Abstracts presented at the
14th International Workshop on Co-morbidities and
Adverse Drug Reactions in HIV
Washington DC, USA, 19–21 July 2012
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International Medical Press
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ORAL PRESENTATIONS
ABSTRACT 001

Antiviral Therapy 2012; 17 Suppl 2:A3

Progression and spontaneous regression of high-grade anal intraepithelial neoplasia in HIV-infected and uninfected men

WWY Tong1, F Jin2, L McHugh1, T Maher1, B Sinclair1, R Hillman1, A Carr1

1Centre for Applied Medical Research, St Vincent’s Hospital, Sydney, Australia; 2Kirby Institute for Infection and Immunity in Society, University of New South Wales, Sydney, Australia; 3Westmead Hospital, Sydney, Australia

Objectives: Controversy exists as to whether high-grade anal intraepithelial neoplasia (HGAIN) necessitates treatment. Spontaneous regression of HGAIN has not been reported. At St Vincent’s Hospital, a dedicated AIN clinic was established in 2004. As HGAIN was not routinely treated in this clinic, we reviewed the rates of progression to, and regression of, histologically-confirmed AIN3. Age, HIV status, HIV duration, and CD4+ T-cell counts were examined for relationship with AIN3 progression or regression.

Methods: We retrospectively reviewed all AIN clinic patients through January 2011. Histology diagnoses were abstracted as per current terminology, as well as age, date of HIV diagnosis and CD4+ T-cell counts. The cohort enrolment date was set as the date of each participant’s first anal pap smear or high-resolution anoscopy (HRA). Progression was defined as having histologically confirmed AIN3 with preceding lower-grade histology, normal HRA or negative cytology. Regression was defined as histologically confirmed AIN3 that proceeded to lower-grade histology, normal HRA or negative cytology. For both outcomes, the most abnormal result 1 biopsy was collected at any one HRA. Progression was defined as having histologically confirmed AIN3 with preceding lower-grade histology, normal HRA or negative cytology. Regression was defined as histologically confirmed AIN3 that proceeded to lower-grade histology, normal HRA or negative cytology. For both outcomes, the most abnormal result was used if >1 biopsy was collected at any one HRA. For analysis of AIN3 regression, results after referral for surgical excision of HGAIN were censored.

Results: Of 575 patients, median age at enrolment was 46 years (IQR 37–52), 99.3% were men and 73.0% were HIV+ (median HIV duration 13.8 years [IQR 6.4–19.8]), median CD4+ T-cell count 500 cells/µL [IQR 357–662] and 83.5% had undetectable plasma HIV viral load). Median follow-up was 1.06 years (IQR 0.26–2.76). Mean number of clinic visits was 2.7, with 324 (56%) patients having more than one clinic visit. For those with more than one clinic visit, the mean time between visits was 0.5 years.

The progression rate to AIN3 was 9.69 per 100 person-years (PY; 95% CI 6.73, 13.94). Rates of progression increased with increasing age (P trend = 0.001). The hazard ratio (HR) for progression to AIN3 was higher (2.66 [95% CI 1.21–5.86]) in HIV+ versus HIV-uninfected (P=0.015) and 3.61 (95% CI 1.56, 8.36) in HIV+ with nadir CD4+ T-cell count <200 cells/µL versus HIV-uninfected (P=0.003). Progression rates did not significantly associate with duration of HIV infection, current CD4+ T-cell count or time-weighted average CD4+ T-cell count.

The regression rate from AIN3 was 63.50 per 100 PY (95% CI 44.12, 91.37). The HR for regression from AIN3 was lower (0.43 [95% CI 0.19, 0.97]) in HIV+ versus HIV-uninfected (P=0.042), and 0.35 (95% CI 0.13, 1.00) in HIV+ with nadir CD4+ T-cell count <200 cells/µL versus HIV-uninfected (P=0.049). Regression rates did not significantly associate with age, duration of HIV infection, current CD4+ T-cell count or time-weighted average CD4+ T-cell count.

Conclusions: This is the first study to report spontaneous regression of AIN3, which was more common than progression to AIN3.

ABSTRACT 002

Antiviral Therapy 2012; 17 Suppl 2:A3

Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers

AH Borges1, MJ Silverberg2, D Wentworth1, A Grulich4, G Fätkenheuer6, R Mitsuyasu8, G Tambussi2, C Sabin8, J Neaton3, JD Lundgren1,9, the INSIGHT SMART, ESPRIT and SILCAAT Study Groups

1Copenhagen HIV Programme, University of Copenhagen, Faculty of Health Sciences, Copenhagen, Denmark; 2Division of Research, Kaiser Permanente, Oakland, CA, USA; 3Department of Biostatistics, University of Minnesota, Minneapolis, MN, USA; 4Kirby Institute, University of New South Wales, Sydney, NSW, Australia; 5First Department of Internal Medicine, University Hospital of Cologne, Cologne, Germany; 6UCLA Center for Clinical AIDS Research Department of Infectious and Tropical Diseases San Rafael Scientific Institute Via Stamira d’Ancona, Milano, Italy; 7University College London Medical School, London, UK; 8Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark

Aim: IL-6 may serve as an autocrine and paracrine stimulator of tumour growth. Alongside other inflammatory and coagulation biomarkers, elevated serum levels of IL-6 may stimulate the development of cancer. This study is aimed at investigating the relationship between inflammatory (IL-6 and CRP) and coagulation (d-dimer) biomarkers and the risk of cancer during HIV infection.

Methods: Participants in the control arms (that is, use of continuous antiretroviral therapy) of the SMART, ESPRIT and SILCAAT trials with IL-6, CRP and d-dimer...
determined at study-entry were included (n=5,023) in an analysis of predictors of cancer (any type, infection-related or infection-unrelated). Hazard ratios (HRs) with 95% confidence intervals (CI) of each endpoint for IL-6, CRP and D-dimer levels (log2-transformed) were calculated using Cox models: (1) stratified by study and otherwise unadjusted, (2) adjusted for age, sex, race, continent, study-entry and time-updated CD4+ counts and (3) adjusted also for the three biomarkers. To assess the possibility that biomarker levels were elevated at entry due to undiagnosed cancer, analyses were repeated excluding early cancer events (that is, diagnosed during the first 2 years of follow-up).

**Results:** During 23,509 persons-years of follow-up, 172 patients developed cancer (71 infection-related; 101 infection-unrelated). In the partially adjusted models 1 and 2, higher levels (that is, per 1 log2 increase) of IL-6, CRP and D-dimer levels were associated with a doubling of the biomarker excluding early cancer. Thus, interventions to reduce IL-6 levels to lower the risk of cancer should be investigated in HIV-positive individuals.

**Conclusions:** Activated inflammation and coagulation, as demonstrated by higher IL-6, CRP and D-dimer levels, predisposes HIV-infected individuals to cancer. This association was stronger for IL-6 and persisted after excluding early cancer. Thus, interventions to reduce IL-6 levels to lower the risk of cancer should be investigated in HIV-positive individuals.

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**ABSTRACT 003**

*Antiviral Therapy* 2012; 17 Suppl 2:A4

Increased risk of serious non-AIDS defining events and mortality among immunological non-responders to antiretroviral therapy in the Italian MASTER cohort

G Lapadula1, L Chateneaud2, A Gori1, C Torti1, S Di Giambenedetto3, F Maggiolo1, A Scalzini3, N Ladisa1, L Sighinolfi5, M Di Pietro4, A Pan4, G Carosi3, the MASTER Cohort

1Clinic of Infectious Diseases, AO ‘San Gerardo de’ Tintori’, Monza (MB), Italy; 2'Mario Negri’ Institute for Pharmacological Research, Milan, Italy; 3Clinic for Infectious and Tropical Diseases, University of Brescia, Brescia, Italy; 4Clinic of Infectious Diseases, ‘Sacro Cuore’ Catholic University of Rome, Rome, Italy; 5Clinic of Infectious Diseases, Ospedali Riuniti, Bergamo, Italy; 6Division of Infectious Diseases, Spedali Civili, Brescia, Italy; 7Clinic of Infectious Diseases, Ospedale Sant’Anna, Ferrara, Italy; 8‘Sacro Cuore’ Catholic University of Rome, Rome, Italy; 9Clinic of Infectious Diseases, Ospedale S.M. Annunziata, Florence, Italy; 10Clinic of Infectious Diseases, Istituti Ospitalieri, Cremona, Italy

**Background:** Immunological non-response (INR) despite virological suppression has been associated with AIDS-related events (ADE) or death. Little is known about its association with serious non-AIDS-defining events (nAIDS).

**Methods:** Patients initiating first HAART with <200 CD4+/μl were enrolled if they had confirmed viral load <50 copies/ml within 15 months of treatment and were categorized as INR if CD4+ at year 1 were <200/μl. The outcome of interest was time to nAIDS (malignancies, severe infections, renal failure [that is, eGFR <30], cardiovascular events, liver decompensation, acute pancreatitis, non-AIDS related death). Predictors of nAIDS were assessed using univariable and multivariable Cox models. Follow-up was right-censored in case of cART discontinuation, viral load >50 for ≥180 days or AIDS-related death.

**Results:** A total of 1,229 patients (75.3% male, 16.7% intravenous drug users [IVDU]) were observed over a mean follow-up of 3.9 (±3.1) years. Pre-HAART CD4+ was 87 (±62)/μl and 55.2% of patients had experienced an ADE. After 1 year, CD4+ increased to 318 (±177), but 26% of patients were INR. Thereafter, 102 nAIDS (24.5% malignancies, 20.6% infectious, 18.6% renal, 15.7% cardiovascular, 8.8% hepatic, 5.8% other non-fatal, 5.8% deaths due to other non-AIDS-related causes) and 70 ADE were observed. The incidence of nAIDS was 2.13 (95%CI 1.76, 2.58) per 100 PYFU.

INR had significantly higher risk of nAIDS (HR 1.80 [95%CI 1.20, 2.68]; P=0.004). Older age (per year,
Table 1. Difference in mean changes in lipids, markers of inflammation and coagulation and vitamin-D between cases and controls (Abstract O04)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mean Change from index visit</th>
<th>Un-adjusted difference of change (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/l</td>
<td>-0.113</td>
<td>0.001 (-0.352, 0.355)</td>
<td>0.994</td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>-0.018</td>
<td>-0.14 (-0.217, 0.008)</td>
<td>0.035</td>
</tr>
<tr>
<td>LDL-C, mmol/l</td>
<td>-0.019</td>
<td>-0.060 (-0.333, 0.213)</td>
<td>0.667</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>-0.127</td>
<td>0.409 (-0.056, 0.875)</td>
<td>0.085</td>
</tr>
<tr>
<td>Log CRP, mg/l</td>
<td>0.119</td>
<td>-0.055 (-0.541, 0.432)</td>
<td>0.826</td>
</tr>
<tr>
<td>Log IL-6, pg/ml</td>
<td>-0.086</td>
<td>0.123 (-0.418, 0.665)</td>
<td>0.655</td>
</tr>
<tr>
<td>Log dimer, ng/ml</td>
<td>0.224</td>
<td>0.014 (-0.302, 0.330)</td>
<td>0.929</td>
</tr>
<tr>
<td>Log Fibrinogen, g/l</td>
<td>-0.052</td>
<td>-0.053 (-0.173, 0.066)</td>
<td>0.382</td>
</tr>
<tr>
<td>Log vitamin D, nmol/l</td>
<td>-0.022</td>
<td>0.003 (-0.111, 0.116)</td>
<td>0.965</td>
</tr>
</tbody>
</table>

C-reactive protein (CRP), interleukin-6 (IL-6), d-dimer, fibrinogen and vitamin D were natural log-transformed for analysis. Case, those who sero-converted during the follow-up; controls, those who never seroconverted during the follow-up; HDL-C: high-density lipoprotein cholesterol; index visit, pre-seroconversion visit for cases and corresponding first visit for controls; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

HR 1.03 [1.01, 1.05]; P=0.008), IVDU (HR 1.55 [1.00, 2.41]; P=0.050) and hepatitis coinfection (HR 1.49 [0.92, 2.43]; P=0.103) were also associated with nADE. After adjusting for baseline characteristics, INR remained independently associated with nADE (HR 1.61 [1.07, 2.43]; P=0.023). The occurrence of ADE during the follow-up increased the risk of nADE (HR 3.49 [1.99, 6.12]; P=0.001). A separate model adjusted for ADE as time-varying covariate confirmed the association between INR and the outcome (HR 1.67 [1.12, 2.51]; P=0.012).

