, cells/field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>18.9 ± 2.6</td>
<td>1.8 ± 0.3</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>53/13</td>
<td>20.1 ± 2.3</td>
<td>2.6 ± 0.7</td>
<td>4.0 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>106/26</td>
<td>18.9 ± 2.3</td>
<td>2.5 ± 0.6</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>Indinavir/ritonavir</td>
<td>20/20</td>
<td>23.8 ± 4.9</td>
<td>3.3 ± 1.1</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>40/40</td>
<td>20.9 ± 1.2</td>
<td>3.0 ± 1.0</td>
<td>3.8 ± 0.5</td>
</tr>
</tbody>
</table>

rifinavir (20 or 40 mg/kg, respectively) did not cause any effect on leukocyte parameters as shown in Table 1.

Discussion: These studies indicate that acute exposure to lopinavir and indinavir does not induce leukocyte recruitment, and suggest that lopinavir and indinavir are not responsible of precipitating the cardiovascular diseases observed in HIV-infected patients treated with PIs as part of combined antiretroviral therapy.

ABSTRACT P-40

Antiviral Therapy 13 Suppl 4:A52

Longitudinal evaluation of cardiovascular disease-associated biomarkers in relation to abacavir therapy

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Objectives: Data from the D:A:D study indicate that recent use of abacavir, but not stavudine or zidovudine, is associated with increased risk of myocardial infarction (MI). The aim of this study was to evaluate longitudinal biomarkers of cardiovascular relevance in abacavir therapy and test whether risk profiles were higher with abacavir treatment compared with untreated HIV, or with stavudine or zidovudine treatment.

Methods: Samples were obtained retrospectively from the West Australian HIV observational cohort, and there was no MI in the study population. The longitudinal effect of abacavir treatment was considered in three study groups: (1) antiretroviral therapy (ART)-naive patients initiating abacavir but not stavudine or zidovudine (n=15), (2) previously abacavir-naive patients switching from thymidine nucleoside reverse transcriptase inhibitor (tNRTI) therapy (n=13) or (3) ongoing abacavir use in patients switching tNRTI treatment (n=13). D-dimer and Hs-CRP were measured by latex immunosay and latex-enhanced nephelometry, respectively. All other analytes interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-α, monocyte chemotactic protein (MCP)-1, hepcotcyte growth factor (HGF), leptin and adiponectin were determined using the LINCOplex kits (Luminex xMAP Technology). Mixed effects models were used for statistical analyses to accommodate multiple measures per person, with all data log-transformed to satisfy distributional assumptions.

Results: Within 1 year of initiating abacavir from ART-naive baseline, D-dimer levels and CRP were unchanged (P=0.6 and 0.3, respectively), and adiponectin increased (P=0.004). After >1 year from baseline, D-dimer decreased, adiponectin and HGF were unchanged from baseline (P=0.03, 0.9, 0.8, respectively), whereas leptin increased (P=0.003) and IL-8, TNF and MCP-1 were decreased (all P-values <0.03). IL-6 increased marginally from baseline (P=0.05). The initial rise in adiponectin levels as compared with baseline was not observed in samples beyond 1 year post-initiation of abacavir.

Initiating abacavir after switching from thymidine-based regimens was associated with no changes in the above analytes (all P-values >0.4), except that leptin increased (P=0.002) and TNF marginally increased (P=0.04). Continuing abacavir after switching from thymidines was also associated with no changes in analytes (all P-values >0.1).

Conclusions: No significant change in biomarker profile known to be related to cardiovascular risk was detected in association with abacavir use. In fact, all significant changes from baseline appeared beneficial, possibly attributable to either anti-HIV effects or cessation of thymidines.

ABSTRACT P-41

Antiviral Therapy 13 Suppl 4:A52

Factors associated with hyperhomocysteinaemia

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Background: Homocysteine, a sulfur-containing amino acid, is a potential risk factor for cardiovascular disease and other medical conditions. Little data exist regarding levels of homocysteine in HIV-infected patients, a population at high cardiovascular risk.

Method: In a cohort of HIV-infected patients, we measured serum homocysteine with a chemiluminescence
immunoassay (Immulite 2500, normal value: 5–12 μmol/l). We also assessed the possible association of its levels with sociodemographic details, other cardiovascular risk factors, CD4+ T-cell count, HIV RNA and any antiretroviral treatment taken by patients.

**Results:** A total of 125 patients were included: 87 (70%) were male, median (interquartile range [IQR]) age was 42 (37–46) years, 71 (57%) were parenteral drug users and 77 (62%) were coinfected with hepatitis C virus. Median (IQR) of homocysteine levels was 10.4 (8.3–13.2) [μmol/l].

**Conclusions:** Hyperhomocysteinaemia was common among the HIV-infected patients of our cohort. We found an association of higher levels of homocysteine with male gender, lower plasma levels of folic acid (P=0.011) and lower plasma levels of high-density lipoprotein (HDL)-cholesterol (P=0.024). No association was found between homocysteine levels and other sociodemographic characteristics, cardiovascular risk factors, hepatitis C virus coinfection, CD4+ T-cell count, HIV RNA and treatment received by patients.

**Conclusion:** MIF is a noted cardiovascular biomarker. It has been shown to correspond with probable inflammation due to HIV-related viraemia and would be a suitable biomarker for case-control studies in cardiovascular disease in HIV.

**ABSTRACT P-43**

*Antiviral Therapy 13 Suppl 4:A53*

**Effect of pioglitazone on myocardial glucose and palmitate metabolism in HIV-associated metabolic syndrome: a preliminary report**

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**Objective:** To examine the effect of pioglitazone (PIO) on myocardial glucose and fatty acid (FA) metabolism in individuals with the HIV-associated metabolic syndrome (HIV+MS).

**Background:** HIV+MS is associated with peripheral and hepatic insulin resistance, and increased mobilization of FAs (lipolysis). We have found impairments in myocardial glucose and FA utilization in HIV+MS. We are testing whether the insulin sensitizer pioglitazone beneficially alters myocardial glucose and FA utilization, and cardiac contractile function in HIV+MS.

**Methods:** HIV+MS was defined by a modification of the ATP-III criteria. Seven men and one woman with HIV+MS (42 ± 6 years) received PIO (30 mg/day) for 16 weeks. Myocardial perfusion (MBF), oxygen consumption (MVO₂), glucose extraction fraction (GLUEF), glucose utilization (GLUT), glucose utilization/serum insulin (GLUT/INS), FA extraction fraction (FAEF) and FA oxidation (FAO) were quantified pre- and post-PIO using ¹¹C- and ¹³O-tracers and positron emission tomography (PET) imaging. Whole-body insulin sensitivity was determined by fasting HOMA and euglycaemic-hyperinsulinaemic clamp. Cardiac contractile function was measured pre- and post-PIO using 2D, Doppler and tissue Doppler imaging to examine relationships between myocardial function and metabolism.

**Results:** PIO reduced fasting homeostasis model assessment of insulin resistance 19% (P=0.003), improved the ability of insulin to suppress hepatic glucose output 25% (P=0.02), and improved peripheral glucose disposal rate under fasting (42%, P=0.02) and hyperinsulinaemic (56–63 μU/ml) conditions (23%, P=0.001). PIO did not significantly alter fasting serum lipid/lipoprotein profiles; triglycerides slightly increased (16%, P=NS; Table 1).
Diastolic blood pressure tended to increase following PIO (pre: 68 ±9 versus post: 73 ±8 mmHg, P<0.08), but no adverse effects of PIO on cardiac function have been noted. **Conclusions:** Preliminary findings indicate that PIO improves whole-body insulin sensitivity and has a tendency to increase myocardial FA utilization and oxidation, without increasing myocardial glucose utilization rate. This may reflect a predominant PPARα-agonist action of PIO in the heart. It might be metabolically beneficial because baseline myocardial FA utilization rates were lower in HIV+MS than healthy controls. Cardiac contractile function was unchanged after 16 weeks of PIO. The long-term effects and mechanism of action of PIO on myocardial function and substrate utilization requires further study.

**Table 1. (Abstract P-43)**

<table>
<thead>
<tr>
<th></th>
<th>MBF, ml/g/min</th>
<th>MVO₂, j/g/min</th>
<th>GLUEF, %</th>
<th>GLUT, nmoi/g/min</th>
<th>GLUT/INS, nmoi/g/min/mU</th>
<th>FAEF, %</th>
<th>FAO, nmoi/g/min</th>
<th>FAUT, nmoi/g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>0.91 ±0.10</td>
<td>4.9 ±1.3</td>
<td>2.1 ±1.4</td>
<td>100 ±56</td>
<td>18 ±32</td>
<td>38 ±5</td>
<td>89 ±26</td>
<td>171 ±52</td>
</tr>
<tr>
<td>Post</td>
<td>0.92 ±0.13</td>
<td>4.6 ±1.1</td>
<td>2.6 ±0.8</td>
<td>119 ±45</td>
<td>15 ±11</td>
<td>42 ±7</td>
<td>116 ±41</td>
<td>213 ±53</td>
</tr>
<tr>
<td>Delta</td>
<td>0.01</td>
<td>-0.3</td>
<td>0.5</td>
<td>19</td>
<td>-3</td>
<td>4</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>P-value</td>
<td>NS</td>
<td>0.18</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.08</td>
<td>0.06</td>
</tr>
</tbody>
</table>

FAEF, fatty acid extraction fraction; FAO, fatty acid oxidation; GLUEF, glucose extraction fraction; GLUT, glucose utilization; INS, serum insulin; MBF, myocardial perfusion; MVO₂, oxygen consumption.

We measured plasma levels of tumor necrosis factor-α (TNF-α), soluble TNF receptors (sTNFR1, sTNFR2), interleukin-6 (IL-6), high sensitivity C-reactive protein (hsCRP), myeloperoxidase (MPO), as well as levels of three endothelial markers, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and von Willebrand factor (vWF), prior to HAART and 2 years after initiation of HAART. Lipids, chemistries, HIV and antiretroviral history, and concomitant medications/illnesses were recorded for both time points. Pre-existing diabetes, cardiomyopathy or confounding inflammatory conditions were exclusionary. **Results:** Twenty-eight HIV- and CAD-positive individuals and 28 HIV-positive, CAD-negative matched controls were identified. Subjects were 91% male, 61% Caucasian, 61% smokers and had a median (range) age of 44 (25–75) years and BMI of 24 (14–42) kg/m². Demographics, BMI, duration of HIV, PI use, baseline CD4, triglyceride, cholesterol levels and blood pressure were similar between groups (all P>0.2). At the pre-HAART time point, all markers were similar between groups (TNF-α 93.7 versus 116.5 pg/ml, sTNFR1 2,534 versus 2,744 pg/ml, sTNFR2 2,672 versus 2,925 pg/ml, IL-6 7.5 versus 11.0 pg/ml, hsCRP 2.55 versus 7.1 mg/ml, sICAM-1 344 versus 349 ng/ml, sVCAM-1 336 versus 411 ng/ml, vWF 230 versus 306 U/ml and MPO 29,984 versus 33,124 pg/ml [all P>0.2]). After 2 years of HAART, CD4 count increased significantly for both groups (CAD-positive +121 cells/mm³ [P=0.018]; CAD-negative +197 cells/mm³ [P<0.001]), without between-group differences. hsCRP was the only marker where the mean (±sd) change from baseline to 2 years post-HAART approached statistical significance (CAD-positive +27.8 ±61 mg/ml [P=0.054]; CAD-negative +29.2 ±61 mg/ml [P=0.07]; all others P>0.1). The rest of the markers did not change significantly within groups (all P>0.1) or between groups (P>0.3). **Conclusions:** HIV-positive individuals with CAD had similar changes in proinflammatory cytokines and endothelial activation markers after 2 years of HAART when compared with HIV-positive individuals without CAD. Larger studies investigating earlier time points after HAART initiation are needed to confirm these findings.

**ABSTRACT P-44**

**Antiviral Therapy 13 Suppl 4:A54**

Can changes in proinflammatory cytokines and endothelial activation markers after HAART predict subsequent coronary artery disease (CAD)?

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**Background:** HIV-positive patients are at an increased risk of CAD, and inflammation and endothelial dysfunction may play a role. This study investigates whether HIV-positive individuals who developed CAD had a smaller decrease in inflammation and endothelial activation markers after the first 2 years of highly active antiretroviral therapy (HAART) when compared with HIV-positive patients who did not develop CAD.

**Methods:** HAART-treated HIV-positive patients ≥18 years of age with documented CAD (myocardial infarction or surgical/interventional coronary procedure) were matched to HAART-treated HIV-positive patients without CAD by age (±2 years), gender, body mass index (BMI; ±1 kg/m²), protease inhibitor (PI) versus no PI use, smoking status, and duration of HAART (±2 months).

**Results:** Twenty-eight HIV- and CAD-positive individuals and 28 HIV-positive, CAD-negative matched controls were identified. Subjects were 91% male, 61% Caucasian, 61% smokers and had a median (range) age of 44 (25–75) years and BMI of 24 (14–42) kg/m². Demographics, BMI, duration of HIV, PI use, baseline CD4, triglyceride, cholesterol levels and blood pressure were similar between groups (all P>0.2). At the pre-HAART time point, all markers were similar between groups (TNF-α 93.7 versus 116.5 pg/ml, sTNFR1 2,534 versus 2,744 pg/ml, sTNFR2 2,672 versus 2,925 pg/ml, IL-6 7.5 versus 11.0 pg/ml, hsCRP 2.55 versus 7.1 mg/ml, sICAM-1 344 versus 349 ng/ml, sVCAM-1 336 versus 411 ng/ml, vWF 230 versus 306 U/ml and MPO 29,984 versus 33,124 pg/ml [all P>0.2]). After 2 years of HAART, CD4 count increased significantly for both groups (CAD-positive +121 cells/mm³ [P=0.018]; CAD-negative +197 cells/mm³ [P<0.001]), without between-group differences. hsCRP was the only marker where the mean (±sd) change from baseline to 2 years post-HAART approached statistical significance (CAD-positive +27.8 ±61 mg/ml [P=0.054]; CAD-negative +29.2 ±61 mg/ml [P=0.07]; all others P>0.1). The rest of the markers did not change significantly within groups (all P>0.1) or between groups (P>0.3).

**Conclusions:** HIV-positive individuals with CAD had similar changes in proinflammatory cytokines and endothelial activation markers after 2 years of HAART when compared with HIV-positive individuals without CAD. Larger studies investigating earlier time points after HAART initiation are needed to confirm these findings.
ABSTRACT P-45

Antiviral Therapy 13 Suppl 4:A55

Subclinical coronary artery atherosclerosis and endothelial dysfunction are not predictors of erectile dysfunction in HIV-infected males


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Objectives: To evaluate the association between erectile dysfunction (ED) and subclinical coronary artery atherosclerosis to endothelial dysfunction in HIV-infected people.

Methods: An observational retrospective cross-sectional study was performed. Evaluation tools included the International Index of Erectile Function (IIEF-15) to measure ED, multislice computed tomography for coronary artery calcifications (CAC) to measure subclinical atherosclerosis, ultrasound assessment of brachial artery to measure endothelial dysfunction and visual analogue scale (VAS) of the face and body to measure patients’ aesthetic satisfaction.

Multivariable backward stepwise logistic regression was performed including the following variables: CAC, FMD, VAS face, testosterone, smoke habit, alcohol habit, HIV infection duration, log10 viral load, body mass index and diabetes.

Results: A total of 133 consecutive male patients were enrolled: 39 (29.32%) had mild dysfunction, 14 (10.53%) had moderate dysfunction and 26 (19.55%) had severe dysfunction (see Table 1).

In logistic regression analysis, ED was related to VAS face (odds ratio [OR] 0.85; 95% confidence interval [CI] 0.73–0.99) and age (OR 1.73; 95% CI 1.02–2.94).

Conclusions: In HIV-infected people, aesthetic satisfaction of the face and age, but not CAC and FMD, were predictors of ED.

ABSTRACT P-46

Antiviral Therapy 13 Suppl 4:A55

Carotid vessels lesions in experienced HIV-1-infected subjects affected or not by hypertension and/or diabetes mellitus

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Objectives: To describe the carotid vessels lesions by echotomographic criteria in a group of experienced HIV-1-infected individuals that underwent colour Doppler ultrasonography of the epiaortic vessels.

Methods: A retrospective study in which HIV-1-positive individuals were regularly followed at our clinic and evaluated by colour Doppler ultrasonography between November 2005 and October 2007. The epiaortic findings were grouped on echotomographic criteria as follows: type 1 – normal intima-media thickness (IMT ≤1 mm); type 2 – IMT >1 and ≤2 mm; type 3 – presence of fibrous homogeneous plaque (IMT >2 mm); and type 4 – presence of dishomogeneous plaque (irregular or ulcerated surface, presence of calcifications or haemorrhage inside the lesion).

Socio-demographic characteristics, HIV disease, clinical history and laboratory parameters were collected from internal database; the nearest result to the date of the ultrasonographic study was chosen.

Results are reported as median (Q1–Q3) or as frequency (%). Differences among groups were evaluated by Kruskal–Wallis test or χ2 test as appropriate.