Conclusions: Immunological non-responders run a greater risk of serious nADE. Improved management of this fragile population and innovative immune therapies are urgently needed.

ABSTRACT O04
Antiviral Therapy 2012; 17 Suppl 2:A5

Changes in metabolic, inflammatory and coagulation biomarkers after HIV sero-conversion – the Health In Men (HIM) Biomarker sub-study

AC Achhra1, J Amin1, MG Law1, AE Grulich1, J Yeung1, A Kelleher1, DA Cooper1
1The Kirby Institute for Infection and Immunity in Society, University of New South Wales, Sydney, Australia

Objective: To evaluate the impact of HIV seroconversion on selected biomarkers of cardiovascular and mortality risk.

Methods: The study participants were drawn from the Health In Men study, a cohort of initially HIV-negative gay men. Participants with incident HIV infection (n=26) were compared with HIV-negative controls (n=52) matched on age at enrolment, date of visit and reported intravenous drug use. Levels of metabolic (lipids, vitamin D), inflammatory (C-reactive protein, interleukin-6) and coagulation (d-dimer and fibrinogen) biomarkers were measured at pre- and post-HIV seroconversion visits and corresponding visits for controls. Random effect models were used to compare changes in markers between cases and controls.

Results: The median gap between pre and post seroconversion or matched first and second visits in controls was 12 months. HIV seroconversion was associated with decline in high density lipoprotein (HDL-C) and non-significant elevation in triglycerides (Table 1). There were no significant differences in changes in markers of inflammation, coagulation or vitamin D (Table 1).

Conclusion: Decline in HDL-C seems to be the main pro-atherogenic change within 1–1.5 years after HIV seroconversion. HIV seroconversion is not associated with profound changes in other lipids, or markers of inflammation, coagulation and vitamin D.

ABSTRACT O05
Antiviral Therapy 2012; 17 Suppl 2:A5

Proteinuria as an early marker of tenofovir renal toxicity

A Milinkovic1, M Pavlov1, A Copas1, S Edwards4, JO Connolly3, A Arenas-Pinto1,2, R Gilson1,2, I Williams1,2

Background: Tenofovir (TDF) is a common component in antiretroviral therapy (ART) regimens, but can cause renal impairment. Identifying risk factors for, and early laboratory markers predictive of TDF renal toxicity (TDF-RT) would be clinically helpful.
Methods: For routine clinical practice, we monitor markers of renal function including Up/c in patients treated with TDF. In patients who experienced either a decrease in eGFR, hypophosphataemia or elevation in Up/c, a diagnosis of TDF-RT was confirmed with tests of proximal renal tubule dysfunction, including tubular proteinuria (urine retinol binding protein) and phosphate reabsorption capacity. We used Cox regression to model the instantaneous hazard of developing TDF-RT, with respect to renal function biomarkers and other potential risk factors. The association of renal function biomarkers with the risk of TDF-RT was explored at the time of starting TDF (‘baseline’) and at the ‘current’ value, to assess their long- and short-term effect, respectively.

Results: 1,293 patients, who started TDF between 01/01/2007 and 01/12/2009, were identified from the clinic database. Baseline characteristics (median, IQR): age 41 (34–46) years, CD4 count 330 (220–500) cells/µl, eGFR 100 (87–116) ml/min/1.73 m², 82% male, 63% Caucasian, 54% ART-naïve. Median (IQR) duration of TDF use: 1,054 (834–1,266) days. Of 107 (8.3%) who discontinued TDF, 29 (2.2% of cohort) stopped because of TDF-RT.

In univariable analysis, older age, elevated current and baseline Up/c, lower current and baseline eGFR, elevated current serum creatinine (Scr), lower baseline serum phosphate, and concomitant use and duration of a boosted protease inhibitor (PI/r) were associated with an increased hazard of TDF-RT. CD4 count, current serum phosphate, gender and ethnicity were not associated.

For multivariable analysis we considered all the risk factors found significant in the univariable analysis. A forward stepwise selection procedure identified the key predictors to be current Up/c and Scr, and concomitant PI use. HR (95% CI): Up/c per twofold increase: 3.86 (2.69, 5.51), Scr (per 10 µmol/l increase): 1.36 (1.13, 1.64), PI/r use: 3.43 (1.24, 9.41).

Approximately half of patients who developed TDF-RT maintained normal eGFR levels (>75 ml/min/1.73 m²) throughout follow-up. We explored the predictive value of Up/c among patients with normal eGFR throughout and found that elevated values of Up/c are predicative of TDF-RT, even in this sub-cohort. HR (95%CI) Up/c (mg/mmol): ≤13: 1.0, 13–30: 6.15 (0.64, 59.3), >30: 51.3 (6.3, 415).

Conclusions: We have demonstrated a strong association between elevated Up/c levels and increased risk of TDF-RT even in patients with normal eGFR. We suggest proteinuria (Up/C) is an early marker of TDF-RT, and we recommend all patients receiving TDF should have Up/c ratios as part of routine monitoring. Similar to previously reported studies we found older age, impaired renal function and PI/r use were associated with increased risk of TDF-RT.

ABSTRACT 006

Antiviral Therapy 2012; 17 Suppl 2:A6

Prospective evaluation of microalbuminuria in HIV infection

CM Hadigan1, E Edwards1, E Atkinson1, A Rosenberg2, J Purdy1, E Fleischman1, L Howard4, JM Micans3, K Sampath1, A Oyalowo4, A Johnson1, A Adler4, C Rehm1, M Smith6, L Lai6, JB Kopp4

1Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; 2Clinical Research Directorate/CMPR, SAIC-Frederick, Inc., NCI-Frederick, Frederick, MD, USA; 3Department of Critical Care Medicine, National Institutes of Health, Bethesda, MD, USA; 4Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; 5Department of Infectious Diseases, Washington Hospital Center, Washington, DC, USA

Objectives/Aim: Microalbuminuria may serve as an early marker of glomerular disease in HIV-infected patients, yet there are few data that address the diagnostic accuracy of a single sample to identify persistent microalbuminuria. The purpose of this study was to determine the period prevalence of microalbuminuria in an HIV-infected clinic population and to test the predictive value of a single urine specimen.

Methods: We conducted a prospective cohort study of 182 HIV-infected subjects (64% male, 59% Black, mean duration of HIV 14 years, mean CD4 count 513 cell/µl) without diabetes or pre-existing macroproteinuria. Subjects were patients who attended the HIV clinic at the National Institute of Allergy and Infectious Diseases outpatient clinic in Bethesda (MD, USA) or the Washington Hospital Center Infectious Diseases clinic in Washington (DC, USA) between January 2007 and January 2011. Subjects completed three research visits within 9 months. Evaluations included a detailed medical history, blood pressure measurement, serum creatinine, and urine protein, albumin and creatinine determinations. Microalbuminuria was defined as an albumin–creatinine ratio (ACR) geometric mean of 25–355 mg/g for women and 17–250 mg/g for men.

Results: The period prevalence of microalbuminuria was 14%. There was no increased propensity for microalbuminuria among Black versus non-Black subjects (χ²=0.06, P=0.8). Subjects with microalbuminuria were more likely to have hypertension (P=0.02) and be on antihypertensive therapy (P=0.04). However, there was no difference between the two groups in measured blood pressure. While duration of HIV and HIV viraemia was similar
between groups, those with microalbuminuria had significantly lower mean CD4 T-cell counts ($P=0.02$) and were more likely to have a CD4 count <200 cells/µl ($P=0.0003$). Low CD4 count remained a significant independent predictor of microalbuminuria ($P=0.002$) after adjustment for race and hypertension. There was no significant difference between those with and without microalbuminuria with regard to current or cumulative exposure to tenofovir or exposure to any one class of antiretroviral agents. The negative predictive value of a single urine ACR determination was 98%, whereas the positive predictive value was only 74%.

Conclusion(s)/discussion: These data demonstrate a prevalence of microalbuminuria among an HIV-infected clinic population that is similar to earlier reports, and identify hypertension and impaired immune function as risk factors. A single normal ACR determination largely excludes microalbuminuria, whereas an elevated ACR requires confirmation. Future investigation is needed to determine the natural history and progression of microalbuminuria in the context of HIV infection and to determine whether, how and when to treat microalbuminuria.

ABSTRACT 007

Antiviral Therapy 2012; 17 Suppl 2:A7

Increase in fibroblast growth factor 23 (FGF23) in response to vitamin D3 supplementation in HIV-infected adolescents and young adults on tenofovir-containing combination antiretroviral therapy (cART): Adolescent Trials Network (ATN) study 063

PL Havens1, K Mulligan2, MD Van Loan4, BN Rutledge5, J Bethel6, CG Pan7, PM Flynn8, J Lujan-Zilberman9, CM Gordon5, LR Woodhouse1, JJ Kiser9, WA Meyer III10, AM Baker11, NX Liu6, CM Wilson12, CB Stephensen4

1Medical College of Wisconsin and Children’s Research Institute, Milwaukee, WI, USA; 2University of California San Francisco, San Francisco, CA, USA; 3Pediatric, Adolescent, and Maternal AIDS Branch, Eunice Kennedy Shriver NICHD, NIH, Bethesda, MD, USA; 4USDA Western Human Nutrition Research Center, Davis, CA, USA; 5Westat, Bethesda, MD, USA; 6St Jude Children’s Research Hospital, Memphis, TN, USA; 7University of South Florida College of Medicine, Tampa, FL, USA; 8Boston Children’s Hospital, Boston, MA, USA; 9University of Colorado Denver, Aurora, CO, USA; 10Quest Diagnostics, Baltimore, MD, USA; 11Tulane University Health Sciences Center, New Orleans, LA, USA; 12University of Alabama at Birmingham, Birmingham, AL, USA

Objective: Tenofovir (TDF) is associated with elevated parathyroid hormone, increased bone turnover, hypophosphatemia and phosphaturia, a biochemical profile similar to that found in persons with vitamin D deficiency. FGF23 is low in persons with vitamin D deficiency and increases in a counter-regulatory response to elevations in 1,25 dihydroxy vitamin D (1,25-OHD, the active form of vitamin D). Changes in vitamin D binding protein (VDBP) may alter free 1,25-OHD concentrations, thus changing vitamin D-related metabolic responses. We compared FGF23 and VDBP before and after vitamin D3 (VITD) supplementation in youths treated with cART with or without TDF.

Methods: Randomized controlled trial of VITD 50,000 IU versus placebo (PL) every 4 weeks for 3 directly observed oral doses with evaluation at baseline and week 12, in HIV+ youths ages 18–24, with viral load (VL) <5,000 copies/ml, and unchanged cART for ≥90

Table 1. Median FGF23 (pg/ml) at baseline and change at week 12 by TDF and VITD (Abstract O07)

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th></th>
<th></th>
<th></th>
<th>noTDF</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>$P$-value</td>
<td>Baseline</td>
<td>Change</td>
<td>$P$-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VITD</td>
<td>39.04</td>
<td>+6.80</td>
<td>0.008</td>
<td>41.35</td>
<td>-3.95</td>
<td>0.943</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>38.15</td>
<td>-0.84</td>
<td>0.882</td>
<td>37.87</td>
<td>-1.00</td>
<td>0.999</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values are by Wilcoxon signed rank test, corrected for multiple comparisons by Sidak’s method.

14th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV A7
days. Participants were enrolled based on cART treatment with TDF (TDF, N=118) or without TDF (noTDF, N=85) and randomized within those groups to VITD (N=102) or PL (N=101). We measured FGF23 and VDBP and calculated free 1,25-OHD at baseline and at week 12, and compared values by TDF/noTDF and by VITD randomized treatment group.

**Results:** At baseline, VITD and PL groups were similar in age, race/ethnicity, BMI, and vitamin D and calcium intake. Participants on noTDF had longer duration of HIV infection and cART, higher VL and more advanced CDC stage of HIV disease. Participants on TDF had higher VDBP, but similar FGF23 and similar free and total 1,25-OHD, compared with noTDF. The TDF-associated elevation in VDBP was observed in participants with sufficient vitamin D (25-OHD≥20 ng/ml), but not in those with deficient/insufficient vitamin D status (25-OHD<20 ng/ml).

At week 12, VDBP showed no change from baseline, but free and total 1,25-OHD increased in the VITD but not PL groups, independent of TDF use. FGF23 increased in the TDF group receiving VITD, but not in the noTDF group receiving VITD or the PL groups (Table 1). The increase in FGF23 in the TDF/VITD group was statistically significant in participants with deficient/insufficient baseline vitamin D (15% increase; *P*=0.009) and was marginally significant (18% increase; *P*=0.095) in those with sufficient baseline vitamin D. Baseline vitamin D status did not alter the FGF23 change in the noTDF group.

**Discussion:** These results suggest that TDF-containing cART may alter the FGF23 response to vitamin D in HIV-infected adolescents and young adults.

**ABSTRACT 008**

*Antiviral Therapy* 2012; 17 Suppl 2:A8

Renal function improves with long-term telbivudine therapy in patients with chronic hepatitis B

E Gane1, HLY Chan2, G Deray3, T Piratvisuth4, S Zeuzem5, J Jia6, H Ren7, A Uddin8, S Bosset9, Y Dong9, A Trylesinski9

1Auckland City Hospital, Auckland, New Zealand; 2The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China; 3Pitié Salpêtrière Hospital, Paris, France; 4Prince of Songkla University, Bangkok, Thailand; 5JW Goethe University Hospital, Frankfurt am Main, Germany; 6Capital Medical University, Beijing, China; 7Chongqing Medical University, Chongqing, China; 8Novartis Pharma Corporation, East Hanover, NJ, USA; 9Novartis Pharma AG, Basel, Switzerland

**Objectives:** Renal dysfunction is common in decompensated chronic hepatitis B (CHB) cirrhosis. Mortality in untreated patients is high with 86% over 5 years. But also in compensated CHB, almost 20% of the overall patients in Europe had baseline glomerular filtration rate (GFR) of 60–90 ml/min, in patients >45 years of age, this rate goes up to 50–68%. However, a recent study on decompensated CHB showed that renal function significantly improved with telbivudine therapy. We assessed the effect of telbivudine treatment on renal function in several clinical studies in compensated and decompensated CHB patients.

**Methods:** We analysed data from four randomized telbivudine clinical studies in CHB patients for estimated GFR (assessed by Modification of Diet in Renal Disease [MDRD] formula) at baseline, week 52, 104 and 208 in studies: GLOBE (2 years telbivudine roadmap with lamivudine in compensated CHB (*n*=1,370)); 2,303 (2 additional years telbivudine in GLOBE extension (*n*=1,869)); 2,301 (2 years telbivudine versus lamivudine in compensated CHB (*n*=232)); 2,410 (2 years telbivudine roadmap with tenofovir add-on (*n*=100)).

**Table 1. (Abstract 008)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (n)</th>
<th>Baseline GFR</th>
<th>GFR change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Week 52</td>
</tr>
<tr>
<td>GLOBE 2 year</td>
<td>Telbivudine (n=489)</td>
<td>104</td>
<td>2.3*</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (n=505)</td>
<td>106</td>
<td>-3.3*</td>
</tr>
<tr>
<td>2303 4 year</td>
<td>Telbivudine (n=637/511)</td>
<td>94</td>
<td>14</td>
</tr>
<tr>
<td>2301 2 year</td>
<td>Telbivudine (n=114)</td>
<td>102</td>
<td>-1.1</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (n=114)</td>
<td>100</td>
<td>-4.5</td>
</tr>
<tr>
<td>2410 2 year</td>
<td>Telbivudine (n=55/43)</td>
<td>93.3</td>
<td>6.9*</td>
</tr>
<tr>
<td></td>
<td>Telbivudine+tenofovir (n=44/38)</td>
<td>91.07</td>
<td>7.8*</td>
</tr>
</tbody>
</table>

*Telbivudine versus lamivudine *P*<0.0001. "Telbivudine versus lamivudine *P*<0.0231. "Week 52 versus baseline *P*<0.005. "Week 104 versus baseline *P*<0.0168. "Week 52 versus baseline *P*<0.0035. "Week 104 versus baseline *P*<0.02.
Results: GFR was significantly improved in decompensated and compensated CHB patients receiving telbivudine monotherapy or combination (Table 1). In GLOBE study, GFR improvement versus baseline was 8.5% in telbivudine versus -0.5% in lamivudine ($P<0.0005$); in patients with reduced GFR (60–90) at baseline, 17.2% of telbivudine but only 4.3% of lamivudine patients had improved to normal GFR (GFR $>90$ ml/min/$1.73$ m$^2$). Of GLOBE patients with reduced GFR at baseline, 72.3% (185/256) shifted to normal after 104 weeks in telbivudine versus 52.6% (123/234) in lamivudine group ($P<0.0001$). From the GLOBE cohort, 57 patients continued telbivudine treatment for 6 years, out of 39 with reduced GFR at baseline, 37 (95%) had normal GFR at 6 years. Similarly in study 2410, patients with reduced baseline GFR, 50% and 43% had normal GFR at week 104 in telbivudine and telbivudine-tenofovir groups, respectively. Conclusions: Long-term telbivudine monotherapy is associated with consistent improvement of renal function in patients with compensated and decompensated CHB. Improvement of eGFR was also shown in combination with potentially nephrotoxic drugs such as tenofovir. The potential mechanism for this renal protective effect remains to be determined.

ABSTRACT 009

Antiviral Therapy 2012; 17 Suppl 2:A9

The role of HIV proteins or AZT on arterial stiffening and intima-media thickening

L Hansen$^1$, I Parker$^3$, RL Sutliff$^3$, MO Platt$^{1,4}$, RL Gleason Jr$^{1,2,4}$

$^1$The Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA; $^2$The George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA, USA; $^3$Department Medicine, Emory University/ Atlanta VAMC, Atlanta, GA, USA; $^4$The Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA, USA

Background: The increased use of highly active antiretroviral therapy (HAART) has corresponded with the emergence of early onset cardiovascular disease in HIV-positive patients. However, the role of HAART drugs and the HIV virus itself have not yet been elucidated. The goal of this study is to test the hypothesis that both drugs and virus can lead to subclinical markers of atherosclerosis including arterial stiffening and intima-media thickening.

Methods: To study the effects of the HIV proteins, male heterozygous HIV-1 Tg (NL4-3Δ gag/pol) mice, which contain the transgene that codes for the viral proteins env, tat, nef, rev, vif, vpr and vpu, and their wild-type (FVB/N) littermates were used. For the HAART group the nucleoside reverse transcriptase inhibitors (NRTI) azidothymidine (AZT) was administered to wild-type FVB/N mice via oral gavage at 100 mg/kg for 35 days. An additional group of control mice were given water via oral gavage for 35 days. Carotid arteries were excised and mounted on a custom built mechanical testing device for pressure-diameter and force-length mechanical tests. Thickness was quantified using both haematoxylin and eosin stained histological slides and multiphoton confocal imaging. Additionally, elastin and collagen content of the arteries was quantified using the Fastin and Sirius red assays, respectively.

Results: The mechanical tests showed arterial stiffening in both the HIV Tg mice and the AZT-treated mice. The HIV carotids at had significantly smaller diameters than the wild-type litter mates at pressures between 60–100 mmHg and the AZT-treated mice were significantly smaller than the water-treated controls at pressures between 10–60 mmHg. Additionally, Peterson’s modulus, a measure of stiffness, was also higher for both the HIV Tg and AZT mice at pressures between 20–60 mmHg and 60–80 mmHg, respectively ($n=9$; $P<0.05$). Histology revealed increased intima-media thickness for the both the HIV and AZT-treated arteries as compared to their controls. ($n=6$; $P<0.05$) Additionally, the confocal imaging of the HIV arteries suggested that the increased thickness was limited to the intima-media layer for both groups of mice while the adventia thickness increased in the HIV mice but decreased in the AZT mice ($n=6$; $P<0.05$). Interestingly, collagen and elastin quantification showed a significant decrease in elastin for both groups ($n=6$; $P<0.05$), but a trend toward an increase in collagen for the HIV Tg mice only ($n=6$; $P<0.069$).

Conclusions: Both the HIV proteins and antiretroviral therapy AZT appear to play a role the development of cardiovascular disease with mice exposed to both showing both arterial stiffening and increase intima-media thickness. However, the difference in advential thickening and the collagen content of the vessels suggests that the mechanisms of these changes may be different and merit further investigation.
ABSTRACT O10
Antiviral Therapy 2012; 17 Suppl 2:A10
Evidence of coronary vessel wall thickening in asymptomatic young HIV-positive patients using MR imaging of HIV-associated vasculopathy
E Edwards1, KZ Abd-Elmoniem2, DA Hammoud3, JB Purdy4, R Hazra5,6, RI Pettigrew2, AM Gharib2, CM Hadigan2
1National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD, USA; 2Biomedical and Metabolic Imaging Branch, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, Bethesda, MD, USA; 3Center for Infectious Disease Imaging (CIDI), Radiology and Imaging Sciences, Clinical Center, NIH, Bethesda, MD, USA; 4Critical Care Medicine Department (CCMD), Clinical Center, NIH, Bethesda, MD, USA; 5Pediatric, Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda, MD, USA; 6HIV and AIDS Malignancy Branch, National Cancer Institute (NCI), Bethesda, MD, USA

Objectives: HIV-infected patients demonstrate premature and more severe vasculopathy relative to controls. Therefore, development of a reproducible vascular imaging biomarker in this population is important. The purpose of this study was to assess coronary artery wall thickness in patients who acquired HIV in early life compared to healthy controls using a novel black-blood coronary vessel wall MR imaging technique.

Methods: We prospectively studied 20 young HIV-infected adults and 12 HIV-uninfected control subjects. Participants were free of known active cardiovascular disease or symptoms at the time of the scan. MR imaging of the proximal right coronary artery (RCA) wall was performed using phase-sensitive dual inversion-recovery black-blood vessel wall imaging. Group comparisons were performed to evaluate differences in proximal RCA wall thickness and potential associations between clinical variables and wall thickness were evaluated using linear regression analyses.