Results: A total of 162 individuals were evaluated; overall characteristics were age 50.0 (43.5–55.2) years, 144 (89%) men, HIV-1 infection for 12.6 (9.5–17.5) years, antiretroviral exposure of 10.3 (7.5–12.8) years, CDC C stage 45 (28%), CD4+ 498 (350–713) cells/ml, CD4% 22.7 (16.3–28.1), CD4 nadir 189 (91–304) cells/ml and HIV RNA <50 copies/ml in 114 (74%).

Individuals were distributed as follows: 40 (23.1%) type 1, 69 (42.6%) type 2, 37 (22.8%) type 3 and 16 (9.9%) type 4. Individuals (%) affected or not by hypertension (HP) and/or diabetes mellitus (DM) were not similarly distributed (P<0.0001) in relation to the epiaortic findings (see Table 1).

No differences were detected among the four groups in relation to gender (P=0.084), stage of disease (P=0.575), years of exposure to HIV-1 infection (P=0.960), years of antiretroviral regimen (P=0.826), CD4 nadir (P=0.105), CD4+ cells (P=0.428), CD4% (P=0.474) and HIV-1 RNA (P=0.169). Among metabolic parameters, no differences were detected for triglycerides (P=0.321), total cholesterol...
Age was significantly different among groups (type 1 45.2 [41.8–50.1], type 2 49.7 [43.2–54.3], type 3 53.1 [46.2–59.5] and type 4 55.1 [53.4–62.5], P<0.0001) as well as fasting glucose (type 1 86 [78–92], type 2 90 [84–106], type 3 93 [85–131] and type 4 97 [84–107], P<0.041). Also the use of lipid-lowering drugs was differently distributed (type 1 7 [18%), type 2 19 [28%], type 3 14 [38%] and type 4 9 [56%], P=0.024).

Conclusions: In this study 52% of individuals not affected by diabetes and/or hypertension showed an increased

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Table 1. (Abstract P-46)

<table>
<thead>
<tr>
<th>HP/DM</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>9 (13)</td>
<td>21 (30)</td>
<td>28 (41)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>No</td>
<td>31 (33)</td>
<td>48 (52)</td>
<td>9 (10)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HP, hypertension.

(P=0.084), high-density lipoprotein (P=0.286) and low-density lipoprotein cholesterol (P=0.293).
IMT and 15% had fibrous or dishomogeneous plaques. These findings strengthen usefulness of a screening with ultrasonographic examination of epiarterial vessels in HIV-1-infected individuals, even if free of co-morbidity, especially if they are older or treated with lipid-lowering drugs. In presence of fibrous wall degeneration (IMT>1), a well known indicator of increased cardiovascular risk, periodic follow-up is warranted to evaluate the course of the carotid vessels lesions.

ABSTRACT P-47

Antiviral Therapy 13 Suppl 4:A57

Aortic stiffness determinants in HIV-infected patients

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Aim: HIV-infected patients under active antiretroviral therapy (ART) are at higher risk of cardiovascular disease because of metabolic complications, such as lipodystrophy syndrome (LD), insulin resistance, and dyslipidaemia. Whether the LD and ART, particularly protease inhibitors (PIs), have an impact on the vasculature remains debated. We investigated the impact of LD and ART on aortic stiffness, a surrogate marker of cardiovascular events in this specific population.

Methods: Aortic stiffness was evaluated using carotid-femoral pulse wave velocity (PWV) by the SphygmoCor® technology in 175 consecutive HIV-infected outpatients (mean age 48.2 ±8.7 years, 86% of men, 38% smokers, 31% hypertensive, 24% had a metabolic syndrome [NCEP-ATPIII] and 4.6% diabetics).

Results: In the entire cohort, the mean duration of HIV infection was 12.3 ±6.5 years, and 86% of the cohort was treated with ART. Seventy-nine patients (45%) were LD-positive (LD+) and 77 patients (44%) were under PIs. Thirty-nine percent were under the combination of lopinavir/ritonavir and 41% under atazanavir/ritonavir. LD+ patients were thinner (23.3 ±3.1 versus 24.7 ±3.4 kg/m², P=0.004), had lower high-density lipoprotein cholesterol (149.8 ±85.9 versus 129.3 ±36.2 mg/dl, P=0.04), triglyceridaemia (241 ±167 versus 189 ±134, P=0.02), total cholesterol (231 ±64 versus 210 ±45 mg/dl, P=0.01), longer duration of HIV infection (14.1 ±6 versus 10.8 ±6.6 years, P=0.007), lower nadir of CD4 cell count (174 ±149 versus 319 ±212/mm³, P<0.0001) and displayed lipodystrophy syndrome more frequently (61% versus 32%, P<0.0001) compared with patients without PIs. However, aortic stiffness was similar in patients with or without LD (9.7 ±1.9 versus 9.8 ±2.5 ms¹, P=0.8) and in patients with or without PIs (9.8 ±2.6 versus 9.78 ±1.9 ms¹, P=0.7). In univariate analysis, aortic stiffness was associated with age, waist to hip ratio, hypertension and systolic, diastolic and mean arterial pulse pressures, but not the presence of LD or PIs. Multiple linear regression analysis showed an association between aortic stiffness, age and mean arterial pressure.

Conclusions: Our study showed that in this cohort of HIV-infected patients, with a long duration of HIV infection and exposure to the last generation of PIs, aortic stiffness was related to traditional cardiovascular risk factors.

ABSTRACT P-48

Antiviral Therapy 13 Suppl 4:A57

Heart rate and blood pressure before and after knowing blood analyses results

B Roca, MC del Monte, ME Celades, CM Evaristo, JJ Fanco and G Cebrian

Hospital General of Castellon, University of Valencia, Spain

Objectives: Psychological stress can influence blood pressure levels and may limit the usefulness of its measurement in the office, but information in this field is limited. We aim to determine the impact on heart rate and blood pressure of the state of anxiety that HIV-infected patients experience when they are about to be informed of immunological and virological tests and other blood analysis results in clinical visits.

Methods: In a cohort of HIV-infected patients, we measured heart rate and blood pressure of every individual twice, just before we reported them lymphocyte CD4 cell count, HIV-viral load and other blood analysis results, and 5–10 mins afterwards. We compared results of both determinations and searched for factors associated with differences between both determinations, when present.

Results: We included 127 patients, the median of age was 42 years (interquartile range: 37–47), 88 (69%) were male, 16 (13%) had been diagnosed with hypertension previously, 20 (16%) had been diagnosed with diabetes, 25 (20%) had been diagnosed with dyslipidaemia.
and 95 (75%) were smokers and 101 (80%) were taking antiretroviral medication. 

Table 1 shows results before and after patients knew test results (systolic and diastolic blood pressure measured in mmHg). 

An association was found between descent in blood pressure after knowing test results by patients and the following variables: younger age \((P=0.026)\) and female gender \((P=0.016)\).

**Conclusion:** The anxiety that HIV-infected patients experience when they are about to be informed of their blood analyses results frequently provokes an increase in systolic blood pressure.

### ABSTRACT P-49

*Antiviral Therapy* 13 Suppl 4:A58

**Blood pressure (BP): influence of boosted atazanavir and lopinavir**

**E Deig**, P Garcia, I Vidal and E Pedrol

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**Background:** High blood pressure prevalence in HIV-infected patients differ from the studies published and it has been attributed to different reasons; the pathogenic role of antiretrovirals is unclear. The aim was to investigate the changes in BP in two groups of patients who have started highly active antiretroviral therapy (HAART) that included boosted atazanavir (ATV) or lopinavir (LPV). 

**Methods:** This was an observational and prospective study that included patients who were treated during ≥18 months with a HAART schedule with ATV (group 1) or LPV (group 2). We collected data every 3 months and BP measurements were made following international recommendations. 

**Results:** We included 58 patients, 34 in group 1 (mean age 40 years, 70% male, mean weight 71.6 kg, 82% smokers and 17% hypercholesterolaemia) and 24 in group 2 (mean age 42.7 years, 79% male, mean weight 69.2 kg, 71% smokers and 8% hypercholesterolaemia). The mean BP was 138/85 mmHg (group 1) and 127/78 mmHg (group 2). At baseline, 26% of group 1 patients were hypertensive (158/94) versus 8.3% of group 2 (149/87). Table 1 shows the changes from baseline of systolic (SBP) and diastolic (DBP) along the 18 months follow-up. Those hypertensive at baseline in group 1 had SBP and DBP mean decreases of 6 mmHg and in group 2 SBP mean increase of 8 mmHg and DBP mean decrease of 2 mmHg.

**Conclusions:** The findings in our pilot study were similar to other studies, showing a progressive increase in BP, especially SBP. Patients treated with ATV presented a lower non-significant increase of SBD and a non-significant decrease of DBP compared with those treated with LPV.

### Table 1 (Abstract P-48)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median of heart rate, per min</td>
<td>84.5</td>
<td>83</td>
<td>0.025</td>
</tr>
<tr>
<td>Median of SBP, mmHg</td>
<td>130</td>
<td>125</td>
<td>0.000</td>
</tr>
<tr>
<td>Median of DBP, mmHg</td>
<td>77</td>
<td>78</td>
<td>0.744</td>
</tr>
<tr>
<td>Patients with SBP ≥140, n (%)</td>
<td>42 (33)</td>
<td>30 (24)</td>
<td>0.017</td>
</tr>
<tr>
<td>Patients with DBP ≥90, n (%)</td>
<td>19 (15)</td>
<td>21 (16)</td>
<td>0.791</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure.

### Table 1 (Abstract P-49)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>+1</td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>-2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>+0.8</td>
<td>+1.4</td>
<td></td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; SBP, systolic blood pressure.

### ABSTRACT P-50

*Antiviral Therapy* 13 Suppl 4:A58

**Metabolic syndrome in HIV-positive naive patients: the HERMES study**

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1Luigi Sacco Hospital, Milan, Italy; 2Amedeo di Savoia Hospital, Turin, Italy; 3Careggi Hospital, Florence, Italy; 4Padua Hospital, Padua, Italy; 5Perugia Hospital, Perugia, Italy; 6Spallanzani Hospital, Rome, Italy; 7Sassari Hospital, Sassari, Italy; 8SMA Hospital, Florence, Italy; 9Galliera Hospital, Genoa, Italy; 10Busto Arsizio Hospital, Busto Arsizio, Italy

**Background:** It is not clear whether metabolic syndrome (MS) can be induced by the HIV infection *per se*. In previous studies, the hypothesis that the increased MS...
prevalence in HIV patients could be an effect of antiretroviral therapy was advanced.

**Objectives:** To assess prevalence and characteristics of MS in a population of HIV-positive naive patients.

**Methods:** HERMES is a prospective study including all naive patients attending scheduled visits at the hospitals in the CISAI group in 2007. MS was diagnosed using the National Cholesterol Education Program (NCEP) definitions, when a patient fulfilled three or more of the following criteria: waist measurement (>102 cm for men and >88 cm for women), high triglycerides (≥150 mg/dl), low high-density lipoprotein (HDL) cholesterol (<40 mg/dl for men and <50 mg/ml for women), hypertension (≥130/≥85 mmHg) and high blood glucose (≥110 mg/ml).

**Results:** A total of 292 patients were enrolled (mean age 38.9 years [SD ±9.2], 75% of them males). The prevalence of MS was 12.3%. Low levels of HDL cholesterol were the most frequent abnormality (43.8%); the most frequent trio of abnormalities that led to the diagnosis of MS was blood pressure, triglycerides and HDL. The univariate analysis showed that the following variables were associated with MS: age, education, physical activity and severity of HIV disease (Centers of Disease Control and Prevention C stage or HIV RNA viral load ≥100,000 copies and CD4 <100 cells). In the multivariate analysis, trends of increasing age (odds ratio [OR] 1.6, P=0.02) and educational level (OR 0.5, P=0.03) were still associated with MS. An increased risk was also associated with severity of HIV disease (OR 2.8, P=0.03).

**Conclusions:** The high prevalence of the lipid components of MS in our cohort provides support to earlier suggestions that these modifications can be induced by the HIV infection per se. The increased risk of MS observed in patients with AIDS or with a more aggressive infection confirms this data.

**ABSTRACT P-51**

*Antiviral Therapy* 13 Suppl 4:A59

Virological failure and metabolic syndrome in patients with HIV infection

**N Squillace, S Zona, G Guaraldi, C Stentarelli, B Beghetto, G Nardini and G Guaraldi**

Infectious Diseases Clinic, University of Modena and Reggio Emilia, Italy

The objective was to assess the association between HIV RNA viral load (VL) and metabolic syndrome (MS) in antiretroviral therapy (ART)-experienced HIV patients with lipodystrophy (LD).

The cross-sectional observational study included HIV-infected patients receiving ART for at least 2 years. LD and MS were defined according to MACS classification and to NCEP-ATP III criteria, respectively.

A total of 1,348 patients were analysed (850 [63.1%] males, mean age 44.8 years [±7.1]). Obesity was diagnosed in 78 patients (5.8%). MS prevalence was 24.4% and 84.8% of patients had viral load <400 copies/ml. Our study results are in Tables 1 and 2.

Our study highlights that HIV-infected patients experiencing virological failure are more at risk to develop MS. It is necessary to obtain virological suppression to prevent AIDS-related opportunistic infections, but also cardiovascular events and diabetes related to MS.

**ABSTRACT P-52**

*Antiviral Therapy* 13 Suppl 4:A59

Statistical agreement between metabolic syndrome ATP-III, IDF, EGIR and ACE classification in HIV-infected patients and association with body fat redistribution.

**N Squillace, S Zona, G Guaraldi, C Stentarelli, G Orlando, R D’amico, I Mazeu, and R Esposito**

Department of Medicine and Medical Specialties, Infectious Diseases Clinic, University of Modena and Reggio Emilia, Modena, Italy

**Introduction:** The aim of our study is to assess k statistic of Metabolic Syndrome (MS) Adult Treatment Panel III (ATP-III), International Diabetic Federation (IDF), European Group for the study of Insulin Resistance (EGIR) and American College of Endocrinology (ACE) classification in HIV-infected patients and association with body fat redistribution.

**Methods:** This was a cross-sectional observational study that included all consecutive HIV-infected patients seen at the metabolic clinic of the University of Modena and Reggio Emilia, Italy, between January 2006 and January 2008 who had received antiretroviral therapy for at least 2 years.

**Results:** A total of 1,348 patients were analysed, 850 (63.1%) were males and mean age was 44.8 (±7.1). Prevalence of MS was of 24.4% according to ATP-III definition and 29.7%, 43.7% and 7.9%, respectively, according to IDF, EGIR and ACE definitions. Cohen’s k shows a low level of agreement between MS classifications (Table 1).

Body fat changes (LD definition and objective anthropometric variables) were included in univariable and multivariable logistic analysis (see Table 2).

**Conclusions:** Concordance between MS classification is less than ideal. The impact of body mass index and visceral adipose tissue/total adipose tissue is high for any MS definition. Visceral adipose tissue/total adipose tissue appears to be more predictive of MS according to ATP-III definition, but the higher prevalence of lipatrophy in our sample (45%) could have been interfered with this result. Lipodystrophy phenotypes are associated to MS diagnosis especially using EGIR and ACE definitions.
Table 1. (Abstract P-51)

<table>
<thead>
<tr>
<th></th>
<th>MS-positive</th>
<th>MS-negative</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>129.8 ±14.4</td>
<td>117.72 ±14.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>86.88 ±11.01</td>
<td>76.43 ±12.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>107.73 ±34.57</td>
<td>91.74 ±13.84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>35.85 ±8.63</td>
<td>48.84 ±16.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>300.91 ±206.15</td>
<td>179.15 ±159.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA &gt;3.8, n (%)</td>
<td>210 (65.02)</td>
<td>354 (35.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log,(\log_{10})VL</td>
<td>2.17 ±0.94</td>
<td>2.02 ±0.79</td>
<td>0.0048</td>
</tr>
<tr>
<td>CD4 current, median</td>
<td>500 (342–701)</td>
<td>502 (357–681)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Adjustment OR (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR (95% confidence interval)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log10 VL</td>
<td>1.23 (1.01-1.65)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age (per 10-year increment)</td>
<td>1.41 (1.18-1.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>1.05 (1.03-1.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA &gt; 3.8</td>
<td>2.49 (1.89-3.29)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; HOMA, homeostasis model assessment; MS, metabolic syndrome; TAT, total adipose tissue; VAT, visceral adipose tissue; VL, viral load.

Table 2. (Abstract P-51)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR (95% confidence interval)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log10 VL</td>
<td>1.23 (1.01-1.65)</td>
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<tr>
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<tr>
<td>Waist, cm</td>
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</tr>
<tr>
<td>HOMA &gt; 3.8</td>
<td>2.49 (1.89-3.29)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HOMA, homeostasis model assessment; OR, odds ratio; VL, viral load.