Results: HIV-infected subjects ranged in age from 23 to 47 years, with an average age of 29.3 years (42% male). The average RCA wall was significantly thicker in HIV-infected patients compared to controls (P=0.0015), despite the fact that controls were significantly older (P=0.0001). In HIV-infected subjects, linear regression analysis did not show significant correlation between the RCA wall thickness and duration of disease, current or nadir CD4 counts, levels of total cholesterol, LDL cholesterol or triglycerides.

Conclusions: We have demonstrated statistically significant increased proximal RCA wall thickness as a likely surrogate marker of generalized vascular disease in a group of young patients who acquired HIV in early life compared to HIV-uninfected subjects. Although we did not find a significant correlation between the vessel wall thickness and markers of infection such as CD4 counts, we believe studying a larger sample size is warranted to determine more definitively if such a correlation exists.

ABSTRACT O11
Antiviral Therapy 2012; 17 Suppl 2:A10
Cardiovascular biomarkers in SUPPORT: 96-week results of fosamprenavir/ritonavir (FPV/r) versus efavirenz (EFV) with abacavir/lamivudine (ABC/3TC) in antiretroviral-naïve subjects
P Kumar1, E DeJesus2, G Huhn1, L Sloan3, F Garcia4, C Small4, H Edelstein5, F Felizarta6, R Hao7, L Ross9, B Stancil10, B Ha10, the SUPPORT study team
1Georgetown University, Washington, DC, USA; 2Orlando Immunology, Orlando, FL, USA; 3Ruth M. Rothstein CORE Center, Chicago, IL, USA; 4North Texas Infectious Disease Consultants, Dallas, TX, USA; 5Valley AIDS Council, Brownsville, TX, USA; 6New York Medical College, Valhalla, NY, USA; 7Alameda County Medical Center, Oakland, CA, USA; 8Private Practice, Bakersfield, CA, USA; 9Chase Brexton Health Services, Baltimore, MD, USA; 10GlaxoSmithKline, RTP, NC, USA

Objectives: Recent reports indicate conflicting findings for select cardiovascular biomarkers during post hoc analyses of ABC/3TC-containing regimens, with differences noted by third drug component. We prospectively evaluated changes in inflammation, thrombotic and endothelial activation markers in an under-represented population receiving ABC/3TC-containing regimens.

Methods: In this 96-week, open-label, randomized study, we compared once-daily ABC/3TC 600 mg/300 mg with FPV 1,400 mg/r 100 mg or EFV 600 mg in antiretroviral-naive, HLA-B*5701-negative, HIV-1-infected subjects with entry viral load (VL) >5,000 copies/ml. Subjects were stratified by screening VL < or ≥100,000 copies/ml. We evaluated changes in hs-CRP, plasminogen, sVCAM-1, D-dimer, interleukin-6, and fibrinogen in real-time from baseline to weeks (W) 4, 12, 24, 48 and 96. Biomarker data were log-transformed before analysis and change from baseline was assessed by geometric mean ratios with 95% confidence intervals.

Results: SUPPORT enrolled 32% (32/101) women and 79% (80/101) non-Caucasians. Baseline and demographic characteristics were generally similar between treatment arms. A total of 67 subjects (66%) completed the study through W96, with lost to follow-up
being the most common reason for discontinuation (6 in each group). By ITT missing-equals-failure analysis, for FPV/r versus EFV, 79% (15/19) versus 77% (13/17) had VL <50 copies/ml in the high VL stratum; 53% (17/32) versus 61% (20/33) had VL <50 copies/ml in the low VL stratum. At W96, plasminogen, sVCAM, D-dimer and fibrinogen levels decreased significantly from baseline for EFV (by 39%, 42%, 39% and 12%, respectively), and sVCAM and D-dimer decreased significantly for FPV/r (by 48% and 37%, respectively; see Table 1). sVCAM-1 and D-dimer decreased significantly from baseline at all time points for both groups. For FPV/r, biomarkers tended to decrease over time; significant changes were noted at W24 (increase for plasminogen) and at W48 (decrease for IL-6).

Conclusions: Through 96 weeks, in this diverse population, treatment initiation with ABC/3TC-containing regimens resulted in consistent and favourable decreases in thrombotic activity (as reflected by D-dimer) and in endothelial activation (as reflected by sVCAM-1). More variability was observed for the other biomarkers even in this real-time analysis.

ABSTRACT O12

Antiviral Therapy 2012; 17 Suppl 2:A11

Effects on post-prandial lipids and arterial stiffness of ritonavir-boosted atazanavir versus ritonavir-boosted darunavir in HIV-uninfected adults

FJ Lee1, WWY Tong1, R Richardson1, K Sinn1, N Mackenzie2, A Carr1

1Clinical Research Program, St Vincent’s Centre for Applied Medical Research, Sydney, Australia

Objectives/aims: Only about 50% of the cardiovascular risk associated with protease inhibitor (PI)-based therapy can be explained by PI-related fasting dyslipidaemia. Other PI effects on the vasculature may occur via means other than on circulating lipids; in vitro models suggest that PIs directly induce endothelial dysfunction, and may promote the conversion of macrophages to atherogenic foam cells. Low-dose ritonavir alone causes in HIV-uninfected adults both a fasting and post-prandial dyslipidaemia; the latter is also a predictor of cardiovascular disease. No study has evaluated post-prandial lipids with PI-based combination antiretroviral therapy (cART). We compared the effects of ritonavir-boosted atazanavir to ritonavir-boosted darunavir on post-prandial plasma lipids of HIV-uninfected adults. We also assessed arterial stiffness, which is associated with coronary artery disease and is an independent predictor of cardiovascular mortality, safety, glycaemic parameters (glucose, insulin) and inflammatory markers (C-reactive protein, D-dimer).

Methods: Twenty HIV-uninfected, adult volunteers with body mass index 20–30 kg/m², fasting triglycerides <2.0 mmol/l and total cholesterol <6.0 mmol/l were randomized 1:1 to open-label atazanavir/ritonavir (300/100 mg) once daily or darunavir/ritonavir (800/100 mg) once daily for 4 weeks. Individuals with diabetes mellitus, or receiving anti-hypertensive or statin therapy, were excluded. Participants consumed a standardized meal (energy content 5,795 kJ) at baseline and week 4, with blood samples collected at fasting, then hourly for 4 h post-meal. Arterial stiffness, assessed as the heart-rate corrected augmentation index (AIX-75), was measured by radial artery tonometry. The primary variables of interest were the between-group differences in the change in incremental area under the curve (ΔAUC) at week 4 for post-prandial lipids (total/low-density lipoprotein [LDL]/high-density lipoprotein [HDL] cholesterol, triglycerides) and apolipoproteins A1 and B. One-way analysis of variance and Mann–Whitney U tests were used to compare between-group differences.

Results: Baseline characteristics of the 20 participants were 50% male, mean age 38 years, 30% smokers, 35% family history of cardiovascular disease, mean weight 72 kg and mean blood pressure 113/72 mmHg. Between-group differences in ΔAUC for post-prandial lipids did not reach statistical significance, but showed trends for a greater mean fall in ΔAUC with atazanavir/ritonavir versus darunavir/ritonavir for LDL cholesterol (-0.25 ±0.23 versus 0.15 ±0.28 mmol/l, P=0.28, respectively), apolipoprotein A1 (-0.44 ±0.52 versus 0.27 ±0.28 mmol/l, P=0.25, respectively), and apolipoprotein B (-0.32 ±0.26 versus 0.15 ±0.21 mmol/l, P=0.17, respectively), with a trend for a lesser fall for HDL cholesterol (-0.11 ±0.18 versus -0.47 ±0.23 mmol/l, P=0.24, respectively). Atazanavir/ritonavir induced a significantly greater mean post-prandial fall in ΔAUC for AIX-75 than darunavir/ritonavir (-27.60 ±11.63 versus 0.08 ±4.68 h%, P<0.04, respectively). No difference was observed for any other parameters between the study arms.
Conclusions/discussion: Post-prandial arterial stiffness was greater with darunavir/ritonavir than with atazanavir/ritonavir in HIV-uninfected adults, despite non-significant effects on post-prandial lipids. This result may partially explain the PI-induced impact upon cardiovascular risk otherwise not explained by fasting dyslipidaemia.

ABSTRACT 013

Antiviral Therapy 2012; 17 Suppl 2:A12

Randomized, double-blind, placebo-controlled trial of recombinant human growth hormone (rhGH) and rosiglitazone (rosi) for HIV-associated abdominal obesity with insulin resistance

MJ Glesby1, J Albu1, YL Chu1, K Ham1, E Engelson2, V Mithukrishnan1, Q He2, DP Kotler2

1Weill Cornell Medical College, New York, NY, USA; 2St Luke’s Roosevelt Hospital Center, New York, NY, USA

Objectives: rhGH reduces visceral adipose tissue (VAT) volume but may worsen glucose homeostasis and lipoatrophy. We aimed to determine if adding rosi to rhGH would abrogate the adverse effects of rhGH on insulin sensitivity (SI) and subcutaneous adipose tissue (SAT) volume.

Methods: Randomized, double-blind, placebo-controlled, multicenter trial using a 2×2 factorial design in which HIV-infected subjects with abdominal obesity by anthropometric criteria and insulin resistance (QUICKI<0.33) but not diabetes were randomized to rhGH 3 mg daily, rosi 4 mg twice daily, combination rhGH+rosi, or double placebo (control) ×12 weeks. The primary end point was change in SI by frequently sampled intravenous glucose tolerance test (FSIVGTT) from entry to week 12. Secondary end points included changes in 2-h oral glucose tolerance test (OGTT) parameters and body composition by whole body MRI and DEXA.

Results: 77 subjects were randomized, of whom 72 initiated study drugs. Mean age ranged from 46.6–49.3 years across study arms, CD4 539–617 cells/mm³, waist circumference 99.7–107 cm, and hip circumference 96.1–103.5 cm; 68–82% were male, 35–53% on protease inhibitors, and 23–42% on thymidine analogues. Mean baseline QUICKI was 0.31 in all 4 arms. Data on the primary end point were available on 22/22 on rhGH/rosi, 17/18 on rosi, 13/15 on rhGH and 17/17 on double placebo. Change in SI from entry to week 12 differed significantly across the 4 arms by 1-way ANOVA (P=0.02); by pair-wise comparisons, only rhGH (decreasing SI; P=0.03) but not rhGH/rosi differed significantly from control. There was no significant rhGH × rosi interaction for change in SI by 2-way ANOVA (P=0.53); pooling across arms, the rhGH main effect (decreasing SI; P=0.002) but not rosi main effect (P=0.68) was statistically significant. Change in glucose area under the curve from entry to week 12 was the only OGTT parameter that differed across arms (1-way ANOVA; P=0.004), increasing in the rhGH arm relative to control (P=0.026) but not differing in the other arms. By 2-way ANOVA, the rhGH × rosi interaction was borderline significant (P=0.09). 27% on rhGH/rosi, 18% on rosi alone, 46% on rhGH alone, and 27% on double placebo shifted OGTT categories adversely at week 12. VAT decreased significantly in the rhGH arms (-17.5% in rhGH/rosi and -22.7% in rhGH) but not in the rosi alone (-2.5%) or control arms (-1.9%). SAT did not change significantly in any arm. DEXA results were consistent with the MRI data. There was no significant rhGH × rosi interaction for any body composition parameter.

Conclusions: The addition of rosi abrogated the adverse effects of rhGH on insulin sensitivity and glucose tolerance while not significantly modifying the lowering effect of rhGH on VAT.

ABSTRACT 014

Antiviral Therapy 2012; 17 Suppl 2:A12

Associations between visceral adipose tissue and hypertriglyceridaemic waist circumference phenotype in a randomized prospective comparison between atazanavir/ritonavir and lopinavir/ritonavir each in combination with tenofovir DF/emtricitabine in antiretroviral-naive HIV-1-infected subjects

G Mayle1, H Hardy2, M DeGrosky1, D McGrath3

1St Stephens Centre, Chelsea and Westminster Hospital, London, UK; 2Bristol–Myers Squibb, Plainsboro, NJ, USA; 3Bristol–Myers Squibb, Wallingford, CT, USA

Objectives/aim: Hypertriglyceridaemic waist circumference (WC) phenotype has been used as a marker of excess visceral adipose tissue (VAT) storage and is associated with elevated risk of cardiovascular disease and diabetes mellitus. We evaluated the incidence of combination of elevated WC and hypertriglyceridaemia and changes in VAT in treatment-naive HIV-1-infected subjects enrolled in the CASTLE lipodystrophy substudy.

Methods: CASTLE was a randomized, open-label, prospective study comparing once-daily atazanavir/ritonavir with twice-daily lopinavir/ritonavir, both in combination with tenofovir DF/emtricitabine. VAT and subcutaneous adipose tissue (SAT) were
Table 1. Paired WC/TG at BL and week 96 by treatment by gender (Abstract O14)

<table>
<thead>
<tr>
<th>Category</th>
<th>ATV/r B/L</th>
<th>ATV/r Week 96</th>
<th>LPV/r B/L</th>
<th>LPV/r Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n</td>
<td>67</td>
<td>67</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Low WC/low TG</td>
<td>38 (57%)</td>
<td>26 (39%)</td>
<td>30 (71%)</td>
<td>22 (52%)</td>
</tr>
<tr>
<td>Low WC/high TG</td>
<td>11 (16%)</td>
<td>9 (13%)</td>
<td>0</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>High WC/low TG</td>
<td>15 (22%)</td>
<td>21 (31%)</td>
<td>10 (24%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>High WC/high TG</td>
<td>3 (4%)</td>
<td>11 (16%)</td>
<td>2 (5%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Female, n</td>
<td>29</td>
<td>29</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Low WC/low TG</td>
<td>14 (48%)</td>
<td>8 (28%)</td>
<td>8 (33%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Low WC/high TG</td>
<td>5 (17%)</td>
<td>5 (17%)</td>
<td>5 (21%)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>High WC/low TG</td>
<td>6 (21%)</td>
<td>10 (34%)</td>
<td>6 (26%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>High WC/high TG</td>
<td>4 (14%)</td>
<td>6 (21%)</td>
<td>5 (21%)</td>
<td>9 (38%)</td>
</tr>
</tbody>
</table>

Table 2. Mean VAT, cm³ (±se) by WC/TG category and treatment arm at week 96 (Abstract O14)

<table>
<thead>
<tr>
<th>Category</th>
<th>Low WC/low TG</th>
<th>Low WC/high TG</th>
<th>High WC/low TG</th>
<th>High WC/high TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>ATV/r (n=33)</td>
<td>ATV/r (n=14)</td>
<td>ATV/r (n=28)</td>
<td>ATV/r (n=19)</td>
</tr>
<tr>
<td>VAT, cm³</td>
<td>78.05 (4.13)</td>
<td>98.15 (9.35)</td>
<td>124.93 (10.29)</td>
<td>123.23 (10.77)</td>
</tr>
<tr>
<td>mean (±se)</td>
<td>71.61 (5.14)</td>
<td>98.56 (10.87)</td>
<td>129.33 (12.36)</td>
<td>132.45 (9.86)</td>
</tr>
</tbody>
</table>

measured by computed tomography. The published definition of hypertriglyceridaemic waist circumference is triglycerides (TG) ≥177 mg/dl and WC ≥90 cm for men, and TG ≥133 mg/dl and WC ≥85 cm for women. Subgroup analyses by baseline characteristics were conducted.

Results: 224 subjects (125 on atazanavir/ritonavir; 99 on lopinavir/ritonavir) were included in the sub-analysis. By week 96, differences from baseline were observed in VAT, SAT and WC/TG. The lowest baseline body mass index (BMI <22 kg/m²) and lowest CD4 strata (<50 cells/mm³) had significantly greater gains in SAT for atazanavir/ritonavir compared to lopinavir/ritonavir (76% vs 25%; P < 0.05). In the lowest baseline BMI, those on atazanavir/ritonavir had a 19% increase in VAT versus a reduction of 5% for those on lopinavir/ritonavir (P < 0.05); differences in changes in VAT were not seen in higher BMI strata. The highest baseline BMI (≥27 kg/m²) had a mean increase in TG of 6% on atazanavir/ritonavir, compared to a 70% increase of TG on lopinavir/ritonavir. At baseline, the majority of subjects fell into the low WC/low TG category. New onset/treatment emergent hypertriglyceridaemic WC in males was observed to increase by 12% on atazanavir/ritonavir and 19% on lopinavir/ritonavir and for females 7% versus 17%, respectively (Table 1). High WC/High TG was observed in those with the highest VAT (Table 2).

Conclusion: Increases in VAT after initiation of a boosted PI-containing regimen may represent a return to health and influence body composition/metabolic disturbances differently based on the specific regimen or patients’ baseline characteristics. Prevalence of the hypertriglyceridaemic WC phenotype was less in the atazanavir/ritonavir arm than in the lopinavir/ritonavir arm at week 96.

ABSTRACT O15

Antiviral Therapy 2012; 17 Suppl 2:A13

Skeletal muscle toxicity associated with raltegravir-based combination antiretroviral therapy in HIV-infected adults

FJ Lee1, J Amin2, M Bloch3, SL Pett2, D Marriott4, A Carr5

1Clinical Research Program, St Vincent’s Centre for Applied Medical Research, Sydney, Australia; 2The Kirby Institute, University of New South Wales, Sydney, Australia; 3Holdsworth House Medical Practice, Sydney, Australia

Objectives/aim: The HIV-1 integrase inhibitor raltegravir is associated with rare cases of rhabdomyolysis, and pooled safety data from Phase II and III clinical trials show a higher rate of grade 3–4 creatine kinase (CK) elevation in patients receiving raltegravir versus controls (4.2% versus 2.5%). We compared the frequency of skeletal muscle toxicity in HIV-infected adults receiving raltegravir compared to a control group not receiving raltegravir, analysed for associated factors and also assessed for evidence of myocardial toxicity.
Methods: We consecutively evaluated 159 patients receiving raltegravir and 159 receiving non-raltegravir-based treatment (control group). No restrictions were placed on statin use or recent physical exercise for study entry. Patients with an acute illness, receiving zidovudine or another integrase inhibitor were excluded. Participants underwent a physical examination and had blood taken for CK, high-sensitivity troponin T and raltegravir trough levels. Vigorous exercise in the 7 days prior to study procedures was recorded using a questionnaire. The primary end point was the frequency of skeletal muscle toxicity, defined as either: (1) isolated CK elevation; (2) myalgia without motor weakness; (3) proximal myopathy on physical examination; or (4) rhabdomyolysis. Logistic regression was used to determine associations between muscle toxicity, raltegravir and other patient/treatment characteristics.

Results: Characteristics of the 318 participants were: 98% male, 89% white, median age 51 years, median CD4 cell count 585 cells/µl, 91% HIV-1 RNA<50 copies/ml, mean duration of raltegravir therapy 28 months, recent vigorous exercise 42%, and 24% concomitant statin use. At least one feature of skeletal muscle toxicity was present in 37% of the raltegravir versus 19% of the control group (P<0.01): isolated CK elevation (14% versus 16%, respectively; P=0.64); myalgia without weakness (19% versus 3%, respectively; P<0.01); and proximal myopathy (4% versus 0%, respectively; P=0.03). Most CK elevation was mild (< grade 1), with only one recorded grade 3–4 elevation, which occurred in the control group. Rhabdomyolysis was not reported. Low-level (<0.05 ng/ml) troponin T elevations were recorded in 6 raltegravir versus 3 control group participants (P=0.50), of which 5 had a past history of myocardial disease. No participant had signs of congestive cardiac failure. In univariate analysis, the association between statin and raltegravir use approached borderline significance (odds ratio, 95% confidence interval, P: 1.89, 0.98–2.92, 0.06). In multivariate analysis, only raltegravir use (2.64, 1.57–4.45, P<0.01) and exercise (2.26, 1.36–3.77, P<0.01) were independently associated with skeletal muscle toxicity. No association was found between any component of skeletal muscle toxicity and duration of raltegravir, or raltegravir levels.

Conclusions/discussion: Raltegravir-based therapy is associated with a higher prevalence of symptomatic skeletal muscle toxicity, which does not appear to be concentration or time-dependent. Proximal myopathy may be an uncommon but significant side effect of raltegravir exposure.

ABSTRACT 016

Antiviral Therapy 2012; 17 Suppl 2:A14

Dipeptidyl peptidase IV inhibition does not adversely affect immune and virological status of HIV+ men and women

SR Goodwin1, DN Reeds1, M Royal1, H Struthers1, E Laciny1, KE Yarasheski1

1Washington University School of Medicine, St Louis, MO, USA

Background: People living with HIV are at higher risk for developing insulin resistance, diabetes and cardiovascular disease than the general population. Dipeptidyl peptidase IV (DPPIV) inhibitors (for example, sitagliptin) are a new class of glucose-lowering medications with pleiotropic actions that may benefit HIV-infected people. However, the immune and virological safety of DPPIV inhibition in HIV is unknown. DPPIV is identical to CD26 – a cell surface glycoprotein involved in T-cell activation and chemokine (SDF1α [stromal-derived factor 1 α]; RANTES [regulated upon activation normal T-Cell expressed and secreted]) processing.

Objective/aim: We hypothesized that DPPIV inhibition would not adversely affect immune (CD4+ T-cell count) or virological (plasma HIV RNA) status, increase immune activation (sTNFRII; soluble TNF receptor-II), or inactivate immune cell CD26 activity (promote HIV entry) in HIV-infected adults.

Methods: We conducted a randomized, placebo-controlled, double-blind trial of sitagliptin (100 mg/d) or matching placebo for up to 24 weeks in non-diabetic HIV-infected men (n=17) and women (n=3) (38 ±12 years, 10 ±6 years HIV+), taking anti-HIV therapy, with stable immune (625 ±134 CD4+ T-cells/µl) and virological (<48 copies HIV RNA/ml) status. CD4+ T-cells and HIV RNA were measured every 4 weeks; fasting serum RANTES, SDF1α, sTNFRII and oral glucose tolerance (oGTT) were quantified at baseline, week 8 and end of study. ANOVA was used for between group comparisons; P<0.05 was considered significant.

Results: Compared to placebo, sitagliptin did not reduce CD4+ number; HIV RNA remained <48 copies/ml in all participants, RANTES and sTNFRII concentrations did not increase. Sitagliptin reduced total serum SDF1α concentration (P<0.0002) at week 8 and study end. oGTT glucose levels improved more in the sitagliptin versus placebo group.