Table 1. (Abstract P-52)

<table>
<thead>
<tr>
<th></th>
<th>EGIR</th>
<th>ACE</th>
<th>NCEP ATP-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDF</td>
<td>0.27* [64.61%]</td>
<td>0.07* [56.01%]</td>
<td>0.41* [71.66%]</td>
</tr>
<tr>
<td>EGIR</td>
<td>-</td>
<td>0.21* [74.33%]</td>
<td>0.38* [75.74%]</td>
</tr>
<tr>
<td>ACE</td>
<td>-</td>
<td>-</td>
<td>0.35* [81.68%]</td>
</tr>
</tbody>
</table>

ACE, American College of Endocrinology; EGIR, European Group for the study of Insulin Resistance; IDF, International Diabetic Federation; NCEP ATP-III, National Cholesterol Education Program Adult Treatment Panel III.
ABSTRACT P-53

Antiviral Therapy 13 Suppl 4:A61

A comparison of cardiac function between HIV-infected and HIV-seronegative people with and without metabolic syndrome

WT Cade, L de las Fuentes, K Mondy, DN Reeds, V Davila-Roman, A Waggoner, S Lassa-Claxton, P Herrero, KE Yarasheski and LR Peterson
Washington University School of Medicine, St. Louis, MO, USA

Objective: To determine whether cardiac function is impaired in HIV-infected (HIV+) and HIV-seronegative (HIV-) people with metabolic syndrome (MS). Background: HIV and highly active antiretroviral therapy (HAART) have been associated with cardiovascular disease (CVD). Diastolic dysfunction is common in HIV+ people with MS, but little is known about cardiac function in HIV+ people with and without MS.

Methods: Echocardiographic parameters were compared among four groups (n=180): HIV+/MS+ (43 ± 8 years, 20% women, CD4 543 cell/µl and undetectable HIV RNA), HIV+/MS- (42 ± 7 years, 22% women, CD4 493 cell/µl and undetectable HIV RNA), HIV-/MS+ (42 ± 8 years and 15% women) and HIV-/MS- (44 ± 5 years and 17% women). In HIV, MS was defined as having three or more of the following: hypertriglyceridaemia, low high-density lipoprotein (HDL)-cholesterol, glucose intolerance/insulin resistance, central adiposity or hypertension/blood pressure (BP) medication. In HIV+/MS+, the ATP-III criteria were used to define MS. Resting systolic and diastolic function was measured using 2D, pulsed-wave Doppler, and tissue Doppler imaging echocardiography. Indices of left ventricular (LV) systolic function included ejection fraction (EF) and systolic mitral annular velocity (Eₘ). Indices of LV diastolic function included transmitral early to late diastolic filling velocity ratio (E/A), deceleration time (DT), isovolumic relaxation time (IVRT) and early diastolic mitral annular velocity (Eₘ). Two-way ANOVA was used to compare cardiac function parameters among groups.

Results: Age was similar among groups. MS+ groups had higher systolic BP and serum triglycerides and lower HDL-cholesterol than MS- groups (P<0.003). Diastolic BP and fasting glucose was highest in HIV+/MS+ (P<0.003) compared with all other groups. Body mass index was highest in HIV+/MS+ (P<0.003; Table 1). LVMI was higher in both HIV+ groups compared with HIV-/MS- (P<0.003; Table 1).

When HIV+ groups were combined, EF and SepSm were significantly lower than in HIV-seronegative groups (7.8 ± 1.0 versus 8.4 ± 1.9 cm/s, P<0.03).

Conclusions: Impaired diastolic function was noted in HIV+ and HIV- with MS. Impaired systolic function was noted in HIV+ and HIV- as a group. It appears that metabolic complications are associated with diastolic dysfunction, but HIV infection and/or HAART may strengthen this association. HIV infection is associated with subclinical systolic dysfunction, irrespective of the presence of metabolic complications.

ABSTRACT P-54

Antiviral Therapy 13 Suppl 4:A61

Lipoatrophy and lipohypertrophy are associated with increased predicted 10-year cardiovascular risk

HM Crane1, C Grunfeld2, RD Harrington1 and MM Kitahata2

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Background: Lipoatrophy and lipohypertrophy are associated with metabolic abnormalities, but little is known about their impact on predicted cardiovascular disease risk (CVDR). The few prior studies have typically been
Cardiovascular disease

[Page 62]

Table 1. (Abstract P-53)

<table>
<thead>
<tr>
<th>MS+ (group 1)</th>
<th>MS- (group 2)</th>
<th>All HIV+ (groups 1+2)</th>
<th>MS+ (group 3)</th>
<th>MS- (group 4)</th>
<th>All HIV- (groups 3+4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>54</td>
<td>59</td>
<td>113</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>EF, %</td>
<td>61 ±6</td>
<td>59 ±6*</td>
<td>60 ±6*</td>
<td>62 ±6</td>
<td>63 ±5</td>
</tr>
<tr>
<td>S', cm/s</td>
<td>7.7 ±0.9†</td>
<td>7.9 ±1.1</td>
<td>7.8 ±1.0†</td>
<td>8.4 ±2.5</td>
<td>8.4 ±1.2</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3 ±0.5†</td>
<td>1.5 ±0.5</td>
<td>1.4 ±0.5</td>
<td>1.5 ±0.5</td>
<td>1.6 ±0.5</td>
</tr>
<tr>
<td>DT, cm/s</td>
<td>203 ±35††</td>
<td>200 ±38</td>
<td>202 ±37</td>
<td>202 ±38</td>
<td>184 ±34</td>
</tr>
<tr>
<td>IVRT, cm/s</td>
<td>89 ±13</td>
<td>88 ±16</td>
<td>88 ±15</td>
<td>90 ±19</td>
<td>84 ±13</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>9.8 ±1.8**</td>
<td>10.6 ±2.3**</td>
<td>10.2 ±2.1</td>
<td>10.0 ±2.2</td>
<td>11.6 ±2.0</td>
</tr>
</tbody>
</table>

*P<0.03 versus group 4, †P<0.01 versus all HIV-, ††P<0.10 versus groups 3 and 4, ‡P<0.003 versus all HIV-, §P<0.03 versus group 4, ‡‡P<0.07 versus group 4 and **P<0.02 versus group 4. DT, deceleration time; E/A, included transmitral early to late diastolic filling velocity ratio; EF, ejection fraction; E, early diastolic mitral annular velocity; IVRT, isovolumic relaxation time; MS, metabolic syndrome; S', systolic mitral annular velocity.

small and/or did not examine lipoatrophy and lipohypertrophy separately. We sought to estimate the association between body morphology abnormalities and predicted 10-year CVDR by examining the independent effects of lipoatrophy and lipohypertrophy.

Methods: This is a cross-sectional study of a convenience sample of 634 patients in the University of Washington HIV Cohort. Lipoatrophy and lipohypertrophy were assessed using the self-reported body morphology (FRAM) instrument. Responses were scored in two ways to capture (1) presence of lipoatrophy alone, lipohypertrophy alone or both, and (2) severity of these conditions. The 10-year CVDR was estimated using Framingham risk scores, which take into account age, sex, total cholesterol and high-density lipoprotein cholesterol levels, smoking status and blood pressure. We used linear and ordinal logistic regression to examine the association between body morphology abnormality presence and severity and estimated CVDR percentage and category (<10%, 10–20%, and >20% 10-year CVDR) in adjusted analyses.

Results: Among 634 patients, the mean predicted 10-year CVDR was 6% and 166 patients (26%) had a predicted 10-year CVDR ≥10%. Median predicted 10-year CVDR was 4.2% lower for women than for men (P<0.001). Mean predicted 10-year CVDR was higher in patients with lipoatrophy (7.6%, P=0.04), lipohypertrophy (7.5%, P=0.02), and both lipoatrophy and lipohypertrophy (8.1%, P=0.002) than those without body morphology abnormalities (5.9%) in analyses adjusting for demographic and clinical characteristics, such as race, sex, HIV transmission risk factor, hepatitis C virus status, and CD4+ cell count. More severe lipoatrophy and lipohypertrophy were not associated with further increased predicted 10-year CVDR. Findings were similar using CVDR categories. Current CD4+ cell count was not significantly associated with risk.

Conclusions: The Framingham 10-year CVDR provides the opportunity to evaluate overall CVDR rather than focusing only on individual risk factors, which may differ by body morphology. We found that lipoatrophy and lipohypertrophy are independently associated with higher predicted 10-year CVDR. Patients with both lipoatrophy and lipohypertrophy had the highest predicted risk. Further studies including longitudinal follow-up, better understanding of mechanisms and determining the effect on CVDR of risk factor modification are needed. In the interim, providers should consider performing CVDR profiling on HIV-infected patients with lipoatrophy or lipohypertrophy.

ABSTRACT P-55

Antiviral Therapy 13 Suppl 4:A62

Cardiovascular risk estimation in Spanish HIV-infected patients: a multicentre cohort study

E Ferrer1, C Miquez1, A Mariño1, P Geijo1, F Brun1, J Sanz2, M Velasco3, C Cortés4, A Castro4, A Ortí5, LI Force1, P Barrufet1, C Villalonga12 and D Podzamczer1 for the RICO study

1Hospital Universitari Bellvitge, Barcelona, Spain; 2Hospital Gral de Castellon, Castellon De La Plana, Spain; 3Hospital Arquitecto Marcide, Ferrol, Spain; 4H Virgen de la Luz, Cuenca, Spain; 5H Jerez de Frontera, Spain; 6H La Princesa, Spain; 7Fundacion Alcorcon, Alcoron, Spain; 8H de L’Hospitalet, Spain; 9Hospital Juan Canalejo, A Coru–a, Spain; 10H Verge de La Cinta, Tortosa, Spain; 11H de Mataro, Mataro, Spain; 12H Son Dureta, Mallorca, Spain

Objective: To assess estimated cardiovascular risk in a population of adult HIV-infected patients.

Methods: This is an ongoing, prospective, longitudinal, multicentre cohort study of estimated cardiovascular risk (eCVR). After obtaining informed consent, demographic characteristics, metabolic parameters and clinical status including CVR factors of patients enrolled from February to August 2006 at 12 Spanish sites were recorded in a central database using an Access dataset. eCVR was evaluated by the Framingham equation. For analysis purposes patients were grouped into low eCVR (<10% at 10 years; group 1) or moderate/high eCVR (>10%; group 2). Descriptive statistics were expressed as median (interquartile range) for
quantitative variables and as percentages for qualitative variables. Logistic regression was used to identify the factors that might account for a higher eCVR. Baseline data are presented.

Results: A total of 807 patients were included: 73% men, median age 41 (18–83) years, 42% drug users, 26% AIDS, CD4 465/µl, 51% undetectable viral load, 74% taking highly active antiretroviral therapy (51% PI and 49% NNRTI regimens), 64% smokers, 10% hypertension, 5% diabetes, 3.5% coronary or cardiovascular disease (CVD). Group 1 (<10 eCVR) contained 81% of patients and group 2 contained 19% (>10 eCVR).

Group 2 patients were more frequently men, older, non-drug users, smokers, diabetics, hypertensive, had CVD, lipid disturbances, greater waist circumference, greater body mass index (BMI), undetectable viral load, and used more stavudine and indinavir. On univariate analysis, male sex (odds ratio [OR] 8.51), coronary disease (5.77), CVD (3.87), diabetes (3.87), hypertension (3.66), smoking (1.96), age (1.16), lipid alterations (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], tryglicerides, no-HDL and TC/HDL, 1.02–1.52), waist circumference (1.04) and BMI (1.04) were associated with increased eCVR, whereas detectable viral load was associated with a low eCVR (0.47). First or current antiretroviral drugs were not associated with increased eCVR. On multivariate analysis, male sex (OR 19.96), age (25.08), smoking (24.12), hypertension (5.41) and total cholesterol (1.04) remained significantly associated with increased eCVR, whereas detectable viral load (0.38) and HDL (0.94) remained significantly associated with a low eCVR.

Conclusions: Traditional cardiovascular risk factors are associated with increased eCVR in our HIV population, and seem to have a stronger role than highly active antiretroviral therapy and HIV infection. Lower eCVR in patients with detectable viral loads is probably related to younger age, lower waist circumference and systolic blood pressure, and a better lipid profile. Patients with higher eCVR may benefit from lipid-friendly antiretroviral therapy, but interventions on life habits are crucial.
ABSTRACT P-56
Antiviral Therapy 13 Suppl 4:A65

In vitro alterations in hepatocyte mitochondrial RNA expression and DNA content following long-term exposure to reverse transcriptase inhibitor combinations

TP Barnes and PWG Mallon

School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland; Mater Misericordiae University Hospital, Dublin, Ireland

Objectives: Although exposure of adipose tissue to nucleoside reverse transcriptase inhibitors (NRTIs) has been shown to decrease both mitochondrial DNA (mtDNA) content and mitochondrial RNA (mtRNA) expression in vivo, it is unclear if this effect occurs in other tissues such as the liver. We aimed to evaluate the effect of prolonged exposure of hepatocytes to physiological concentrations of common NRTIs and nucleotide reverse transcriptase inhibitor combinations on mtDNA content, mtRNA expression and the expression of peroxisome proliferator-activated receptor gamma (PPARG).

Methods: HepG2 human hepatocytes were cultured for 25 days in the presence of drug combinations at concentrations equivalent to the adjusted maximum concentration (Cmax). The drug combinations were zidovudine (AZT; 4.5 µM)/lamivudine (3TC; 5 µM), abacavir (ABC; 3 µM)/3TC, stavudine (d4T; 8.5 µM)/3TC and tenofovir (TDF; 0.6 µM)/3TC. First strand complementary DNA was prepared and expression of two mitochondrial genes, MTO1 and MTCYB, and the nuclear gene PPARG were measured by real-time PCR and expressed as a ratio to a housekeeping gene (ACTINB). mtDNA content was measured by real-time PCR of extracted DNA expressed as the ratio to mtDNA (MTO1) to nuclear DNA (PPARG). Change in any parameter was measured as a percentage of the relevant control.

Results: Although exposure to AZT/3TC and TDF/3TC decreased mtDNA [mean [SEM] % change of -12.9.2% for AZT/3TC and -14.7% for TDF/3TC], only exposure to d4T/3TC resulted in significant decreases in mtDNA (-24.5 [8.2%], P=0.024). This was accompanied by a significant increase in expression of both MTO1 (50.2 [14.7%], P=0.014) and PPARG (39.9 [11.1%], P=0.011). In contrast, significant decreases in MTO1 expression were observed with exposure to AZT/3TC (-17.7 [4.7%], P=0.006) and ABC/3TC (-28.4 [7.6%], P=0.01) without accompanying changes in PPARG expression. Expression of MTCYB was not affected. mtRNA expression correlated with PPARG expression (r²=0.274, P=0.012 for MTO1 and r²=0.445, P=0.001 for MTCYB), but not with mtDNA content (r²=0.069, P=0.3 for MTO1).

Conclusion: These experiments demonstrate expected decreases in mtDNA with exposure to physiological concentrations of d4T/3TC with corresponding increases in mitochondrial and nuclear gene expression, which could be compensatory in nature. The contrasting decrease in MTO1 expression seen with exposure to AZT/3TC and ABC/3TC, and the lack of correlation between MTO1 expression and mtDNA content suggest an alternative route for these drug toxicities that is not mediated through mtDNA. To our knowledge, decreases in mtRNA expression with ABC/3TC have not been previously described. The strong correlations between mitochondrial and PPARG gene expression have been previously observed in vivo and warrant further investigation.

ABSTRACT P-57
Antiviral Therapy 13 Suppl 4:A65

Uridine supplementation with Mitocnol attenuates mitochondrial cardiomyopathy induced by zidovudine and zalcitabine

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Background: Zidovudine is an antiretroviral nucleoside analogue reverse transcriptase inhibitor (NRTI). Long-term use of zidovudine is linked to cardiomyopathy and various other tissue toxicities, which are associated with mitochondrial DNA (mtDNA) depletion. Because zidovudine inhibits thymidine kinases, the mechanism of mtDNA depletion might involve a restriction in the availability of phosphorylated pyrimidine nucleosides, which are required as mtDNA and mtRNA building blocks. We investigated whether cardiomyopathy is a class effect of antiretroviral nucleoside analogues and whether mitochondrial cardiotoxicity can be prevented with uridine as a pyrimidine nucleotide precursor.

Methods: Balb/c mice were fed zidovudine (100 mg/kg/day) or zalcitabine (13 mg/kg/day). Mice were cotreated with...
or without Mitocnol (340 mg/kg/day), a dietary supplement with high uridine bioavailability. Cardiac muscle was examined after 9 weeks of treatment.

Results: Zidovudine and zalcitabine both induced mitochondrial cardiotoxicity. Compared with untreated controls the histopathological cardiomyopathy score was increased after treatment with zalcitabine (312%, \(P<0.001\)) and zidovudine (540%, \(P<0.001\)). Mitochondria were enlarged and their cristal architecture was disrupted. The organelles contained low mtDNA copy numbers (zidovudine 87.1%, \([P=0.02]\) and zalcitabine 86.4%, \([P=0.01]\), compared with controls) and reduced cytochrome c oxidase (COX) activity. The expression of the mtDNA-encoded COX I subunit, but not of nucleus-encoded COX IV protein, was impaired. Uridine supplementation attenuated or normalized all pathology and had no intrinsic effects.

Conclusion: Both zidovudine and zalcitabine induced a mitochondrial cardiomyopathy, which is antagonized by uridine supplementation. The results provide proof of the importance of pyrimidine pools in the pathogenesis of zidovudine cardiomyopathy. Because uridine supplementation is tolerated well by humans, this strategy should be investigated in clinical trials.