Conclusions: Despite lowering total serum SDF1α levels, sitagliptin appears safe in healthy, non-diabetic HIV-infected men and women; no adverse effect on immune or virological status, no increase in an immune activation biomarker, and improved glycaemia. Cardiovascular efficacy outcome studies are underway.
ABSTRACT O17

Antiviral Therapy 2012; 17 Suppl 2:A15

The interplay of the osteoprotegerin/RANKL axis and dysfunctional HDL in HIV-infected adults: ACTG NWCS 332/A5078 study

T Kelesidis1, MA Kendall2, OO Yang1, JS Currier1

1University of California, Los Angeles, CA, USA; 2Harvard School of Public Health, Boston, MA, USA

Objectives/aim: Limited data exist regarding the relationship between dysfunctional HDL (dys-HDL) and the osteoprotegerin (OPG)/receptor activator of the NF-κB ligand (RANKL) in HIV infection. Oxidized HDL (dys-HDL) has been shown to activate the NF-κB pathway in vitro. In view of this observation and the important role of biomarkers of activation of the NF-κB pathway (RANKL/OPG axis) in systemic inflammatory conditions, we used a novel assay that measures oxidation of HDL to explore possible associations between dys-HDL with RANKL/OPG and parameters that may predict these biomarkers.

Methods: We used cryopreserved serum samples from a prospective study where subjects were enrolled as risk-factor-matched triads of HIV-infected subjects (prospective study where subjects were enrolled as risk-factor-matched triads of HIV-infected subjects (n=55) and HIV-uninfected individuals (n=36). Relationships between HIV infection, RANKL, OPG, RANKL/OPG and dys-HDL were assessed using Wilcoxon tests and mixed-effects linear regression analysis. The baseline covariates considered in the analysis are shown in Table 1 and also included fasting glucose and lipids, insulin, use of statins, anthropometric parameters of obesity, years of protease inhibitors (PI) use, and nadir CD4+ T-cells. Significant (P<0.05) variables were considered in multivariate models. RANKL and OPG were assessed by ELISA and dys-HDL by a fluorometric assay based on the oxidation rate of dihydrorhodamine (DOR), which reflects the oxidative (functional) properties of HDL.

Results: Baseline measurements of 91 subjects appear in Table 1. HIV infection was associated with significantly lower baseline levels of RANKL and RANKL/OPG (Table 1). Within the HIV-infected subjects, baseline RANKL/OPG was significantly associated with baseline DOR (P=0.02; Table 2).

Conclusion(s)/discussion: RANKL/OPG axis may be regulated differently in HIV-infected compared to -uninfected adults and is independently associated with changes in functional properties of HDL in HIV-infected subjects. These data are consistent with previous in vitro results that have shown that oxidized HDL may affect the NF-κB pathway.

Table 1. Baseline subject variables by group [Abstract O17]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=91)</th>
<th>HIV (n=55)</th>
<th>Not HIV (n=36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>84 (92%)</td>
<td>52 (95%)</td>
<td>32 (89%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>Median (IQR)</td>
<td>41 (36–45)</td>
<td>41 (37–45)</td>
<td>40 (36–45)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>White non-Hispanic</td>
<td>69 (76%)</td>
<td>42 (76%)</td>
<td>27 (75%)</td>
</tr>
<tr>
<td>HIV RNA, copies/ml</td>
<td>&lt;50</td>
<td>46 (84%)</td>
<td>46 (84%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Baseline CD4+ T-cells, cells/mm³</td>
<td>Median (IQR)</td>
<td>488 (354–692)</td>
<td>488 (354–692)</td>
<td></td>
</tr>
<tr>
<td>DOR, ×10⁶ FU/min</td>
<td>Median (IQR)</td>
<td>24.1 (19.8, 27.6)</td>
<td>24.6 (20.2, 28.1)</td>
<td>23.9 (19.3, 27.0)</td>
</tr>
<tr>
<td>RANKL, pg/ml</td>
<td>Median (IQR)</td>
<td>22,124 (10,352, 44,003)</td>
<td>15,059 (7,764, 26,537)</td>
<td>42,829 (17,249, 70,496)</td>
</tr>
<tr>
<td>OPG, pg/ml</td>
<td>Median (IQR)</td>
<td>1,054 (781, 1,535)</td>
<td>1,087 (781, 1,601)</td>
<td>1,013 (772,1,289)</td>
</tr>
<tr>
<td>RANKL/OPG</td>
<td>Median (IQR)</td>
<td>18.23 (9.98, 48.81)</td>
<td>13.32 (6.72, 27.80)</td>
<td>37.68 (18.16, 75.54)</td>
</tr>
</tbody>
</table>

*Fisher’s exact test. Wilcoxon Test

Table 2. Baseline serum levels of RANKL and RANKL/OPG predict oxidative (functional) properties of HDL (reflected by the rate of oxidation of the fluorogenic probe dihydrorhodamine-DOR) in HIV-infected subjects [Abstract O17]

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate models</th>
<th>Multivariate models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter estimate [95% CI]</td>
<td>P-value</td>
</tr>
<tr>
<td>Baseline DOR (per 10,000 FU/min)</td>
<td>-3.97 [-6.94, -0.99]</td>
<td>0.012</td>
</tr>
<tr>
<td>Baseline RANKL, per 1,000 pg/ml</td>
<td>0.07 [0.01, 0.13]</td>
<td>0.020</td>
</tr>
<tr>
<td>Baseline OPG, per 100 pg/ml</td>
<td>-0.06 [-0.33, 0.21]</td>
<td>0.644</td>
</tr>
<tr>
<td>Baseline RANKL/OPG, per 10 units</td>
<td>0.87 [0.22, 1.53]</td>
<td>0.012</td>
</tr>
</tbody>
</table>

14th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV
SPIRIT study: switching to emtricitabine/rilpivirine/tenofovir DF (FTC/RPV/TDF) single-tablet regimen (STR) from a ritonavir-boosted protease inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs) maintains HIV suppression and improves serum lipids in HIV-1 infected subjects at week 24

P Tebas1, F Palella2, B Gazzard3, P Ruane4, D Shamblaw5, M Fisher6, J van Lunzen8, R Ebrahimi9, K White9, B Guyer9, J Goodgame9, T Fralich9, H Graham9, B Elbert9

1University of Pennsylvania, Division of Infectious Diseases, Clinical Trials Unit, Philadelphia, PA, USA; 2Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; 3Chelsea and Westminster Hospital Foundation Trust, London, United Kingdom; 4Peter J Ruane, IMD, Inc., Los Angeles, CA, USA; 5La Playa Medical Group and Clinical Research, San Diego, CA, USA; 6Kaiser Permanente, Sacramento, CA, USA; 7Brighton and Sussex University Hospitals, Brighton, UK; 8University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 9Gilead Sciences, Foster City, CA, USA

Objectives: Antiretroviral regimen simplification can improve both quality of life and long-term medication adherence and potentially reduce the risk for virological failure (VF) and long-term drug-related toxicities, including hyperlipidaemia. As HIV-infected persons age, the risk increases for cardiovascular events and the need for lipid neutral ART becomes more important. FTC/RPV/TDF is a well-tolerated, once-daily STR treatment option. This is the first study to evaluate the efficacy, safety and potential cost savings of switching from a ritonavir-boosted protease inhibitor (PI+RTV) based HAART to a simplified regimen of the STR FTC/RPV/TDF.

Methods: A randomized, open-label, international, 48-week study to evaluate the safety and efficacy of switching from a PI+RTV regimen to the STR FTC/RPV/TDF in HIV-suppressed (HIV RNA<50 copies/ml), HIV-1-infected subjects. Subjects were randomized 2:1 to switch to the STR FTC/RPV/TDF or to maintain their current PI+RTV regimen. The primary end point was non-inferiority (12% margin) of the STR FTC/RPV/TDF relative to PI+RTV based regimens in maintaining plasma HIV-1 RNA<50 copies/ml at week 24 (W24) by Snapshot analysis. Serum lipid changes were evaluated, including the implications for NCEP classification and Framingham Risk Score (post hoc). Estimates of pharmacy costs, using the mean wholesale acquisition cost (WAC), were calculated.

Results: A total of 476 subjects were randomized and received at least 1 dose of study drug (317 STR FTC/RPV/TDF; 159 PI+RTV). Baseline characteristics were similar. Switching to the STR FTC/RPV/TDF was non-inferior to maintaining a PI+RTV based regimen (93.7% versus 89.9%) at W24 for HIV RNA<50 copies/ml (95% CI -1.6%, 9.1%). Fewer subjects in the STR FTC/RPV/TDF arm than the PI+RTV demonstrated virological failure or discontinued study drug due to lack of efficacy (0.9% versus 5.0%) with HIV RNA≥50 copies/ml. Total cholesterol, LDL and triglycerides decreased to a greater extent and demonstrated significant improvement in NCEP classification for STR FTC/RPV/TDF than PI+RTV subjects. Improvement in 10-year Framingham scores at W24 was significant for the STR FTC/RPV/TDF compared to PI+RTV subjects (P=0.001). The mean WAC price for switching to FTC/RPV/TDF was 16% less at $10,275 versus staying on a PI+RTV regimen $12,272 at W24.

Conclusions: Switching to the STR FTC/RPV/TDF from a PI+RTV based regimen among HIV-suppressed persons maintains virological suppression, improves serum lipids, reduces projected risk for cardiovascular disease, and decreases medication costs per WAC evaluation.

Table 1. Fasted serum lipids and NCEP category (Abstract O18)

<table>
<thead>
<tr>
<th></th>
<th>FTC/RPV/TDF</th>
<th>PI+RTV</th>
<th>P-value</th>
<th>% Above</th>
<th>FTC/RPV/TDF</th>
<th>PI+RTV</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>-25</td>
<td>-1</td>
<td>&lt;0.001</td>
<td>&gt;200</td>
<td>16.1%</td>
<td>42.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>-16</td>
<td>0</td>
<td>&lt;0.001</td>
<td>≥130</td>
<td>18.8%</td>
<td>35.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>-53</td>
<td>3</td>
<td>&lt;0.001</td>
<td>≥150</td>
<td>18.8%</td>
<td>46.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>-4</td>
<td>-1</td>
<td>&lt;0.001</td>
<td>&lt;40</td>
<td>20.6%</td>
<td>24.0%</td>
<td>&lt;0.48</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>-0.27</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ABSTRACT O19

Antiviral Therapy 2012; 17 Suppl 2:A17

A randomized comparison of raltegravir versus lopinavir/ritonavir on lipid subfractions and high-sensitivity C-reactive protein in healthy volunteers

A Jackson1, P Randell1, A Milinkovic1, M Boffito1, G Moyle1

1Chelsea and Westminster Hospital, London, UK

Background: Inflammatory markers were associated with cardiovascular risk and may be affected with antiretroviral (ARV) agent choice. The impact of ARV on these markers may be best observed in an uninfected population.

Methodology: An open label, two-phase cross-over study in HIV-negative male subjects randomized 1:1 to receive 2 weeks of lopinavir/ritonavir 400/100 mg BID (LPV/R) followed by a 2-week washout period and 2 weeks of raltegravir 400 mg BID (RAL), or RAL initially followed by LPV/R. A hyperinsulinaemic euglycaemic clamp was performed prior to and following each 2-week phase of study medication. Fasting samples for lipids, adiponectin, leptin, vascular inflammation biomarkers and CD36 were also taken at each visit.

Results: 16 HIV-negative male subjects were dosed and completed the study. Two weeks of dosing with RAL did not significantly affect the glucose disposal rate assessed during the euglycaemic clamp, while 2 weeks of dosing with LPV/R resulted in a significant 16.1% reduction in the glucose disposal rate. Triglycerides rose significantly with LPV/R (+0.5 mmol/l, P=0.002) but were unchanged with RAL (+0.09 mmol/l, P=0.97). Total cholesterol rose significantly with LPV/R (+0.4 mmol/l, P<0.0001) but was unchanged with RAL (-0.01 mmol/l, P=NS). High-density lipoprotein (HDL) cholesterol fractions were not significantly impacted. Proatherogenic lipid subfractions of low-density lipoprotein (LDL) cholesterol increased with LPV/R and were unaffected with RAL. LDL MPD, LDL PPD and LDL I significantly decreased with LPV/R (P<0.05), and trend of increased LDL III was detected with LPV/R (+3.7 mmol/l, P=0.06). Leptin and adiponectin were unchanged. High-sensitivity C-reactive protein (hs-CRP) declined significantly with RAL (-0.2 mg/l, P=0.043), and rose significantly with LPV/R (+0.25 mg/l, P=0.03). No significant changes in CD36 and adipophin (ADFP) expression following either RAL or LPV/R treatment, were detected. CD36 expression non-significantly decreased with LPV/R treatment.