**ABSTRACT P-58**

Antiviral Therapy 13 Suppl 4:A66

Uridine supplementation with Mitocnol antagonizes antiretroviral nucleoside analogue-induced mitochondrial peripheral and cerebral neuropathy in vivo

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Objective: Peripheral neuropathy and central nervous system neurodegeneration might be the toxic effects of some antiretroviral nucleoside analogues on mitochondria. We investigated if this neuropathology could be antagonized by uridine supplementation in vivo.

Methods: BalbC mice (7 weeks of age) were fed with zalcitabine (13 mg/kg/day) or zidovudine (100 mg/kg/day) with or without Mitocnol (340 mg/kg/d), a dietary supplement with high uridine bioavailability for 9 weeks. Hippocampus and sciatic nerve ultrastructure and mitochondrial functions were assessed.

Results: Zalcitabine and, to a lower extent, zidovudine induced a significant peripheral and cerebral neuropathy with disrupted mitochondrial architecture, depleted mitochondrial DNA (mtDNA) and reduced levels of cytochrome c oxidase activity (COX) and mtDNA-encoded cytochrome c subunit I (COX I). Mitocnol had no side

### Table 1. (Abstract P-58)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mitocnol</th>
<th>Zidovudine (100 mg/kg/day) plus Mitocnol</th>
<th>Zidovudine (100 mg/kg/day)</th>
<th>Zalcitabine (13 mg/kg/day) plus Mitocnol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischiadic nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mtDNA, copies/nucleus</td>
<td>374 ±49</td>
<td>372 ±38</td>
<td>290 ±65*</td>
<td>346 ±35†</td>
<td>237 ±61†</td>
</tr>
<tr>
<td>mtDNA, copies/nucleus</td>
<td>211 ±51</td>
<td>219 ±80</td>
<td>104 ±32*</td>
<td>145 ±21†</td>
<td>151 ±30*</td>
</tr>
<tr>
<td>Citrate activity, µmoles/min/g protein</td>
<td>100 ±9</td>
<td>107 ±9</td>
<td>48 ±19†</td>
<td>90 ±18†</td>
<td>50 ±15†</td>
</tr>
<tr>
<td>COX II/COX IV ratio, %</td>
<td>1,152 ±201</td>
<td>1,086 ±179</td>
<td>1,124 ±275</td>
<td>1,265 ±314</td>
<td>1,791 ±33*</td>
</tr>
</tbody>
</table>

* \(P<0.05\) versus controls. †Versus no Mitocnol. ‡ \(P<0.001\) versus control. §Percentage of control. COX, cytochrome c oxidase; mtDNA, mitochondria DNA.
effects, but attenuated or fully normalized all pathology of the peripheral and central nervous system (Table 1).

Conclusion: Zidovudine and zalcitabine induce a mitochondrial peripheral and cerebral neuropathology, both of which are antagonized by Mitocnol.

ABSTRACT P-59

Antiviral Therapy 13 Suppl 4:A67

Mitochondrial DNA and RNA content in placental tissue from HAART-treated HIV pregnancies

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Background: To prevent mother-to-child transmission, HIV-infected women are treated with highly active antiretroviral therapy (HAART) that includes two NRTIs during their pregnancy. Nucleoside reverse transcriptase inhibitors (NRTIs) can cross the placenta and could cause mitochondrial toxicity in this rapidly proliferating high energy demand tissue.

Methods: In this prospective cohort study, tissue samples from both the maternal and fetal side of the placenta were collected from HAART-exposed HIV-infected women and non-exposed HIV-uninfected controls, shortly (<2 h) after delivery. Placental mtDNA content, mtRNA and multidrug resistance (MDR1) mRNA levels were assayed. Values were compared between groups using the Mann–Whitney signed-rank test and Pearson’s correlation.

Results: Placenta from 42 HIV-infected women (34 on HAART since the second trimester [group A] and 8 since conception [group B]) and 32 non-exposed HIV-uninfected controls were studied. The HAART NRTI backbone consisted primarily of zidovudine/lamivudine in group A, but varied in group B. Overall, placental mtDNA content was not significantly different between HAART-exposed and controls on both the fetal (P=0.70) and maternal (P=0.57) side of the organ. Maternal and fetal side placental mtDNA levels were similar and very strongly correlated in controls (median [interquartile range] 93 [67–106] versus 94 [62–119], R=0.86, P<0.0001, slope=0.99). However, HAART-exposed mtDNA levels tended to be lower on the fetal side than on the maternal side (85 [62–108] versus 88 [78–95], P=0.081). HAART-exposed fetal and maternal side mtDNA levels were significantly less correlated between them (R=0.55, P=0.006), showing a significantly lower slope (0.53, P=0.03) than controls. There were no notable differences at the mtRNA level. MDR1 placental mRNA levels were not statistically different between exposed and control placentae. Interestingly, the maternal and fetal side MDR1 levels were highly correlated in HAART-exposed (R=0.98, P<0.0001, slope=1.09), but not in controls (R=0.34, P=0.1, slope=0.3).

Conclusions: Exposure to HAART during pregnancy appears to affect placental mitochondria differentially on the maternal than on the fetal side of the organ. This might reflect an adaptation to drug pressure. Multidrug resistance gene induction, a potentially protective mechanism, is highly comparable throughout the tissue in HAART-exposed placentae. Change in mitochondrial function might adversely affect placental metabolism and energy production, which could have serious effects on fetal organ development and function.

ABSTRACT P-60

Antiviral Therapy 13 Suppl 4:A67

In vivo evaluation of the effect of antioxidant supplementation on mitochondrial function and body composition in HIV-infected patients with lipoatrophy

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Objectives: Nucleoside reverse transcriptase inhibitor (NRTI)-containing HAART regimens can damage mitochondria (mt), leading to mtDNA depletion and the onset of lipodystrophy syndrome. Delaying mt damage and oxidative stress with the use of antioxidants might represent a therapeutic strategy for antiretroviral-related lipodystrophy. The aim of this study was to evaluate the mitochondrial impairment in lipoatrophic HIV-infected patients by the comparison of two methods for the in vivo assessment of mt function: mtDNA quantification on CD4+ and CD8+ T-cells and on subcutaneous adipose tissue and 13C-methionine breath test. Furthermore, we investigated the effect of antioxidants supplementation on mtDNA content, 13CO2 exhalation, body composition and lipid and glucose metabolism.

Methods: A total of 60 lipoatrophic HIV-infected patients on treatment with an NRTI-containing antiretroviral regimen for at least 1 year were enrolled in this controlled, open-label study and randomized into one of three supplementation treatment groups: acetyl-l-carnitine 2 g once daily (20 patients), lipoic acid plus N-acetylcysteine 100 mg/150 mg twice daily (20 patients) and no antioxidant supplementation (20 patients) for a 12-month period. Demographic, metabolic and body
mass index (BMI) data were collected at enrolment and after 12 months of antioxidant supplementation. Whole body dual-energy X-ray absorptiometry, 13C-methionine breath test and mtDNA quantification, by real-time PCR, on peripheral CD4+ and CD8+ T-cells and on subcutaneous adipose tissue were performed. Data were analysed by the Student's t-test and by the ANOVA non-parametric test for multiple comparisons.

**Results:** Baseline characteristics were similar in the three groups. A significant increase of 13CO2 exhalation was observed in both supplementation arms between baseline and T12 when compared with the control group; as evidenced by a higher delta over baseline excretion at 45′ (from mean ±SEM of 7.9 ±1.08 to 9.9 ±0.6, P=0.04 in the carnitine arm and from 7.4 ±0.8 to 11.5 ±1.6, P=0.01 in lipoic acid/N-acetylcysteine arm) and by higher cumulative 13CO2 excretion (from mean ±SEM of 3.63 ±0.4 to 4.7 ±0.3 in carnitine arm and from 3.75 ±0.3 to 5.6 ±0.7 in lipoic acid/N-acetylcysteine arm; P=0.001). In a multivariate analysis, after adjusting for the randomization arm, no statistical difference emerged among groups. mtDNA content was significantly increased in CD4+ T-cells from patients who received carnitine, but not lipoic acid, compared with the control group (from mean ±SEM copies/ml of 86 ±3.7 to 172 ±5.6; P=0.028). There was no significant change in mtDNA content of CD8+ T-cell and adipose tissue, lipid profile, insulin sensitivity and body fat mass composition between groups after 12 months of supplementation.

**Discussion:** In HIV-associated lipoatrophy, dietary supplementation with carnitine or lipoic acid/N-acetylcysteine for 12 months significantly improved mt function, but no amelioration of fat mass distribution or lipid and glucose metabolism was obtained.

**ABSTRACT P-61**

*Antiviral Therapy* 13 Suppl 4:A68

**Effect of substituting tenofovir for zidovudine versus continuing zidovudine on physiological correlates of mitochondrial function in HIV-infected subjects on nucleoside-reverse transcriptase inhibitor therapy**

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**Aims:** Mitochondrial dysfunction has been associated with thymidine analogue-based highly active antiretroviral therapy (HAART), and improvements in lipoatrophy and dyslipidaemia have followed changes in treatment with the introduction of newer nucleotide- or nucleoside-reverse transcriptase inhibitors, non-thymidine analogues, such as tenofovir or abacavir. This study compared the effects of a zidovudine-to-tenofovir switch versus continuing zidovudine, on oxygen consumption (VO2 max), a surrogate for mitochondrial function in muscle. Secondary endpoints included body composition, hepatic fat content, insulin resistance (IR), hepatic lactate clearance and symptom distress.

**Methods:** HIV-infected individuals with undetectable HIV RNA, taking zidovudine-containing HAART for an average of 5 years, were prospectively randomized to switch to open-label tenofovir-containing HAART (switch group) or to continue zidovudine (control group). Subjects underwent a standard maximal exercise protocol, calculating VO2 max and other variables. Baseline and peak concentrations and lactate clearance were measured during the exercise test. Whole body MRI, proton MR spectroscopy of the liver and euglycaemic-hyperinsulinaemic clamp estimated body fat, steatosis and IR, respectively. CD4+ T-cell levels, HIV RNA content, routine chemistries and other safety measures were determined monthly during the first 12 weeks post-randomization. A 20-question symptom distress survey was administered monthly. The Kruskall–Wallis non-parametric test was used for between-group statistical analyses of change from baseline to week 24.

**Results:** Five control and seven switch subjects have completed the study thus far. Baseline symptom distress scores were low and did not change in either group. Whole body and lower limb subcutaneous adipose tissue increased in the switch group by 1.1 and 0.4 l, respectively, and decreased in controls by 1.2 and 0.5 l, respectively (P=0.04 for both comparisons). Total visceral adipose tissue increased after switching (0.021) and decreased in controls (-0.5 l, P=0.03). Hepatic fat content decreased in the switch group compared with controls (P=0.17), whereas lactate clearance increased after switching compared with controls (P=0.068). No changes in VO2 max, our primary endpoint, in IR, baseline or peak lactate concentrations, or in their difference, were recorded. Skeletal and cardiac muscle mitochondrial function trended towards longer total exercise time and towards higher percentage of age-predicted peak exercise heart rate. No renal, hepatic or haematological toxicities and no significant changes in HIV RNA or CD4+ T-cell counts were noted.

**Conclusions:** Despite little clinical evidence of mitochondrial dysfunction, switching led to detectable physiological changes in adipose tissue and the liver, the latter as increased lactate clearance and decreased hepatic fat content. Switching to tenofovir from zidovudine had no detectable effects on skeletal muscle as aerobic capacity, peak lactate production and glucose disposal remained unchanged.

A68 Programme B Abstracts
ABSTRACT P-62

Antiviral Therapy 13 Suppl 4:A69

Effects of a 144–week-long CD4-guided HIV treatment interruption on mitochondria

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Introduction: Mitochondrial toxicity of antiretroviral treatment (ARVT), especially the capacity of nucleoside analogues to inhibit DNA polymerase γ, has been proposed as the ethiopathological mechanism that underlies many of the secondary effects of HIV therapy. The aim of this present study was to evaluate whether a prolonged CD4+ T-cell-guided ARVT interruption could reverse mitochondrial toxicity.

Methods: We included 38 patients from the TIBET study, whose peripheral blood mononuclear cells (PBMCs) had been collected at baseline, at 96 and at 144 weeks throughout the study period; 18 of them discontinued ARVT during this time and 20 maintained therapy. Mitochondrial DNA (mtDNA) content was measured by real-time PCR and mitochondrial function through the spectrophotometric measurement of cytochrome c oxidase (COX) enzymatic activity normalized by mitochondrial content using citrate synthase (CS) activity (COX/CS ratio). Results: Whereas mtDNA content showed a similar progressive decrease throughout the study period in both study arms, only the control group was significant either at week 96 (15% decrease, P=0.03) or at week 144 (34% decrease, P=0.01). The COX/CS ratio significantly improved in patients who interrupted ARVT in comparison with those who did not, especially at week 96 (130% increase, P=0.06). The univariate and multivariate analyses performed showed that only CD4+ T-cell value at the time of ARVT initiation and time with viral suppression before the study were associated with changes on the COX/CS ratio.

Conclusions: The mitochondrial function of peripheral blood mononuclear cells improved during a prolonged ARVT interruption despite mtDNA content decrease. The absence of correlation between mitochondrial parameters suggests the existence of a mitochondrial transcriptional or translational upregulation mechanism, which could be increasing mitochondrial protein expression in absence of mtDNA content improvement or could also be the rever- sion of an ARV-mediated mitochondrial toxicity mechanism that was previously disturbing mitochondrial function through a DNA polymerase γ independent way.

This study was supported by: Fundació la Marató de TV3 020210 and 020631, FPSE 36612/06, FIS 40381/04 and 41239/04, Suports a Grups de Recerca de la Generalitat de Catalunya 2005/SGR/0300 and CIBER de Enfermedades Raras (initiative of the ISCIII).

ABSTRACT P-63

Antiviral Therapy 13 Suppl 4:A69

Mitochondrial damage induced by the highly active antiretroviral treatment in non–HIV-infected patients

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Introduction: Antiretroviral (ARV) toxicity, especially of nucleoside analogues, together with HIV infection have both been demonstrated to induce mitochondrial DNA (mtDNA) depletion and mitochondrial dysfunction. The contribution of each mechanism (either HIV or ARV) to the observed mitochondrial damage present in HIV-infected patients on highly active ARV treatment (HAART) is difficult to elucidate. HIV-induced mitochondrial lesions have been studied in HIV-infected but not in non-HAART-treated individuals; however, ARV-related mitochondrial damage has been poorly explored in non-infected patients. The aim of the present study is to assess in vivo mitochondrial toxicity of HAART without HIV infection effects.

Methods: We included six healthy patients under 1 month of prophylactic ARV treatment consisting of FTC+TDF+SQV to prevent HIV infection after risk exposition. All of them remained uninfected 6 months after HAART withdrawal. Mitochondrial studies were performed in mononuclear cells before and after the ARV treatment to assess mtDNA content using real-time PCR and mitochondrial function through the spectrophotometric measurement of the enzymatic activity of both mitochondrial respiratory chain (MRC) complex II (non-mitochondrial encoded) and complex IV (partially encoded in the mitochondrial genome). Statistic analyses compared mitochondrial results before and after ARV therapy using the t-test for repeated measures.

Results: Mitochondrial DNA content was reduced by 20% in the studied patients undergoing ARV treatment (2.17

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Mitochondrial disorder.

In non-HIV-infected patients, 1 month of ARV treatment induced mitochondrial damage, even when considering HAART consisting of FTC+TDF+SQV/r with a theoretical low mitochondrial toxic profile. Mitochondrial changes consisted of slight mtDNA depletion and moderated mtDNA-encoded MRC complex IV dysfunction, although none of these changes were statistically significant. These findings validate HAART-induced mitochondrial toxicity, even in the absence of HIV infection. Further studies should be performed to assess mitochondrial toxicity of different HAART schedules in non-infected individuals to elucidate toxic effects of ARVs without HIV or previous ARV interference.

This study was supported by: Fundació la Marató de TV3 020210 and 020631, FIPSE 36612/06, FIS 40381/04 and 41239/04, Suports a Grups de Recerca de la Generalitat de Catalunya 2005/SGR/0300 and CIBER de Enfermedades Raras (initiative of the ISCIII).

ABSTRACT P-64

Antiviral Therapy 13 Suppl 4:A70

Mitochondrial dysfunction in HIV-infected children receiving or not antiretroviral therapy

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Purpose of the study: Mechanisms of mitochondrial impairment induced by HIV infection itself and highly active antiretroviral therapy (HAART) are well studied in adults. However, there is more left to know in children because they are the first following-up generation with the disease. The aim of this study was to determine whether there are alterations in mtDNA content and MRC dysfunctions in peripheral blood mononuclear cells (PBMCs) in HAART-treated and non-HAART-treated HIV-infected children.

Methods: A transversal study in PBMCs isolated by a Ficoll’s gradient was performed in 33 HAART-treated and 14 non-HAART-treated HIV-infected children as well as nine healthy children. MtDNA was assessed by real-time PCR. MRC complex IV (CIV) function and mitochondrial mass (MM; estimated by cytrate synthase [CS] enzymatic activity) were measured by spectrophotometry. CIV activity was expressed in absolute values, as nmols oxidated substrate/min/mg protein, and relative values by dividing absolute CIV per MM (CIV/CS). Subunits COXII and COXIV of CIV and mt content were assessed by western blot analysis.

Results: No differences in mitochondrial parameters between HAART and non-HAART-treated HIV-infected patients were found. However, mtDNA significantly decreased (32%, P=0.015) in both groups compared with healthy controls. Absolute and relative CIV activities did not differ among groups.

Conclusions: We found a reduction in mtDNA amount in HIV-infected children with respect to healthy controls. However, this depletion was not reflected in MRC CIV activity dysfunction. HAART does not seem to interfere with mitochondrial parameters. Future studies will be performed in order to determine whether this is caused by upregulatory mechanisms or longer time is required to detect alterations in MRC.

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ABSTRACT P-65

Antiviral Therapy 13 Suppl 4:A70

Antiretroviral treatment interruption followed by an increase in mitochondrial DNA content in HIV-infected children

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Purpose of study: HIV infection itself and antiretroviral treatment, especially nucleoside analogue reverse transcriptase inhibitors (NRTIs), cause mitochondrial impairment in HIV-infected patients because of the inhibition of the polymerase, which is the only enzyme responsible for mitochondrial DNA (mtDNA) replication.

Methods: MtDNA was assessed by real-time polymerase chain reaction (RT-PCR) in peripheral blood mononuclear cells (PBMCs) of 13 perinatally HIV-infected paediatric patients, who underwent planned treatment interruption (PTI). MtDNA was measured at the time of PTI and 12 months later. A sequence of a highly conserved mtND2
gene and a fragment of the nuclear-coded housekeeping 18S rRNA gene were amplified separately. Changes in mtDNA amount were expressed as the ratio of ND2 mtDNA with respect to 18S rRNA mtDNA.

**Summary of results:** mtDNA content significantly increased from 0.89 ±0.173 to 1.48 ±0.3429 (66%, \( P<0.05 \)) after 12 months treatment interruption.

**Conclusions:** mtDNA content restoration was found in a group of perinatally HIV-infected paediatric patients after 12 months of highly active antiretroviral therapy interruption. Our results suggest that mitochondrial damage is because of the use of nucleoside analogues rather than to HIV infection itself. In this setting, it is important to investigate new therapeutic treatment-sparing strategies in HIV-infected paediatric patients.

**Supported by:** Fundació la Marató de TV3 (020210 and 020631), FIPSE 36612/06, FIS 40381/04 and 41239/04, Suports a Grups de Recerca de la Generalitat de Catalunya (2005/SGR/0300) and CIBER de Enfermedades Raras (initiative of the ISCIII).

**ABSTRACT P-66**

*Antiviral Therapy* 13 Suppl 4:A71

**Mitochondrial toxicity in HIV patients treated with antiretrovirals manifesting as a syndrome resembling chronic progressive external ophthalmoplegia**

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**Background:** HIV infection as well as antiretroviral agents can affect skeletal muscle. Although mitochondrial (mt) toxicity, muscle mtDNA depletion and myopathy have been described in the context of HIV therapy, the development of mt syndromes such as chronic progressive external ophthalmoplegia (CPEO) has not been previously reported.

**Methods:** Three HIV-infected patients (52–58 years old) on long-term nucleoside analogue-containing HAART (10–15 years old years) were referred for neurology assessment of a CPEO-like syndrome. Chart review and, in one patient for whom quadriceps and levator muscle biopsies were performed, muscle mt enzyme analyses and mtDNA investigations were performed.

**Results:** All three patients presented a complaint of progressive ptosis (eyelid drooping) and occasional diplopia (double vision). Examination revealed ptosis in all three patients and multidirectional ophthalmoparesis in two of them. One patient developed migraine headaches and another dysphagia (difficulty swallowing). All three also had manifestations of HAART-induced mt toxicity, including lipodystrophy, increased serum lactate and increased fatigue. All three patients were on concurrent HIV and statin therapy. Alternative aetiologies including myasthenia gravis were excluded with history, examination, blood work and neurophysiology studies. One patient showed marked improvement of his ocular symptoms after withdrawing HAART for 3 months. The second patient did not show improvement of his symptoms after substituting T20 for didanosine. His levator muscle biopsy revealed ragged-red fibres and COX-deficient fibres, whereas his quadriceps biopsy, including mt enzyme analysis, was unremarkable. Muscle genetic analyses detected a rare 3.9 kb mtDNA deletion (547–4,443) that has previously been associated with CPEO, affecting an estimated 40–60% of mtDNA in both biopsies. No other mutations associated with mt disease were detected. The third patient did not return for follow-up so further assessment and intervention was not possible.

**Conclusions:** These cases suggest that combined mt toxicity from HIV infection and antiretroviral therapy can occasionally produce syndromes resembling mt disorders, which could improve by withdrawing the offending agent. Concurrent statin therapy might have contributed to the muscle symptoms. It is unclear whether HIV infection and mitotoxic agents can produce the syndrome on their own or whether they might exacerbate and unmask previously present subclinical mt disease. Nevertheless, the incidence of this CPEO-like syndrome, a rare disease in the general population (the prevalence of all mt diseases combined is approximately 1/8,500), seems high considering that our total patient population on HAART is approximately 4,500. The observation of CPEO-like syndrome might increase as the number of aging HIV survivors with long-term HAART exposure rises.
Clinical Management of ADRs

ABSTRACT P-67

*Antiviral Therapy* 13 Suppl 4:A73

Impact of body changes on the quality of life of HIV-positive treatment-experienced patients – an online community-based survey

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Objectives: To collect data on the impact of HIV-related lipodystrophy and its management on quality of life of HIV-positive members of pozhealth at yahoo groups.com, a 6-year listserve with close to 3,000 members.

Methods: A link to a survey with 23 questions was posted in pozhealth asking people to share information about demographics, time since diagnosis, HIV medication and thymidine analogue exposure, perceived body changes (BC), incidence of depression/anxiety, suicidal thoughts, medication interruptions, social interaction, self-image, therapeutic interventions and their cost coverage, use of lipoatrophy-related products, incidence of lipid and glucose abnormalities, perceptions on the role that HIV medications play on body changes, and community input for lipodystrophy researchers

Results: A total of 949 people participated, with a majority being white males over 40 years old, with over 10 years since HIV diagnosis, on highly active medications play on body changes, and community input for lipodystrophy researchers

Discussion: We suggest that more information is obtained from other patient populations via targeted outreach venues. More data are essential in justifying funding for programmes and reimbursement of therapies to manage body changes in HIV disease.

Conclusions: Despite the inherent limitations and possible biases of self selection and the limited survey population, body changes appear to take a major toll in the quality of life of patients. The majority of patients in this sample reported eroding self-image, increased isolation and depression/anxiety, and most associate these with drugs used in the treatment of HIV disease. The patients’ belief that there is an association with the treatment drugs they use has a negative effect on patient adherence to prescribed regimens.

ABSTRACT P-68

*Antiviral Therapy* 13 Suppl 4:A73

Health-related quality of life in HIV-infected patients in a private practice in Germany

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Objectives: With improved treatment options, HIV infection has become a well treatable disease. Nevertheless, chronic disease and toxicities of long-term therapy could impair quality of life (QoL).

Methods: This was a cross-sectional study (n=209) that used a self-administered 28-item questionnaire (6 scales measuring QoL, SEL) validated for HIV patients. For statistical analyses non-parametric tests were used. The antiretrovirals used (>10 patients) were the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine/emtricitabine (152), tenofovir (121), abacavir (32) and zidovudine (30); the non-NRTIs (NNRTIs) efavirenz (50) and nevirapine (28); and the protease inhibitors (PI) lopinavir (31), atazanavir (17), saquinavir (12) and darunavir (11).

Results: The mean age was 44 years and 89% were male. CDC stage (1998) was A 44%, B 32% and C 24%. In total, 80% received antiretroviral therapy. No difference in overall QoL between treated (3.62 ± 0.80) and untreated patients (3.66 ± 0.85; P=0.78) was observed. All patients rated their physical state as better (QoL-P; 3.73 ± 0.85) than their cognitive-emotional (QoL-CE; 3.44 ± 0.86; P<0.001), regardless of being treated or not. There was no correlation between CD4+ T-cells and any of the QoL domains. Patients in stage CDC A had a better QoL in all
domains compared with patients with a history of symptomatic infection CDC B or CDC C (P<0.05). Patients on NNRTIs reported a better QoL than patients on PIs for QoL-p (3.91 ±0.79 versus 3.58 ±0.87), QoL-CE (3.65 ±0.83 versus 3.31 ±0.89) and overall QoL (3.80 ±0.81 versus 3.48 ±0.84, all P<0.05). However, a higher proportion of patients with advanced HIV infection were treated with PIs compared with NNRTIs: CDC A 34%/61%, CDC B 59%/42% and CDC C 56%/40% (P<0.05). Overall QoL score was lower in HIV-positive patients (3.63 ±0.79) than in the healthy reference sample (3.81 ±0.53), but better than the older HIV-positive sample (3.51 ±0.62) from the mid-90s. Improved QoL of HIV-positive patients with and without current antiretroviral therapy compared with patients from mid-90s was observed in all QoL domains. Conclusions: HIV-positive patients rate their QoL worse than healthy controls, but better than HIV-positive individuals from mid-90s. Compared with HIV-negative individuals, QoL is impaired in the QoL-CE domain independent of health status. This suggests that being HIV-infected represents an emotional stress despite improved physical wellbeing. Effects of different drug classes should be interpreted carefully because of a potential selection bias.

### ABSTRACT P-69

Antiviral Therapy 13 Suppl 4:A74

Economic modelling of the combined effects of HIV disease, heart disease and lipoatrophy based on ACTG 5142 trial data

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Aims: This study examines the cost and consequences of initiating an antiretroviral (ARV) regimen that includes lopinavir/ritonavir (LPV/r) or efavirenz (EFV) using data from a recent clinical trial in a previously published model of HIV disease.

Methods: We populated the Markov model of HIV disease with data from ACTG 5142 study to estimate the economic outcomes of starting ARV therapy with a protease inhibitor-containing regimen as compared with an NNRTI-containing regimen, given their virological and immunological efficacy and effects on cholesterol and lipoatrophy. Central nervous system toxicities and gastrointestinal tolerability were not included in the model because of their transient nature or low cost remedies, and therefore lack of economic effect. CD4+ T-cell counts and the HIV-1 RNA (viral load) values from the study were used to assign a specific health state (HS) to each patient for each quarter year. The resulting frequencies used as ‘raw’ data directly into the model obviate the reliance on statistical tests and allow the model to reflect actual patient behaviour in the clinical trial. An HS just below the last observed HS was used to replace a missing value.

Results: The modelled estimates (undiscounted) for the LPV/r-based regimen resulted in 1.41 quality-adjusted life months gained over a lifetime compared with the EFV-based regimen. The LPV/r-based regimen incurs a $7,458 (1.8%) greater cost over a lifetime because of differences in drug costs and survival. The incremental cost effectiveness ratio using the discounted cost and quality-adjusted life years (QALYs) is $88,829/QALY. Most of the higher costs accrue before the seventh year of treatment and are offset by subsequent savings. The estimates are highly sensitive to the effect of lipoatrophy on quality of life, but not to the effect of cholesterol levels.

Conclusions: Initiating an LPV/r-containing regimen on ARV-naive patients appears cost effective compared with an EFV-based regimen when the cost and consequences of lipoatrophy are included.

### ABSTRACT P-70

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Cost effectiveness and budget impact of lopinavir/ritonavir (LPV/r) and atazanavir plus ritonavir (ATV+RTV) regimens based on 48-week results from the CASTLE study

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Background: The CASTLE study showed no significant differences in the percentage of patients with viral load <50 copies/ml or in CD4+ T-cell count increase at 48 weeks for the two antiretroviral (ARV) treatment regimens. Total cholesterol (TC) levels were elevated in 18% and 7% of patients receiving LPV/r and ATV+RTV, respectively. The purpose of the study was to conduct a cost-effective analysis and budget impact analysis comparing LPV/r and ATV+RTV for a group of antiretroviral-naive patients with a baseline CD4+ T-cell distribution and TC profile similar to the CASTLE population.

Methods: This decision analysis study used a previously published Markov model of HIV disease, incorporating coronary heart disease (CHD) events to compare the short- and long-term budget impacts and CHD consequences expected for the two regimens.
Hydroxylapatite, polyalkylimide gel, hyaluronic acid and silicone oil. Two products, poly-β-lactic acid and calcium hydroxyapatite, are semi-permanent injectable fillers that last up to 18–24 months, and are approved by the US Food and Drug Administration. Hyaluronic acid is a temporary filler and the effect will last up to a year, whereas polyalkylimide gel and silicone oil are permanent fillers.

Data were collected from these 14 studies on the dosage, treatment schedule, and amount of product administered for each product. Cost of dermal filler for a single site, such as malar, is estimated as the product of the number of visits per course, units of product used per visit and the price per unit of filler.

Typical courses involve four physician visits on average, but could vary from 1 to 3. The unit price for each dermal filler ranges from $123 for 1 ml of poly-β-lactic acid to $1,250 for 1 ml of silicone oil. The cost of a course of dermal-filler treatment at a single facial site ranges from $3,690 to $16,544, which typically is not covered by the payers. Physician fees for similar outpatient procedures reimbursed by insurers are approximately $500, and may vary according to location, specialty and market conditions.

Treatment of HIV-associated lipoatrophy may represent a considerable out-of-pocket expense for many patients with HIV and will influence the decision options and pathways.

**ABSTRACT P-72**

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TREATMENT OF HIV-RELATED FACIAL AND BODY LIPODYSTROPHY WITH POLYMETHYL METHACRYLATE (PMMA): 10 YEARS EXPERIENCE

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**Aim:** Facial atrophy, which compromises a patient’s self-esteem, was the first unesthetic condition related with lipodystrophy that we have been treating with PMMA for the past 10 years. At present, changes of body shape have become another problem that affects a patient’s quality of life. The objective of this study is to present our extensive experience with using PMMA to treat facial and body lipodystrophy.

**Methods:** Series of cases of lipodystrophy patients treated with PMMA in the past 10 years. Treatment consisted of retro-injections in the subcutaneous areas of atrophic parts of the face and body with PMMA hydrogel. Patients were photographed before and after treatment and followed as necessary.

**Results:** Six hundred and sixteen patients were included in this study (543 men and 73 women), with follow-up between 6 and 118 months (median 60 months for face treatment). Five hundred and ninety-seven patients were included in this study, and the average number of treatment courses per patient was 4.6.

**Conclusion:** The use of an ATV+RTV-based regimen in ARV-naive patients with a CHD risk similar to patients in the CASTLE study is not a cost-effective use of scarce resources. The very small added CHD risk incurred by LPV/r treatment is more than offset by its short- and long-term cost savings.

**ABSTRACT P-71**

*Antiviral Therapy* 13 Suppl 4:A75

COST CONSEQUENCES OF HIV-ASSOCIATED LIPODYSTROPHY

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HIV-associated lipoatrophy may affect up to 35% of patients who have received antiretroviral therapy for more than 1 year, and results in depression, social isolation and career barriers. Interventions, such as dermal fillers, are licensed for restoration of facial fat loss in persons living with HIV. As only few insurance plans, if any, provide reimbursement for such procedures, patients must consider the pros and cons of such interventions, weighing against the other costs of daily life. The primary goal of this study was to provide reliable estimates of the costs of treating HIV-associated lipoatrophy, specifically facial lipoatrophy.

Costs were estimated from published studies reporting administration patterns of dermal fillers, publicly available list prices and physician service fees for similar subcutaneous injections of the face.

In total, 14 studies were identified that reported experience with five dermal fillers used to treat HIV-associated facial lipoatrophy. These included poly-β-lactic acid, calcium hydroxyapatite, polyalkylimide gel, hyaluronic acid and...
submitted for facial treatment (a total of 1,536 procedures). One hundred and seventy-five patients were submitted for body-area treatment (97 buttocks, 59 legs, 13 arms and hands, and 6 thoraxes) in the past 5 years (a total of 271 procedures). Median age was 48 years (26–75). CD4+ T-cells ranged from 40 to 1,359 cells/mm³. The amount of PMMA used varied with degree of atrophy and area treated; faces ranged from 6 to 38 ml of PMMA and buttocks from 40 to 250 ml. Most patients needed two to three sessions to achieve good cosmetic results and were satisfied with the results, especially for facial (getting more self confident) and buttock treatment (feeling more comfortable to be seated for longer period of time).

Although most patients were satisfied with treatment, some patients were less satisfied with the treatment to their legs. Immediate side effects observed were: oedema; redness and bruising of the treated area, which for facial problems resolved in 3–7 days with the use of cold compress; and light to moderate pain for the body-treated areas, especially legs, which lasted for 2–5 days and improved with oral analgesic and anti-inflammatory. No infection or inflammatory granuloma was observed. Three patients (0.5%) had long-term adverse effect with swollen treated areas on their face after 1 (one patient) and 3 years (two patients) of treatment with PMMA. All patients were at that moment with an infection close to the site of implantation of PMMA that resolved spontaneously after infection were treated and no other episode was observed. Patients indicated to be satisfied with the procedure and noticed an improvement in their quality of life.