Conclusions: Lopinavir/ritonavir in healthy volunteers reduce insulin sensitivity and unfavourable affects lipid profile and hsCRP, whereas raltegravir is not associated with metabolic disturbance or inflammatory effects.

ABSTRACT O20

Antiviral Therapy 2012; 17 Suppl 2:A17

Lipids target goals attainment is slower achieved in HIV-infected patients compared to HIV-uninfected patients after acute coronary syndrome

F Boccara1, J Miantezila Basilua2, M Mary-Krause2, S Lang3, D Costagliola4, M Guiguet5, A Cohen1, the PACS-HIV investigators

1Department of Cardiology, Saint Antoine Hospital, Univ-Paris 6, AP-HP, Paris, France; 2INSERM, UMR_S 938, UPMC, Paris, France; 3INSERM U943, Paris, France; 4UPMC Univ-Paris 6, UMR S943, Paris, France

Objectives: This study aims to compare the lipid profile and lipid goals attainment in secondary prevention between HIV-infected (HIV+) and uninfected patients (HIV-) after a first episode of acute coronary syndrome (ACS) as part of the observational PACS-HIV study (Prognosis of Acute Coronary Syndrome in HIV-infected patients).

Methods: Fasting lipid parameters (total cholesterol, LDLc, HDLc, non-HDLc, triglycerides, total cholesterol/HDLc ratio), type, duration and tolerance (clinical and biological: serum creatine kinase [CK] >5×ULN and hepatic transaminases >3×ULN) of lipolowering drug (LLD) use were collected at baseline, month 1 and every 6 months during 3 years. The lipid goals were assessed by the updated 2004 NCEP-ATPIII guidelines.

Results: 103 HIV+ and 197 HIV- were prospectively enrolled in 23 French intensive care units. At baseline (in 99 HIV+ and 192 HIV-), lipid parameters were similar in both groups except for a higher level of triglycerides and total cholesterol/HDLc ratio in HIV+ (252 ±192 mg/dl versus 170 ±140, P<0.0001; 5.6 ±2.3 versus 5.1 ±1.8, P=0.03). Statin therapy was predominantly prescribed at discharge and similarly in both groups (89% versus 92%). However, during the entire follow up, the slope of variation in LDLc was much lower among HIV+ than HIV- and particularly during the first 6 months after the ACS (-9.3 versus 39.8; P<0.0001). Concordantly, HIV-infected patients were less likely to achieve lipid goals continuously from M6 to M36 (OR 0.92, 95% CI 0.28, 3.01 for LDLc). However at M36, no differences in achievement of the recommended thresholds were observed (OR 0.92, 95% CI 0.28, 3.01 for LDLc). LLD therapy was generally well tolerated and not different between the two groups (myalgia: 11% versus 9%, hepatic transaminases >3×ULN 3% versus 1%, CK >5×ULN 1% versus 0%).

Conclusion: The slower achievement of therapeutic goals in LDLc during the acute phase observed in HIV+ is an indication that the residual cardiovascular risk
remained high and warrant particular attention. This could have explained the increased rate of recurrent ACS during follow up previously found in HIV+ in the PACS-HIV study.

**ABSTRACT O21**

*Antiviral Therapy 2012; 17 Suppl 2:A18*

The HIV proteins, Tat and Nef, induce moderate senescence and oxidative stress of mesenchymal stem cells, precursors of osteoblasts

*C Beaupere1,2, J Capeau1,2,3, C Lagathu1,2*

1INSERM UMR938, Paris, France; 2UPMC Univ Paris 06, UMRS 938, Paris, France; 3APHP, Hopital Tenon, Paris, France

**Background:** HIV-infected patients naive to treatment or treated with combination antiretroviral therapy (cART) present a lower bone mineral density (BMD) than non-HIV-infected controls and a higher prevalence of osteopenia/osteoporosis. Candidate pathogens proposed to mediate HIV-associated decreased BMD include viral infection and the drug regimen. The HIV proteins Tat, gp120 and gag have been suspected to induce bone loss via alterations of osteoblastic differentiation and activity, but the precise mechanisms involved are unknown. Otherwise, some HIV proteins, including Tat and Nef, are released by infected cells in the extra-cellular medium, and were previously shown to directly induce harmful effects on immune cells, such as oxidative stress, mitochondrial dysfunction, apoptosis or inflammation. Bone mass and turnover are maintained by the coordinated balance between bone formation by osteoblasts and bone resorption by osteoclasts. In this study, we wondered whether the HIV proteins Tat and Nef could induce senescence of osteoblast precursors, namely bone marrow mesenchymal stem cells (MSCs), via oxidative stress and/or inflammation, and reduce their capacity to differentiate into osteoblasts.

**Material and methods:** Senescence, viability (MTT assay), oxidative stress (CM-H<sub>2</sub>DCFDA), mitochondrial dysfunctions (mitochondria labelling, CoxII/CoxIV ratio) and inflammation (IL-6), were studied in proliferating human adult bone marrow MSCs after a 15-day exposure to Tat (40 ng/ml) and Nef (20 ng/ml). The cell fate of MSCs was then assessed by evaluating their capacity to differentiate into osteoblasts and adipocytes.

**Results:** When compared to non-treated cells, long-term Tat and Nef-treated MSCs presented a moderate reduction in their proliferative activity after exposure: by 8% (Tat) and 13% (Nef) of control at day 15. Tat and Nef chronic exposure led to a progressive oxidative stress: 144% (Tat) and 135% (Nef) of control at day 15, mitochondrial dysfunctions (from day 5), inflammation with an increased expression (mRNA) and secretion of IL-6 (from day 10) and senescence, as shown by the senescence-associated beta-galactosidase activity (from day 15). The occurrence of a moderate cell senescence (around 10%) was confirmed by the increased expression of cell-cycle inhibitors (p21WAF1 and p16INK4A). Because age-related bone loss is associated with increased bone marrow fat, we evaluated the impact of HIV proteins-induced senescence on the capacity of MSC to differentiate towards the osteoblastic and adipogenic lineages, after a 20-day exposure. We observed that Tat-induced senescence did not alter the adipocyte/osteoblast differentiation. However, osteoblast and adipocyte differentiation were decreased by a treatment with Nef.

**Conclusion:** These in vitro data show that some HIV proteins could alter osteoblast formation by directly inducing senescence and affecting the osteoblast differentiation potential of MSCs. Thus, they are in keeping with the clinical data of low BMD in HIV-infected patients naive to ART. Overall, these results allow new insight into the pathophysiological mechanisms of decreased bone mineral density in HIV-infected patients.

**ABSTRACT O22**

*Antiviral Therapy 2012; 17 Suppl 2:A18*

The protease inhibitor atazanavir triggers autophagy in human adipocytes

*L Gibellini1, S De Biasi1, M Pinti1, M Riccio1, A De Pol1, JE O’Connor2, M Nasi1, A Cossarizza3*

1Univ. of Modena and Reggio Emilia, Modena, Italy; 2Univ. of Valencia, Spain

**Objectives:** The association between lipodystrophy and HAART is well established, but the precise pathogenesis is still poorly understood. NRTI and PI induce adipocyte dysfunction both in vitro and ex vivo by several mechanisms, including the increase of oxidative stress, the alteration of adipokine and cytokine production, the induction of endoplasmic reticulum stress, or the proteasome inhibition. Recent studies have identified autophagy as a new mechanism involved in antiretroviral-dependent tissue damage. Here we show that, in SW872 human adipocytic cell line, atazanavir (ATV, a protease inhibitor, used at concentrations similar to those present in patients’ plasma) is able to trigger autophagy, a process that can rescue cells from apoptosis or necrosis.

**Methods:** We stably transfected SW872 cells with a fluorescent form of the microtubule-associated light
increase of mtO2 content. Non-apoptotic cells exhibited a dose-dependent correlation (r=0.91); ATV also increased lysosomal autophagosomes and lysosomes colocalized (Pearson's cells treated with 50 μM ATV for 16 h, mitochondria, were only occasionally present after 6 h of treatment. In presence was then confirmed by TEM. Autophagosomes suggesting the formation of autophagosomes, whose treated for 24 h showed Results: The distribution of LC3 was evaluated in cells for up to 24 h with ATV (10–200 μM). Cells treated for 24 h showed LC3-specific punctae, thus suggesting the formation of autophagosomes, whose presence was then confirmed by TEM. Autophagosomes were only occasionally present after 6 h of treatment. In cells treated with 50 μM ATV for 16 h, mitochondria, autophagosomes and lysosomes colocalized (Pearson’s correlation r=0.91); ATV also increased lysosomal content. Non-apoptotic cells exhibited a dose-dependent increase of mtO2−. The highest doses of ATV induced apoptosis. However, cell death was much lower in cells treated with ATV than in those treated with ritonavir. Conclusions: ATV can induce autophagy in human adipocytic cells, especially at doses that are similar to those observed in patients. Such mechanism can be considered an effort of adipocyte to escape apoptotic cell death.

ABSTRACT O23
Antiviral Therapy 2012; 17 Suppl 2:A19

The immunomodulatory peptide, LL-37, is associated with CD4 count and immune restoration in HIV-infected youth

AC Ross1,2, SE Judd3, JA Alvarez2, TR Ziegler2, L Hao3, L Seaton3, GA McComsey4,5, V Tangpricha1

1Emory University School of Medicine, Atlanta, GA, USA; 2Children’s Healthcare of Atlanta, Atlanta, GA, USA; 3University of Alabama at Birmingham, Birmingham, AL, USA; 4Case Western Reserve University, Cleveland, OH, USA; 5Rainbow Babies & Children’s Hospital, Cleveland, OH, USA

Objectives: The antimicrobial peptide cathelicidin, LL-37, is produced in response to active vitamin D to enhance innate immunity, exert immunomodulatory effects and decrease pro-inflammatory cytokines. LL-37 also inhibits HIV replication in vitro. To date, no studies have investigated plasma LL-37 concentrations in HIV-infected patients in vivo. This study sought to investigate the relationship between plasma LL-37 and 25-hydroxyvitamin D (25(OH)D) concentrations, and HIV-related variables in HIV-infected youth.

Methods: HIV-infected subjects and healthy controls ages 1–25 years old were prospectively enrolled. Fasting plasma LL-37 was measured in duplicate with ELISA. Fasting plasma 25(OH)D was measured using an automated chemiluminescent assay. Non-parametric tests were used to assess differences between groups. Spearman coefficients were used to assess correlations with LL-37. Multivariable regression analysis was performed to determine variables independently associated with LL-37.