Conclusions: Treatment of facial and body lipoatrophy related to HIV lipodystrophy with PMMA solution demonstrated to be safe, efficient and long-lasting, with minimum side effects. The treatment had a positive influence on patients, helping them get more self confident and improving their quality of life.

ABSTRACT P-73

Antiviral Therapy 13 Suppl 4:A76

Surgical intervention programme for HIV-associated lipodystrophy patients: experience of the Heliópolis Hospital, São Paulo, Brazil

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Introduction: The HIV-associated lipodystrophy syndrome has an important impact on patients’ quality of life. Once the abnormal distribution of body fat is established, the process of correction is slow and incomplete. For this reason, surgical interventions have been considered the only treatment option. At present, the literature has not shown enough data to claim that lipodystrophy surgical correction is a useful technique for such patients.

Objective: Present the experience in surgical management of HIV-associated lipodystrophy patients in Heliopolis Hospital, São Paulo, Brazil.

Methods: We performed a retrospective review of 336 consecutive patients (192 female and 143 male, mean age 42.9 years, mean body mass index 24.8 kg/m² and no active opportunistic infections) who underwent surgical management of HIV lipodystrophy at a university hospital from 2005 to 2008.

Results: Surgical intervention was performed in 233 patients (156 women and 77 men); ultrasonic-assisted liposuction of the anterior neck (14 patients), posterior neck (86 patients) and trunk (31 patients); dermolipectomy (27 patients); abdominal liposuction (29 patients); dermolipectomy and abdominal liposuction (17 patients); submental fat reduction (14 patients); pubis liposuction (2 patients); breast liposuction (18 patients); mammary prosthesis (1 patient); buttocks prosthesis (12 patients); arms liposuction (6 patients); and facial lifting (2 patients). Complications and sequelae were rare and included seroma, ecchymosis and need for revision, but did not include nerve injury, fat necrosis, skin loss and infection. Soft-tissue volume replacement with injectable polymethylmethacrylate was performed in 185 patients by certified plastic surgeons and in 64 patients by dermatologists with no severe complications.

The primary findings in patients’ body assessment demonstrated a population that was both overweight (24% women and 27% men) and obesity (9% women and 12% men). The assessment of waist–hip and waist–girth demonstrated a high frequency of abdominal obesity in women leading to an increased cardiovascular risk.

Conclusion: The main importance of surgical interventions in HIV-associated lipodystrophy patients lies in providing improvement in patients’ quality of live and self esteem, assuring commitment to antiretroviral treatment. This is a current reality that should be expanded to all HIV centres.

ABSTRACT P-74

Antiviral Therapy 13 Suppl 4:A76

Facial filling with polymethylmethacrylate in São Paulo, Brazil: experience of 650 patients

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Background: Brazil has an estimated total population of 191,791,000, of which 730,000 people are living with HIV or AIDS. Of this, 181,000 are currently receiving
antiretroviral therapy. The National Programme on STD/AIDS is concerned about this issue and published their first recommendation in February 2005 (Act SAS-MS nº 118). This recommendation included access to facial filling with polymethylmethacrylate (PMMA), liposuction, fat transfer and silicon prosthesis implant. The Reference and Training Center in STD and AIDS (CRT-SP) located in São Paulo has currently 4,172 patients being followed up. Prevalence of lipoatrophy in major clinical studies varies from 13 to 67%. Based on this data, we could estimate that 542–2,795 patients have lipoatrophy at CRT-SP.

Methods: Since 2005, 650 patients with severe or moderate lipoatrophy were submitted to injections of PMMA (Metacrill 30%) at the Reference and Training Center in STD and AIDS. They received the filling in the malar area, after topical anaesthesia with lidocaine 4% cream. Clinical pictures were taken before each visit. The patients received as many sessions of filling as needed in order to satisfy both patient and dermatologist.

Results: From May 2005 to December 2007, 650 patients were treated. Patients received 3–6 ml in each malar area; further filling sessions were performed at least 1 month later until an optimal result was obtained. Ecchymosis was observed in some patients soon after the procedure, which is inherent of any procedure involving a needle. We observed four patients with late complications (0.6%). One patient presented transitory bilateral facial oedema 1 week after beginning of interferon therapy, due to hepatitis C. He had been treated with PMMA months before in the same area. Another patient presented oedema at the left malar area 3 days after he had gotten a tattoo on the left cervical region. He had received PMMA 3 months before. This patient also presented recurrence of oedema after a local trauma (a punch). Two patients presented oedema after acute sinusitis and after dental infection. All of them were treated with systemic corticosteroids, with complete resolution.

Conclusions: It is very important that the government have policy statements for prevention and treatment on all aspects of HIV care. The scope of responsibility of AIDS coordination goes beyond the universal access to HAART, which has already been in place since 1996 in Brazil. We observed low incidence of complications after 3 years of filling with PMMA.
Prevalence and determinants of metabolic syndrome among Latin American HIV-infected patients on HAART: RAPID II study

Objective: Recent studies conducted in developed countries suggested that HIV-infected patients receiving highly active antiretroviral therapy (HAART) have a high prevalence of metabolic syndrome. No data are available from Latin America to evaluate the magnitude of this problem. The Registry and Prospective Analysis of Patients Infected with HIV and Dyslipidemia (RAPID II study) evaluates the prevalence and determinants of metabolic syndrome among Latin America HIV-infected patients receiving HAART.

Methods: A longitudinal study to evaluate the metabolic profile, cardiovascular risk (CVR) and associated treatment practices to reduce this risk has been conducted in seven Latin American countries (the RAPID II study). Adult HIV patients with at least 6 months of HAART were enrolled. Metabolic syndrome was defined following ATP-III criteria. Associated factors for metabolic syndrome, such as demographic data, anthropometric parameters, serum biochemical parameters, time living with HIV infection, time on HAART, CD4 cell count and viral load, were compared in patients with and without metabolic syndrome using bivariate and unconditional logistic regression analysis.

Results: A total of 4,010 patients were enrolled, 2,963 (74%) were males. Mean age (sd) was 41.9 (10) years, mean time on HAART was 34.5 (30.8) months, 20.7% were on a protease-based HAART regimen. Mean overall CD4 cell count was 467 (275) cells/mm³ and mean overall viral load was 4.12 (4.8) log₁₀ copies/ml. The prevalence of metabolic syndrome was 20.2% (812/4,010). The overall 10-year risk of developing cardiovascular disease (CVD), as measured by the Framingham risk equation, was 10.4 (24.7). The 10-year CVD risk was higher in patients with metabolic syndrome (22.2 versus 7.4, \( P < 0.001 \)). Variables associated with metabolic syndrome in the multivariate analysis were age, female gender, family history of cardiovascular disease (CVD) and CD4 cell count (see Table 1). Duration of HIV infection and time on HAART were associated with metabolic syndrome in the univariate analysis, but were not retained in the multivariate model after adjusting for covariates.

Conclusions: Metabolic syndrome is prevalent in this cohort of Latin American HIV-infected patients and it is associated with higher risk of CVD. Factors independently associated with metabolic syndrome are age, female gender, family history of CVD and CD4 cell count, but not time living with HIV and duration of HAART.

**Table 1. (Abstract P-75)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted odds ratio</th>
<th>95% Confidence Interval</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment</td>
<td>1.05</td>
<td>1.04–1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.28</td>
<td>1.19–1.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>1.27</td>
<td>1.06–1.52</td>
<td>0.008</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>2.16</td>
<td>1.63–2.86</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease

Background: South Indians are known to be genetically predisposed to diabetes mellitus and cardiovascular diseases. There are several reports of emerging insulin resistance and metabolic syndrome among HIV-infected persons from the western population. This study reports insulin resistance, and consequently metabolic syndrome, among HIV-infected patients initiating highly active antiretroviral therapy (HAART) in Southern India and its outcomes.

Methods: Body mass index (BMI), fasting blood sugar, insulin, lipids (cholesterol, high-density lipoprotein [HDL]...
and triglyceride), 2 h oral glucose tolerance test (OGTT) and blood pressure were evaluated for 78 treatment-naive HIV-infected patients (35 years, 66% male, BMI 19.6 kg/m² and CD4 175 cells/mm³) and 22 HIV-negative individuals (34 years, 68% male and BMI 21.9 kg/m²) as controls at YRG CARE, Chennai, South India. Of the 78 HIV-infected individuals, 38 were initiated with efavirenz-based HAART, the nRTIs being zidovudine/stavudine+lamivudine and all the above parameters were repeated after 12 months of therapy. Homeostasis model assessment (HOMA) was calculated to assess insulin resistance (IR). Modified US National Cholesterol Education Program Adult Treatment Panel III (ATPIII) guidelines were used to define abnormal values.

**Results:** At baseline, in the HIV-positive and -negative groups, respectively, 40% and 36% had IR by HOMA (P>0.001), whereas BP, waist and HOMA were unchanged. The metabolic syndrome identified in five (13%) HIV-infected patients at baseline was decreased to three (7.9%) after 12 months of HAART because of the improvements in HDL.

**Conclusion:** This study shows a high frequency of metabolic syndrome among HIV-positive patients because of low HDL and high insulin resistance. Efavirenz-based HAART, due to its beneficial effect on HDL, has been protective against metabolic syndrome in the first 12 months in this study, but its long-term effects need to be studied. As HAART is available in large-scale government programmes, routine monitoring of metabolic parameters are essential to minimize cardiovascular risk.

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**ABSTRACT P-77**

*Antiviral Therapy 13 Suppl 4:A80*

**Gender differences in metabolic profile and cardiovascular risk among Latin American HIV-infected patients on HAART: RAPID II study**


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**Objective:** Gender difference in cardiovascular risk (CVR) among HIV-infected patients has been reported. Some studies showed higher risk for males, whereas others report the opposite. We compared metabolic profile and CVR by gender among Latin American HIV-infected patients receiving highly active antiretroviral therapy (HAART) using baseline data gathered from the Registry and Prospective Analysis of Patients Infected with HIV and Dyslipidemia (RAPID II) study.

**Methods:** A longitudinal study to evaluate the metabolic profile, CVR and associated treatment practices to reduce this risk, is being conducted in seven Latin American countries (the RAPID II study). Adult HIV-infected patients with at least 6 months of HAART were enrolled. An initial analysis of baseline data is presented here. Metabolic profile, anthropometric parameters, CD4 cell count, viral load determination, time on HAART, drug specific-based HAART, traditional risk factors for cardiovascular disease (CVD) and the 10-year risk of CVD, estimated using the Framingham risk equation were compared by gender using bivariate analysis.

**Results:** A total of 4,010 patients were enrolled, 2,963 (74%) were males. Mean age (sd) was 41.9 (10) years, mean time on HAART was 34.5 (30.8) months, 20.7% were on a protease inhibitor-based HAART, mean CD4 cell count was 467 (275) cells/mm³ and mean viral load was 4.12 (4.8) log₁₀ copies/ml. Men were found to have higher 10-year CVR with more male patients belonging to the high risk category (10-year CVR >20%). No gender difference was found in CD4 cell count, viral load, time on HAART and drug specific-based HAART. Female patients showed higher prevalence of obesity, metabolic syndrome and lack of physical exercise than males. In contrast, male patients were older, had higher prevalence of traditional...
risk factors for CVD such as smoking, hypertension and dyslipidaemia, and had higher 10-year CVR. More male patients belonged to the high risk category (10-year CVR >20%). See Table 1 for further results.

**Conclusions:** Baseline data from this cohort of HIV-infected Latin American adults on HAART showed an overall higher CVR in males, with higher rates of smoking, hypertension and dyslipidaemia. In contrast, obesity metabolic syndrome and lack of physical exercise were more frequent among women. Recognition of gender differences in this setting is important for appropriate intervention on modifiable CVR factors.

**ABSTRACT P-78**

*Antiviral Therapy 13 Suppl 4:A81*

Quality of life and body image in the assessment of psychological impact of facial lipoatrophy: construction and validation of assessment of face & body change and distress questionnaire

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**Aim:** Facial lipoatrophy (F-LA) stigmatises HIV-infected patients, which erodes a patient’s self-image and self-esteem, and causes problems in social and sexual relations, anxiety and depression.

**Methods:** We constructed and tested the validity of a new psychometric questionnaire to assess facial lipoatrophy and measure psychological distress. This questionnaire was coupled to the assessment and body change questionnaire, previously validated in Italian, and built into a single psychometric tool (assessment of face & body change and distress [ABCD-F questionnaire]. Correlations to physical and mental aspects of health-related quality of life were also analysed.

**Results:** Forty-two HIV-infected people of both gender and different ages attending HIV clinic in Modena University were interviewed (type-recorded) in six focus groups in order to evoke description of face lipoatrophy and psychological distress associated with this medical condition. Seventeen new items were added to the pre-existing ABCD questionnaire. Relevant included items were, ‘I fear people may understand I have HIV because of my facial wasting’, ‘I feel upset when people ask me why I have facial wasting’, ‘my facial wasting make me feel sad’ and ‘my facial wasting make me feel insecure in social setting’.

A total of 148 patients completed ABCD-F questionnaires. Interviewed patients were attending the clinic for a regular follow-up visit (74%) or because they were included in a plastic reconstructive surgery programme, with facial filler implants, to correct facial lipoatrophy (see Table 1 for patient demographics, HIV history and psychometric outcomes).

Construct validity of the ABCD-F was tested against the MOS-HIV Health Survey, body mass index (BMI) and CD4+ T-lymphocyte counts. Cronbach’s α for the ABCD-F total score was 0.95. The ABCD-F showed the expected moderate correlations to MOS-HIV scales and to patient or physician lipoatrophy severity score and BMI, but not to CD4.

Factorial analysis allowed the reduction of the 17 added questions in 11 items referring to the following main domains: psychological distress and role functioning.

**Conclusions:** Preliminary evidence supports the reliability and validity of the Italian version of the ABCD-F in people

**Table 1.** (Abstract P-77)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male patients</th>
<th>Female patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Framingham risk score, % (sd)</td>
<td>11.4 (24.7)</td>
<td>7.5 (24.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk category, %</td>
<td>11.1</td>
<td>6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>6.6</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>25.0</td>
<td>16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lack of exercise, %</td>
<td>51.7</td>
<td>58.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial blood, %</td>
<td>34.3</td>
<td>23.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>47.0</td>
<td>37.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidaemia, %</td>
<td>47.0</td>
<td>37.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>19.4</td>
<td>22.7</td>
<td>0.020</td>
</tr>
<tr>
<td>Type 2 diabetes, %</td>
<td>3.7</td>
<td>3.3</td>
<td>0.631</td>
</tr>
<tr>
<td>Current treatment for diabetes mellitus, %</td>
<td>3.0</td>
<td>1.9</td>
<td>0.076</td>
</tr>
</tbody>
</table>

*NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor.*
with HIV and F-LA. This questionnaire may be useful to identify people experiencing greater impact of F-LA, or to evaluate the impact of interventions to treat LD, such as plastic surgery.

**ABSTRACT P-79**

*Antiviral Therapy* 13 Suppl 4:A82

**Brazilian politics on lipodystrophy treatment in the public health system**

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**Introduction:** Brazilian STD/AIDS National Programme started actions on HIV-facial lipoatrophy treatment in 2003 creating a lipodystrophy working group, which comprised dermatologists, plastic surgeons and government technicians from different country regions. This working group established a research protocol, and studied and compared several products used for facial lipoatrophy treatment on technical aspects and their applicability in the public health system. Results were very positive, and showed that polymethylmethacrylate (PMMA) on facial lipoatrophy treatment was the better option when analysing treatment results and cost/benefits, which turns to be possible to use on large scale in the Brazilian public health system. With these results, Brazilian STD/AIDS National Programme’s next step was to elaborate a training project to qualify physicians on facial lipoatrophy treatment with PMMA, especially dermatologists and plastic surgeons, who work in the public health services all over the country. This project started in 2005.

**Methods:** Brazilian doctors with expertise on PMMA implants for HIV facial lipoatrophy were contracted to conduct the training courses for physicians and all professionals involved with AIDS treatment with the objective of implementing this action and guarantee access to this treatment for people living with HIV and AIDS.

**Results:** Between April 2005 and December 2006, six training workshops were done in the five macro regions of the country. The objectives of the workshops were to discuss lipodystrophy and to mobilize health workers, people living with HIV/AIDS and public health managers. The workshops were attended by 225 people: 124 doctors, 42 state and municipals coordinators of sexually transmitted disease/AIDS programmes, 44 social organization delegates and 15 health professionals (psychologists and social workers). Between 2006 and 2008, training and supervising workshops were exclusively aimed at doctors. At present, a total of 77 professionals have attended.

**Discussion:** After these actions, the Brazilian Ministry of Health established a governmental decree in March of 2007 to establish the treatment for lipodystrophy in Brazilian public hospitals by offering two types of interventions: facial lipoatrophy treatment with polymethylmethacrylate (PMMA) and repairing plastic surgery for fat accumulation, especially in the belly, breasts and dorsum cervical (buffalo humps). At this moment, eight public hospitals had attempted to conform to the decree and are started with the procedures. For 2009, the objective is to have 64 public services offering 4,800 facial lipoatrophy treatment and 29 public hospitals realizing 1,600 plastic surgeries. These estimated numbers were based on the numbers of patients taking highly active antiretroviral therapy in the country, which now totals 184,000 persons, and the operative capacity of the public hospitals and health services established in the Brazilian public health system.
Screening for liver fibrosis in HIV-monoinfected patients with increased ALT comparing FibroScan with FIB-4

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Objectives: Increased alanine aminotransferase (ALT) values are frequently observed in HIV-monoinfected patients. Recent studies have reported cases of cryptogenic liver cirrhosis in HIV-positive individuals. Other possible explanations are non-alcoholic or alcoholic steatohepatitis and drug toxicity. We have used two non-invasive methods (liver elastometry [FibroScan, Echosens, Paris] and a serologic fibrosis index [FIB-4]) for liver fibrosis screening in a single centre.

Methods: HIV-infected patients without hepatitis B and C coinfection with at least one increased ALT in 2007/2008 (males >50 U/l, females >35 U/l) were selected for liver elastometry by FibroScan. Antiretroviral medication, comedication, alcohol consumption, smoking, recreational drug use and body mass index (BMI) were assessed. Liver stiffness was classified as <7.2 kPa (no/minimal fibrosis), 7.2–12.5 kPa (moderate fibrosis), >12.5–17.6 kPa (severe fibrosis) and >17.6 kPa (cirrhosis). FibroScans were performed by two trained and experienced investigators (high interobserver correlation, r=0.80, P<0.05). FIB-4 index (age [years] × aspartate aminotransferase [U/l]/platelets [10^9/l] × ALT^0.5 [U/l]) was used for serologic fibrosis assessment. For statistical evaluation SPSS 15.0 was used.

Results: Out of 1,098 HIV-infected individuals, 227 had increased ALT without hepatitis coinfection. Eighty-one patients were consecutively screened by FibroScan. A valid elastometry was obtained in 79/81 (98%) patients. In total, 76/81 were male, median age was 45 years (27–71), median BMI was 24.6 kg/m² (19.1–33.7), median ALT was 60 U/l (38–144) and 70/81 (86%) were on antiretroviral therapy for a median duration of 76 months. HIV RNA was <40 copies/ml in 63/70 (90%) treated patients. Median CD4^+ T-cell count was 618 cells/µl (130–1,635). Alcohol consumption was >24 g/day (males) or >12 g/day (females) in 11% of patients, 41% were smokers and 17% reported consumption of recreational drugs. Median liver stiffness was 5.2 kPa (3.1–8.8). No/minimal fibrosis was found in 70/79 (89%) and moderate fibrosis in 9/79 (11%). No patient had severe fibrosis or cirrhosis. With FIB-4, 62/81 (77%) patients had no/minimal fibrosis, 18/81 (22%) had moderate fibrosis and 1/81 (1%) had advanced fibrosis.

Conclusions: In this ongoing study, approximately 20% of HIV-monoinfected patients had increased ALT. Advanced liver fibrosis was rare in this cohort of HIV-monoinfected individuals and there was good agreement between FibroScan and FIB-4.

Statistical agreement between ultrasound (US) and computerized tomography (CT) for non-alcoholic liver disease (NAFLD) diagnosis

C Stentarelli, S Ballestri, S Zona, L Amedeo, R D’amico, N Squillace, G Orlando, P Loria and G Guaraldi

Objectives: To assess the Cohen’s Kappa statistic of non-invasive imaging evaluations to diagnose non-alcoholic liver disease (NAFLD) by means of ultrasound (US) fatty liver index score and liver-to-spleen attenuation ratio (L/S) by computerized tomography (CT).

Methods: This was a cross-sectional, observational study that included all consecutive HIV-infected patients seen at a metabolic clinic who were screened for NAFLD with US and CT in the same day. Individuals with hepatitis C virus, hepatitis B virus and heavy alcohol users (>20 g/day) were excluded. With CT, NAFLD diagnosis was defined with an L/S<1.1. US scanning was performed by a single operator; the criterion for steatosis was hyperechogenic liver tissue with fine, tightly-packed echoes. The degree of steatosis was assessed by the fall in echo amplitude with depth (rate of posterior beam attenuation), increasing discrepancy of echo amplitude between liver and kidney and loss of echoes from the walls of the portal veins. With US, NAFLD was defined with a score ≥2.

Results: In total, 46 patients were included. NAFLD prevalence with US was 19.57% and with CT was...
50.00% (See Tables 1 and 2). Moreover, Cohen’s Kappa coefficient between L/S\( \leq 1.1 \) and US score \( \geq 3 \) was 0.45 (80.43% agreement) and between US score \( \geq 4 \) was 0.29 (80.43% agreement).

**Discussion:** Non-invasive imaging agreement between US and CT to diagnose NAFLD is less than ideal. Best concordance is found for US\( \geq 3 \) and L/S\( \leq 1.1 \). Liver biopsy studies are needed to validate cutoff of US evaluation and L/S in people living with HIV.

**ABSTRACT P-82**

*Antiviral Therapy 13 Suppl 4: A84*

**Acute liver failure associated with efavirenz-based HAART requiring liver transplantation in a child**

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The role of antiretrovirals is often implied in liver toxicity, but they rarely cause acute liver failure (ALF). We report the case of a 9-year-old boy who developed ALF requiring liver transplantation 13 weeks after starting efavirenz-based antiretroviral therapy (ART).

The child was diagnosed with HIV at 8 months of age and was started on zidovudine, didanosine and nelfinavir. At 9 years of age he had a structured treatment interruption for 10 months, which had to be discontinued in view of recurrent pharyngitis, generalized lymphadenopathy and increasing viral load. He was restarted on Kivexa (lamivudine plus abacavir) and efavirenz, which was subsequently changed to zidovudine, lamivudine and efavirenz because of a rash thought to be related to abacavir. The liver function tests in 2 weeks were normal. Thirteen weeks after ART was re-started he developed jaundice, hepatomegaly, and severely deranged liver function and clotting. His lactate at presentation was normal. There was no eosinophilia, but his immunoglobulin E level was significantly increased. The extensive investigations failed to find a cause for his ALF. Histology of the explanted native liver showed severe hepatitis with multicellular parenchymal cell necrosis without features of mitochondrial toxicity. He had a stormy 3 months in a paediatric intensive care unit and required 2 liver transplants. Having excluded all common causes of ALF, it is possible that the severe liver injury in our patient was related to ART. Nucleoside reverse transcriptase inhibitors are unlikely to be involved as there was no increased lactate or evidence of mitochondrial toxicity on liver histology. Efavirenz, however, may be implicated.

<table>
<thead>
<tr>
<th>Table 1. (Abstract P-81)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
</tr>
<tr>
<td>Duration of HIV infection, months (range)</td>
</tr>
<tr>
<td>CD4+ T-cell count</td>
</tr>
<tr>
<td>Log10 viral load</td>
</tr>
<tr>
<td>NNRTI cumulative exposure, months (range)</td>
</tr>
<tr>
<td>PI cumulative exposure, months (range)</td>
</tr>
<tr>
<td>PI cumulative exposure, months (range)</td>
</tr>
<tr>
<td>AST/ALT</td>
</tr>
<tr>
<td>Waist</td>
</tr>
</tbody>
</table>

*Two-sample test of proportion. †Two-sample unpaired t-test. ‡Wilcoxon signed-rank test. ALT; alanine aminotransferase; AST, aspartate aminotransferase; CT, computerized tomography; NAFLD, non-alcoholic liver disease; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; US, ultrasound.

<table>
<thead>
<tr>
<th>Table 2. (Abstract P-81)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US+ CT+</strong></td>
</tr>
<tr>
<td>All patients (n=70)</td>
</tr>
<tr>
<td>Subgroup without HCV infection (n=46)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CT, computerized tomography; HCV, hepatitis C virus; US, ultrasound.
Background: Chronic hepatitis C and B virus infection are the main risk factors for HCC development. HIV coinfected has been shown to increase the progression of liver fibrosis and therefore is likely to increase the incidence of HCC.

Methods: A retrospective analysis was performed in an HIV outdoor unit in South of France following near 1,000 HIV-infected patients with 40% hepatitis C virus (HCV)-coinfected individuals. Data of patients with HCC diagnosed from January 1996 to June 2008 was selected from our HIV clinical database. The demographic, clinical (tumour presentation and staging) and biological (HIV viral load, CD4+ T-cell count, HCV genotype [G], α-fetoprotein level [AFP] and Metavir fibrosis score) characteristics at the time of HCC were analysed.

Results: A total of 18 cases of HCC (5 between January 1996 to December 2001 and 13 between January 2002 to June 2008) have been recorded. The data of 10 cases of HCC diagnosed between January 2002 to June 2008 have been up to now analysed. Of these, 90% were male with a mean age of 45 (36–60) years. The median CD4+ T-cell count and viral load was 334/mm³ and 2.7 log/ml, respectively. Nine patients were HIV–HCV-coinfected (G1 n=4, G3 n=4 and undetermined n=1) and one hepatitis B-coinfected. The Metavir fibrosis score was F3 in one case, F4 in six and unknown in one. Tumour staging according to TNM classification was T1 n=1, T2 n=3 and T4 n=6 (T4a n=4 and T4b n=2); three patients were N1 and three patients were M1 at the time of HCC diagnosis. The mean size of the largest tumour nodule was 53 (10–160) mm. Median AFP level was 604 ng/ml (minimum 12.3, maximum 158,447). Among the six patients previously treated for HCV infection before HCC, one patient had a sustained virological response (SVR) for 5 years. The Metavir fibrosis score for this patient was F3. The median survival of these 10 patients was 5.4 (1.9–69) months. Six patients died of HCC and one of them died 25 months after a liver transplantation.

Conclusions: The number of HCC cases in our clinical database has increased since 2001. In most cases, HCC has been detected at advanced stages with a poor survival and, in one case, in a patient with a long-term SVR after anti-HCV therapy. These results argue for a prospective detection of HCC in HIV–HCV-coinfected patients, which should concern not only patients with cirrhosis and also patients with SVR after anti-HCV therapy.
ABSTRACT P-84

Antiviral Therapy 13 Suppl 4:A87

Tenovir affects kidney mtDNA and cellular energetic homeostasis

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Hannover Medical School, Hannover, Germany

Objective: In randomized clinical trials, tenofovir (TDF) has rarely been associated with overt renal damage. However, case reports indicate that TDF could lead to tubular damage, which has been hypothesized to result from mitochondrial toxicity.

Methods: Groups of mice were treated with TDF, zidovudine, stavudine or vehicle (20 mice per group) for as long as 9 months with daily human doses adjusted for murine body surface area. To better parallel the pharmacokinetics in humans, drugs were administered via oral gavage. Kidney mitochondrial DNA (mtDNA) content was determined by real-time polymerase chain reaction. The activity of respiratory chain complexes IV and V as well as ATP/ADP ratio were measured photometrically.

Results: Over a period of 9 months, mice receiving TDF gained similar weight and intra-abdominal fat as compared with control animals, and no differences in food and water intake were detected. Analyses of kidney mtDNA content revealed depletion of mtDNA (control 100 ±21%, TDF 39 ±7%, P=0.0317) concomitant with decreased ATP/ADP ratio (control 100 ±7%, TDF 56 ±3.5%, P=0.0004). Interestingly, the activity of complex IV and V from oxidative phosphorylation chain were unaffected. No effects were observed on the circulating levels of adipokines, such as adiponectin and visfatin, or on the glucose tolerance of the treated animals.

Conclusions: In our mouse model, long-term TDF treatment was able to deplete mtDNA in the kidney and to disturb the cellular energetic status of cells this organ.

ABSTRACT P-85

Antiviral Therapy 13 Suppl 4:A87

Evaluation of renal safety for lopinavir/ritonavir (LPV/r) tablets dosed once daily (QD) or twice daily (BID) administered with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in antiretroviral-naive (ARV) subjects: results from Study M05-730

BA da Silva, D Cohen, S Gibbs, L Fredrick and B Bernstein
Abbott Laboratories, Abbott Park, IL, USA

Background: TDF-associated nephrotoxicity has been previously described with studies showing median declines in creatinine clearance (CrCl) of up to 7–8 ml/min. LPV/r increases TDF levels by approximately 30%. Renal safety when LPV/r and TDF are combined is of clinical relevance.

Methods: A total of 664 antiretroviral-naive individuals randomized to LPV/r QD or BID plus TDF+FTC. Safety (based on adverse events [AEs]), renal-associated laboratory parameters and CrCl (as calculated by Cockcroft–Gault formula [CG] and Modification of Diet in Renal Disease [MDRD] equations) were compared through 48 weeks. Dose frequency adjustment of TDF begins at CrCl of 49 ml/min; therefore, CrCl cutoffs were chosen to identify individuals with renal dysfunction and those with a decline in renal function.

Results: Baseline parameters and changes from baseline are listed in Table 1. There were small statistically significant mean changes from baseline at P=0.001, P=0.01 and P=0.05 level, respectively. There were no statistically significant differences between QD and BID changes from baseline. CG, Cockcroft–Gault formula; CrCl, creatine clearance; MDRD, Modification of Diet in Renal Disease.

| Table 1. Mean change from baseline to week 48 (Abstract P-85) |
|-------------------|-----------------|-----------------|-----------------|-----------------|
|                   | QD (n=295)      | BID (n=280)     | Overall (n=575) |
|                   | Baseline mean  | Week 48 mean   | Mean change    | Baseline mean  | Week 48 mean   | Mean change    | Baseline mean  | Week 48 mean   | Mean change    |
| Creatinin, µmol/l| 81.9            | 86.7            | 4.8†            | 82.1            | 85.2            | 3.0†            | 82.0            | 85.9            | 4.0†            |
| Urea, mmol/l     | 5.06            | 5.35            | 0.29†           | 4.90            | 5.34            | 0.44†           | 4.98            | 5.34            | 0.37†           |
| CrCl (CG)*, ml/min| 112.7           | 109.7           | 3.0†            | 110.7           | 108.0           | 2.6†            | 111.6           | 108.8           | 2.8†            |
| CrCl – (MDRD), ml/min/1.73 m²| 98.3            | 91.5            | 6.8†            | 98.0            | 93.4            | 4.6†            | 98.2            | 92.4            | 5.7†            |

* n=290 (once daily [QD]), n=276 (twice daily [BID]) and n=566 (overall). Statistically significant mean change from baseline at P<0.001, P<0.01 and P<0.05 level, respectively. There were no statistically significant differences between QD and BID changes from baseline. CO, Cockcroft–Gault formula; CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease.
significant mean decreases from baseline in CrCl (CG) and CrCl (MDRD) through 48 weeks; however, mean levels remained >100 ml/min and 90 ml/min/1.73m², respectively. Of the 539 subjects with baseline CrCl (CG) ≥70 ml/min, 21 (3.9%) had levels <70 ml/min at week 48. Of the 265 subjects with baseline CrCl (CG) ≥50 ml/min, 2 (0.4%) had levels <50 ml/min at week 48. In total, 6.8% of subjects had a >25% decrease in CrCl (CG) and no subjects had >50% decline in CrCl (CG). Similar findings were noted when CrCl was calculated using the MDRD equation. Lower baseline CrCl, higher age and lower body mass index were predictive of decreased CrCl (<70 ml/min) at week 48. No subjects discontinued for renal-related AEs. Four individuals (0.6%) interrupted antiretrovirals for renal aetiologies. Four additional individuals (0.6%) discontinued TDF and initiated alternative reverse transcriptase inhibitor therapy.

Conclusions: Renal dysfunction was an infrequent complication of therapy and rarely resulted in TDF interruption or discontinuation. Changes were similar or less than those previously reported in literature. Lower baseline CrCl, higher age and lower body mass index were predictive of decreased CrCl at week 48.
ABSTRACT P-86
Antiviral Therapy 13 Suppl 4:A89

Adrenocortisol suppression induced by the interaction between ritonavir and different inhaled corticosteroids

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Background: Case reports of Cushing’s syndromes have been reported with the use of fluticasone (an inhaled corticosteroid) and ritonavir (used as a booster for protease inhibitors). Indeed, drugs acting on cytochrome P450 increase the systemic bioavailability of inhaled corticoid and can induce systemic reactions. We performed a prospective study to evaluate the frequency of this problem in our HIV patients.

Methodology: All HIV patients seen in the past 6 months at our clinic were screened for the concomitant use of inhaled corticosteroids and baby-dose of ritonavir. In cases of this association, we systematically performed basal and 60 min post-synacthene cortisolaemia and basal ACTH dosage (after 3 days of interruption of inhaled corticosteroids). We excluded patients treated with systemic steroids.

Results: A total of 402 patients were evaluated for concomitant use of inhaled corticosteroid and ritonavir. Eighteen patients (six women, median age 54 years) were concerned by this association. All with ritonavir 100 mg/day (N=2). Thirteen patients were on budesonide (800 µg/day, mean length of treatment 20 months [6–46]), four patients were on fluticasone (1,000 µg/day, mean length of treatment 43 months [9–85]) and one patient was on budesonide. Eight of 13 patients on budesonide and three of four on fluticasone were adrenocortical suppressed. No influence of duration of inhaled corticoids treatment on the occurrence of adrenal suppression. No acute clinical adrenal insufficiency (the only symptom reported by patients at the time of the study was asthena). For the adrenal suppressed patients, clinicians switched either the inhaled corticoid treatment or the ART treatment (stopping ritonavir).

Conclusion: Adrenal suppression is a common event in patients treated by inhaled corticosteroids and baby-dose ritonavir and might be undiagnosed if not routinely monitored. Even in a prospective study, we found profound adrenal insufficiency needing systemic supplementation. Fluticasone was already known for this interaction, but budesonide was also of concern.

ABSTRACT P-87
Antiviral Therapy 13 Suppl 4:A89

Diagnosis and treatment of ritonavir (RTV)-induced iatrogenic Cushing syndrome with secondary adrenal insufficiency in an HIV-infected adult receiving inhaled fluticasone

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Chiba Prefectural Togane Hospital, Chiba, Japan

Objectives: Ritonavir (RTV), a protease inhibitor (PI), is a potent inhibitor of cytochrome P450 3A4. Therefore, RTV is usually used as a boosting agent in antiretroviral therapy (ART) as it increases in dosing area under the curve of the second PI. An advantageous drug–drug interaction reduces the pill burden and increases the dosing intervals, thereby facilitating adherence to ART. We report a case of a 37-year-old HIV-infected female with Cushing syndrome caused by the inhaled steroid analogue fluticasone propionate (FP) and accompanied by bronchial asthma.

Results: After changing anti-HIV agents from a combination of stavudine, atazanavir and lamivudine to that of emtricitabine and ritonavir-boosted PIs (atazanavir and tenofovir), the patient developed cushingoid symptoms, such as striae cutis, moon face and weight gain. The blood FP concentration at 8 h after inhalation of 200 µg FP was 0.279 ng/ml. Her adrenocorticotropic hormone (ACTH) level was <5.0 pg/ml (undetectable) and cortisol level <1.0 µg/ml. This pharmacokinetic study and endocrinological examination revealed that FP metabolism by hepatic CYP3A4 was inhibited by oral RTV administration; the patient showed obvious iatrogenic Cushing syndrome and developed adrenocortical insufficiency. ART was continued in the same combination because the viral load was well under control and the concentration of inhaled FP was tapered with careful monitoring of the cortisol level to avoid adrenocortical insufficiency; FP inhalation was replaced by inhaled beclomethasone dipropionate, another synthetic steroid, for the treatment of bronchial asthma.

Discussion: Practitioners should be aware of the effect of coadministration of PI-based ART regimens with inhaled corticosteroids on the adrenal axis. Further, pharmacokinetic study with a detailed analysis of the FP level in blood samples and measurement of the morning ACTH
and cortisol levels greatly contributed to hormone replacement therapy leading to successful recovery from adrenal insufficiency.

**ABSTRACT P-88**

*Antiviral Therapy 13 Suppl 4:A90*

**Age-related comorbidities in people living with HIV**

G Guaraldi1, S Zona1, G Orlando1, N Squillace1, C Sientarelli1, G Nardini1, B Beghetto1, R Esposito1 and F Palella11, 2

1Clinic of Infectious Diseases, Department of Medicine and Medical Specialities, University of Modena and Reggio Emilia, Modena, Italy; 2Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, Il, USA

**Objectives:** To describe prevalence of age-related morbidities across age groups in people living with HIV/AIDS and to analyse care needs in the elderly people.

**Methods:** Consecutive patients attending a metabolic clinic were recruited for this study. Body fat changes, metabolic, cardiovascular, endocrine and renal morbidities were identified as relevant medical conditions requiring drug intervention (either a switch of antiretrovirals or introduction of specific drug classes).

**Results:** See Table 1.

**Discussion:** Metabolic, cardiovascular endocrine, hepatic and kidney disease are age-associated conditions highly prevalent in people living with HIV. Multiple comorbidities increase with age and witness the multidisciplinary care needs of HIV aging population.

**ABSTRACT P-89**

*Antiviral Therapy 13 Suppl 4:A90*

**Measuring gastrointestinal adverse events in clinical trials**

A Hill1,2, M Prakash2 and C Moecklinghoff 2

1Liverpool University, Liverpool, UK; 2Tibotec BVBA, Mechelen, Belgium

**Background:** Gastrointestinal (GI) adverse events (AEs) are one of the most common side-effects of antiretrovirals and can be a leading cause of treatment discontinuation.

<table>
<thead>
<tr>
<th>≥30 Years (n=38)</th>
<th>30-40 years (n=551)</th>
<th>40-50 years (n=1,216)</th>
<th>50-60 years (n=253)</th>
<th>≥60 Years (n=69)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>19 (50)</td>
<td>276 (50.09)</td>
<td>765 (62.91)</td>
<td>205 (81.03)</td>
<td>54 (78.26) &lt;0.001</td>
</tr>
<tr>
<td>Age at HIV diagnosis, years</td>
<td>13.86 ±11.33</td>
<td>25.24 ±49.97</td>
<td>29.63 ±6.05</td>
<td>41.66 ±6.03</td>
<td>53.98 ±6.94 &lt;0.001</td>
</tr>
<tr>
<td>HIV duration, months</td>
<td>127.09 ±89.36</td>
<td>146.78 ±63.02</td>
<td>182.57 ±64.86</td>
<td>154.40 ±65.81</td>
<td>135.75 ±62.49 &lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.00 ±2.19</td>
<td>23.17 ±3.95</td>
<td>23.23 ±3.91</td>
<td>24.74 ±4.36</td>
<td>25.21 ±4.37 &lt;0.001</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>0</td>
<td>25 (4.54)</td>
<td>65 (5.35)</td>
<td>26 (10.28)</td>
<td>9 (13.04) 0.001*</td>
</tr>
<tr>
<td>HOMA IR, median (range)</td>
<td>2.51 (0.10–14.15)</td>
<td>2.76 (0.55–31.16)</td>
<td>3.38 (0.18–80.88)</td>
<td>3.89 (0.17–43.37)</td>
<td>3.46 (0.89–97.40) &lt;0.001</td>
</tr>
<tr>
<td>Body fat changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipodistrophy, n (%)</td>
<td>9 (23.68)</td>
<td>239 (43.38)</td>
<td>562 (46.22)</td>
<td>133 (52.57)</td>
<td>35 (50.72) 2</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidaemia (TC≥200 mg, TG&gt;150 mg), n (%)</td>
<td>17 (44.74)</td>
<td>386 (70.05)</td>
<td>880 (72.37)</td>
<td>209 (82.61)</td>
<td>63 (91.30) &lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome (ATPIII), n (%)</td>
<td>3 (7.89)</td>
<td>69 (12.52)</td>
<td>257 (21.13)</td>
<td>92 (36.36)</td>
<td>25 (36.23) &lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (26.32)</td>
<td>180 (32.67)</td>
<td>400 (32.89)</td>
<td>123 (48.62)</td>
<td>30 (43.48) &lt;0.001</td>
</tr>
<tr>
<td>MIcardial infarction, n (%)</td>
<td>0</td>
<td>1 (0.18)</td>
<td>16 (1.32)</td>
<td>9 (3.56)</td>
<td>8 (11.59) &lt;0.001*</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>5 (13.16)</td>
<td>39 (7.08)</td>
<td>146 (12.01)</td>
<td>55 (21.74)</td>
<td>24 (34.78) &lt;0.001</td>
</tr>
<tr>
<td>Osteoporosis, n (%)</td>
<td>0</td>
<td>1 (0.18)</td>
<td>3 (0.25)</td>
<td>1 (0.40)</td>
<td>0 0.73*</td>
</tr>
<tr>
<td>Hypothyroidism, n (%)</td>
<td>4 (10.53)</td>
<td>60 (10.89)</td>
<td>125 (10.28)</td>
<td>20 (7.91)</td>
<td>9 (13.04) 33</td>
</tr>
<tr>
<td>Kidney disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency (MDRD&lt;60 ml/min), n (%)</td>
<td>1 (2.63)</td>
<td>14 (2.54)</td>
<td>58 (4.77)</td>
<td>21 (8.30)</td>
<td>11 (15.94) &lt;0.001</td>
</tr>
</tbody>
</table>

ANOVA was used for means and χ2 test for proportions unless indicated otherwise. *Fisher’s exact. †Kruskal–Wallis. Prevalence of ≥3 comorbidities in the age group were 7.89% for age ≤30, 24.68% for ages 30–40, 33.72% for ages 40–50, 49.01% for age 50–60 and 60.87% for age >60 years.
However, immunosuppression from HIV infection and infections of the GI tract can also contribute to GI symptoms. Standardized methods would help to assess GI AEs in meta-analyses of clinical trials.

**Methods:** A MEDLINE search for primary publications of clinical trials of antiretrovirals identified trials with data available on GI AEs using the NIAID (DAIDS) classification system. In each trial, GI AEs (diarrhoea, nausea and vomiting) were graded as either 1 (mild), 2 (moderate), 3 (severe) or 4 (life-threatening) and judged to be treatment-related (TR) or unrelated. The endpoints used to classify AEs were recorded for each trial. For the most common endpoint (grades 2–4 TR AEs to week 48), rates of GI AE were compared between treatments.

**Results:** There were 53 trials with graded GI AEs reported. GI AEs were reported in seven different ways: grades 1–4 all cause (AC; 9 [17%]), grades 1–4 TR (4 [8%]), grades 2–4 AC (6 [11%]), grades 2–4 TR (21 [40%]), grades 3–4 AC (9 [17%]), grades 3–4 TR (1 [2%]), AEs leading to discontinuation of treatment (9 [17%]) – six trials reported GI AEs using two systems. The percentage of patients with GI AEs were highly dependent on the endpoint used, for example, in the ALERT trial of FPV/r, 53% of patients had grades 1–4 diarrhoea AEs versus 8% with grades 2–4 TR diarrhoea. Using the most commonly used endpoint of grades 2–4 TR AEs, the median prevalence of grades 2–4 diarrhoea after 48 weeks in naïve patients was 15.5% for LPV/r (interquartile range 12.5–17.5%, 10 trials), 14% for FPV/r, 4% for DRV/r and 2% for ATV/r.

**Conclusions:** Several different endpoints have been used to assess GI AE in HIV clinical trials. Most GI AEs were grade 1 and judged unrelated to study medication. The use of a standardized endpoint appears to lead to similar rates of GI AE’s across similar trials of a standard treatment and consistent differences within the PI class.

**ABSTRACT P-90**

*Antiviral Therapy* 13 Suppl 4:A91

**Gender differences in depression evolution in a cohort of patients attending a metabolic clinic for lipodystrophy management**

**G Orlando, N Squillace, B Beghetto, G Nardini, I Mazeu and G Guaraldi**

Infectious Disease Clinic, Department of Medicine and Medical Specialities, University of Modena and Reggio Emilia, Italy

HIV-related body changes could stigmatize patients, producing an erosion of self-image and self-esteem, problems in social and sexual relations, anxiety and depression. The purpose of our study was to evaluate gender differences in the evolution of depression among patients attending a metabolic clinic for lipodystrophy (LD) diagnosis and treatment.

Patients referring to Modena and Reggio Emilia University metabolic clinic, receiving multidisciplinary treatment for face or body LD, were enrolled. At baseline, biochemical, viroimmunological parameters and LD diagnosis according to MACS classification were collected. At baseline and after 48 weeks, patients filled the Beck Depression Inventory Scale questionnaire (BDI; total possible scores ranged 0–63, mild depression 9–17, moderate depression 18–29 and severe depression >30).

A total of 272 patients enrolled, 36.4% female, median age 47 (7) years and CDC group C 28.7%. At baseline, 59.2% had undetectable viral load and 91.9% had CD4+ T-cell count >200 cell/µl. The percentage of patients that had lipoatrophy, lipohypertrophy and mixed forms was 41.7%, 2.6% and 43.8%, respectively. Patients that underwent surgical treatment for face lipoatrophy during the follow-up period totalled 72.4% (70.6% male and 29.4% female). At baseline, women median (interquartile range) BDI score was significantly higher than that of men: 13 (12) versus 10 (10), *P* = 0.030. There was no statistically significant difference in BDI baseline median scores comparing patients with or without LD and those with different forms of LD.

After 48 weeks BDI median score improved significantly in sample 11 (11) versus 9.5 (12), *P* = 0.001, and in male patients 10 (10) versus 9 (11), *P* = 0.001, but not significantly in women 13 (12) versus 11 (14) *P* = 0.110, even distinguishing women on menopause or not. Among patients undergoing surgical treatment for face lipoatrophy, men only experienced a statistically significant improvement of BDI in the follow-up period: women 12.5 (15.7) versus 12 (13.2, *P* = 0.114) and men 11 (10) versus 9 (10, *P* < 0.0001). As demonstrated in the general population, women with HIV infection seem to be more vulnerable than men to experiencing more severe depression symptoms that still remain even after face lipoatrophy treatment. This issue underlines the need for new studies analysing the gender peculiarity of depression among patients with HIV infection.
ABSTRACT P-91

Antiviral Therapy 13 Suppl 4:A92

Body image is a major determinant of sexual dysfunction in stable HIV-infected women

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Background: Prevalence and factors associated with sexual dysfunction (SD) in HIV-positive women are poorly known. Methods: Cross-sectional studies were carried out in a cohort of HIV-infected women. Clinically stable women were offered to participate in an SD evaluation using the Female Sexual Function Index (FSFI) exploring desire, arousal, lubrication, orgasm, pain and satisfaction. An FSFI score <23 was used for defining SD. The variables evaluated were body appearance satisfaction and interference of body changes with habits, social life, health-related quality of life, hormonal assessment, menopause, cumulative exposure to antiretroviral drug classes and immune-virological parameters. Lipodystrophy was defined according to HIV Outpatient Study definition.

Results: A total of 185 women completed the FSFI. Mean age was 42 years (SD ±5), 27% CDC stage C, mean CD4+ T-cell count 508 cells/μl (SD ±251) and median log HIV RNA 1.7 copies/ml (interquartile range 1.7–2.6). Among 161 evaluable patients, 59 (32%) reported SD. In a multiple linear regression analysis, desire, arousal and satisfaction domains were associated with interference of body changes with habits, social life, health-related quality of life, hormonal assessment, menopause, cumulative exposure to antiretroviral drug classes and immune-virological parameters. Lipodystrophy was defined according to HIV Outpatient Study definition.

Discussion: SD was highly prevalent in this cohort. Self-perceived body changes were identified as its major determinant.

ABSTRACT P-92

Antiviral Therapy 13 Suppl 4:A92

Measurement of 3-methylhistidine in spot urine from HIV-infected persons: an alternative screening method for muscle protein degradation to serum CK?

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1Department of Rheumatology and Clinical Immunology, University Hospital Freiburg, Germany; 2Department of Clinical Chemistry, University Hospital Freiburg, Freiburg, Germany

Background: 3-methylhistidine (3-MH) acts as an in vivo label of the rate of myofibrillar protein breakdown. The aim of this study was to evaluate 3-MH measurement in spot urine as a simple screening method for muscle protein degradation in HIV-infected persons compared with creatine kinase (CK) measurement in blood.

Methods: We prospectively measured serum creatinine (mg/dl) and serum CK (U/l) and 3-MH (μmol/l) in spot urine from 162 HIV-positive patients at each visit. 3-MH was determined by HPLC after derivatization with fluorescamine.

Results: Overall, 162 HIV-positive patients were screened; two patients were excluded because of renal dysfunction. A total of 160 HIV-positive patients (101 male) entered the study and a total of 397 visits were analysed. The median age at all visits was 44 years (range 21–75). Body mass index (BMI) was 24.8 ±5.1 (men 24.9 ±0.29 and women 24.5 ±0.48). Patients were without antiretroviral treatment (ART) at 24% of visits and had an undetectable serum HIV load (<50 copies/ml) at 50% of visits. The median CD4+ T-cell count was 437 cells/μl (SD ±205.1). CK, creatinine and 3-MH did not correlate with the number of visits. A positive correlation with the BMI was found for CK and creatinine, but not for 3-MH. Compared with men, women had significantly lower levels of 3-MH (195.5 ±10.5 versus 252.2 ±9.6, P=0.0002), creatinine (0.68 ±0.01 versus 0.85 ±0.01, P<0.0001) and CK (106 ±7.6 versus 156.9 ±8.2, P<0.0001). Patients with CK levels >300 U/l (n=31) had significantly higher 3-MH levels than patients with CK <50 U/l (n=41, P=0.037). Otherwise there was no correlation between CK and 3-MH. ART in general, and zidovudine (177 visits) and tenofovir (90 visits) in particular, did not influence the levels of CK, creatinine and 3-MH.

Conclusion: In conclusion, measurement of 3-MH on spot urine samples is not useful for assessing changes in muscular protein degradation. A meat-free diet, 24 h urine collection and refraining from physical activity might reduce confounding factors of 3-MH secretion.