Results: HIV+ subjects (36 ART-experienced; 27 ART-naïve) and 31 healthy controls were enrolled. ART-experienced subjects were similar to the two other groups (ART-experienced: median [interquartile range; IQR] age =17.9 years [14.6–20.2], 94% black, 58% male), except that ART-naive had more males (85%). Plasma 25(OH)D concentrations did not differ between groups (ART-experienced: median [IQR] 25(OH)D=15.5 ng/ml [10.8–19.6]). Eighty-three percent of ART-experienced were currently on ART (81% HIV-1 RNA<80 copies/ml). ART-experienced had a median current/nadir CD4 count of 431/183 cells/mm3, respectively, versus 297/296 cells/mm3, respectively, in ART-naive. In ART-experienced, CD4 restoration after ART (∆CD4= current - nadir CD4) was 229 cells/mm3 with 14.5 median years of HIV infection. There was no difference in median (IQR) LL-37 between the HIV+ group and controls (HIV+: 58.3 μg/ml [46.4–69.5] versus controls: 51.3 [40.8–98.2]; P=0.57); however, ART-experienced had higher levels than ART-naive (ART-experienced: 66.2 μg/ml [55.4–77.0] versus ART-naive: 48.9 μg/ml [38.9–57.9], P<0.001). In univariate analysis, LL-37 was positively correlated with 25(OH)D in controls (R=0.43; P=0.02), but not in the HIV+ group as a whole or when the ART-experienced and ART-naive groups were considered separately. LL-37 was not correlated with age, body mass index, CD4 nadir or HIV-1 RNA in any group. However, LL-37 was positively correlated with current CD4 count in ART-experienced (R=0.37; P=0.02), but not in ART-naïve. LL-37 was positively correlated with ∆CD4 in ART-experienced (R=0.40; P=0.02). After adjustment for age, race, sex and HIV duration, the association between LL-37 and current CD4 count remained significant (P=0.03) but not between LL-37 and ∆CD4 (P=0.09).
Conclusions: Plasma LL-37 was positively associated with plasma 25(OH)D concentrations in healthy controls but not in HIV+ subjects. Plasma LL-37 was higher in ART-experienced HIV+ subjects compared to ART-naive, and plasma LL-37 was associated with CD4 counts and immune restoration after ART. These findings suggest that HIV+ status and/or HIV-related variables may interfere with the expected positive relationship between vitamin D and LL-37, and LL-37 may play an important role in immunomodulation and immune restoration in HIV disease.

ABSTRACT 024
Antiviral Therapy 2012; 17 Suppl 2:A20

Comorbidity and ageing in HIV-1 infection: the AGEhIV Cohort Study

J Schouten1,2, FW Wit2,3, IG Stolte4, M van der Valk1, SE Geerlings1, F de Wolf5, M Prins3,4, P Reiss2,3, on behalf of the AGEhIV Cohort Study Group

1Academic Medical Center, Department of Neurology, Amsterdam, the Netherlands; 2Academic Medical Center, Department of Global Health and Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands; 3Academic Medical Center, Division of Infectious Diseases, Amsterdam, the Netherlands; 4Public Health Service Amsterdam, Infectious Diseases Research, Amsterdam, the Netherlands; 5HIV Monitoring Foundation, Amsterdam, the Netherlands

Background: HIV-positive patients may be at increased risk of premature onset of age-associated non-communicable comorbidity (AANCC).

Methods: Comprehensive assessment for AANCC in an ongoing prospective cohort study of HIV-1-infected patients ≥45 years from a tertiary care HIV-outpatient clinic, and concurrently recruited HIV-uninfected municipal sexual health clinic attendants, comparable regarding age, gender and ethnicity. Baseline data on AANCC (self-reported AANCC and/or objectively measured hypertension/COPD) were analysed.

Results: Baseline characteristics from the first consecutively enrolled 381 HIV-positive and 349 HIV-negative subjects are listed in Table 1. 74.5% of HIV-patients and 61.6% of controls experienced ≥1 AANCC (P<0.001). The mean number of AANCC was 1.4 and 1.0, respectively (P<0.001).

Hypertension, angina pectoris, myocardial infarction, peripheral arterial insufficiency, cerebrovascular disease, cancer and chronic liver disease were significantly more prevalent among HIV-patients. The proportion of HIV-patients experiencing ≥1 AANCC increased from 59.8% (45–50 age stratum) to 94.9% (65+ age stratum) (P for trend <0.0001), compared to 49.6% to 88.5% (P for trend <0.0001) among controls. The mean number of AANCC among HIV-patients increased from 0.87 (45–50 age stratum) to 2.03 (65+ age stratum), versus 0.69 to 1.73 among controls. In each age stratum the mean number of AANCC was higher among HIV-positives. By ordinal logistic regression analysis, adjusting for age, gender and pack years of smoking, documented duration of HIV-seropositivity was associated with a significantly greater risk of a higher number of AANCC (OR 1.17 per 5 years, 95% CI 1.07–1.27; P=0.0003). Among HIV-patients, after adjustment for age, gender and pack years of smoking, documented duration of ART use (OR 1.24 per 5 additional years of ART use, 95% CI 1.06–1.46; P=0.009) and lower nadir CD4 count (OR...

Table 1. General demographic and HIV-related characteristics (Abstract O24)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-neg [n=349]</th>
<th>HIV-pos [n=381]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51.7 (47.5–58.1)</td>
<td>53.1 (48.5–59.8)</td>
<td>0.022</td>
</tr>
<tr>
<td>Male gender</td>
<td>84.2%</td>
<td>90.6%</td>
<td>0.010</td>
</tr>
<tr>
<td>Dutch</td>
<td>81.7%</td>
<td>75.9%</td>
<td>0.307</td>
</tr>
<tr>
<td>MSM</td>
<td>65.0%</td>
<td>71.7%</td>
<td>0.055</td>
</tr>
<tr>
<td>Smoking, pack years</td>
<td>3.0 (0.0–19.0)</td>
<td>7.6 (0.0–30.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>Current smokers</td>
<td>22.6%</td>
<td>31.8%</td>
<td>0.006</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>7.2%</td>
<td>2.9%</td>
<td>0.008</td>
</tr>
<tr>
<td>XTC abuse</td>
<td>9.5%</td>
<td>4.2%</td>
<td>0.005</td>
</tr>
<tr>
<td>Years documented HIV-1 seropositive, years</td>
<td></td>
<td>12.4 (6.8–17.5)</td>
<td></td>
</tr>
<tr>
<td>Mean CD4-count in year prior to enrollment, cells/mm³</td>
<td>548 (421–728)</td>
<td>330 (230–450)</td>
<td>0.003</td>
</tr>
<tr>
<td>Nadir CD4-count, cells/mm³</td>
<td>843%</td>
<td>21.0%</td>
<td></td>
</tr>
<tr>
<td>HIV RNA&lt;40 copies/ml during year prior to enrollment</td>
<td></td>
<td>92.4% (67.2% started from naïve; 25.2% started ART-experienced)</td>
<td></td>
</tr>
<tr>
<td>Prior AIDS</td>
<td></td>
<td>11.4 (5.3–14.9)</td>
<td></td>
</tr>
</tbody>
</table>

A20 Programme & Abstracts
1.12 per 100 less cells, 95% CI 0.99–1.28; *P*=0.074) were each associated with an increased risk of a higher number of AANCC, whereas documented duration of infection was not. 

**Conclusion:** In HIV-positive persons ≥45 years of age AANCC was more prevalent compared to controls, and the risk of having a higher number of comorbidities was independently associated, not only with age and smoking history, but also with duration of ART use and severity of documented prior immunodeficiency.

**ABSTRACT 025**

*Antiviral Therapy* 2012; 17 Suppl 2:A21

**Free testosterone should be used to diagnose hypogonadism in HIV-infected men**


1Johns Hopkins University School of Medicine, Division of General Internal Medicine, Baltimore, MD, USA; 2Johns Hopkins University School of Medicine, Division of Endocrinology and Metabolism, Baltimore, MD, USA; 3Division of Infectious Diseases, Feinberg School of Medicine of Northwestern University, Chicago, IL, USA; 4Department of Infectious Diseases and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA; 5Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Los Angeles, CA, USA

**Objectives/aim:** The Endocrine Society recommends the morning measurement of total testosterone (T) to diagnose hypogonadism in men. However, elevated sex hormone-binding globulin (SHBG) in HIV-infected men can falsely elevate total T, potentially leading to missed diagnosis of hypogonadism. Therefore, free T may more accurately diagnose hypogonadism in HIV-infected men. In this analysis we determined the prevalence of hypogonadism among men in a substudy of the Multicenter AIDS Cohort Study (MACS) and compared the diagnosis of hypogonadism by total T and free T assays.

**Methods:** Participants (*n*=945) were older than 40 years, weighed less than 300 pounds, and had no history of coronary heart disease. The present analysis included men who had a blood sample drawn before 10 AM and were on antiretroviral therapy. T and SHBG were measured from archived serum by LC-tandem MS and RIA, respectively. Free T was calculated using the Vermeulen equation. Low total T and low free T were defined as <300 ng/dl and <48 pg/ml, respectively.

**Results:** Of 943 men in the substudy, T assays were not performed in 89 men. These men had insufficient/no stored serum (18 men) or were on T therapy (71 men). Ninety-nine percent (70/71) of men excluded for receiving T therapy were HIV-infected. Of the 508 men who met all inclusion criteria for the present analysis, 342 (67.3%) were HIV-infected and 166 (32.7%) were HIV-uninfected. The prevalence of chemical hypogonadism, as diagnosed by either low FT or low T was similar in HIV-infected (31/342=9.1%) and HIV-uninfected (12/166=7.2%) participants (*P*=0.61). Of the 31 HIV-infected men with hypogonadism, 10 (32%) had normal total T, but low free T. In contrast, of the 12 HIV-uninfected men with hypogonadism, no men were in this category (*P*=0.04).

**Conclusion(s)/discussion:** Our data suggest that using AM total T to diagnose hypogonadism in HIV-infected men will result in missing about 30% of the cases. Morning free T should be measured in all HIV-infected men in whom hypogonadism is suspected.
POSTER PRESENTATIONS
ABSTRACT P01
Antiviral Therapy 2012; 17 Suppl 2:A25
Rilpivirine + emtricitabine/tenofovir DF (FTC/TDF) demonstrates similar efficacy with differences in tolerability compared with efavirenz (EFV) plus emtricitabine/tenofovir DF (FTC/TDF) at week 96 treatment-naive, HIV-1-infected adults age <45 and ≥ age 45 at: Pooled ECHO and THRIVE Studies

1 Anthony Mills MD Inc., Los Angeles, CA, USA; 2Whitman Walker Clinic, Washington, DC, USA; 3UMDNJ-New Jersey Medical School, Newark, NJ, USA; 4Community Research Initiative of New England, Boston, MA, USA; 5Janssen Infectious Diseases BVBA, Beerse, Belgium; 6Gilead Sciences Inc., Foster City, CA, USA

Background/objective: Advancing age among antiretroviral (ART)-treated HIV-infected persons necessitates careful analysis of long-term safety of ART regimens in older patients, specifically risks known to increase with age. The FTC/TDF subset of ECHO and THRIVE is particularly relevant due to direct comparison of RPV versus EFV and the availability of single-tablet regimens with these components.

Methods: Week 96, post-hoc analysis by age was completed with <45 and ≥45 years as younger (YN) and older (OL) age strata using the pooled ECHO and THRIVE studies. To achieve a minimum of 100 OL subjects per study arm, stratification used 45 years – younger (YN) and older age strata using the pooled ECHO and THRIVE studies (all < YN age stratum only, somnolence was more common with EFV. In OL age stratum only, somnolence was more common with EFV (all P<0.05). In both strata, week 96 changes in low-density lipoprotein cholesterol (LDL-C; mg/dl) were lower with RPV versus EFV (YN: -2 versus +11; OL: 0 versus +12), as well as rates of Grade 1–3 LDL-C (>130 mg/dl) (YN: 25% versus 50%; OL: 35% versus 56%), respectively (all P<0.01). HDL-C changes favoured EFV in both strata (YN: 3 versus 9 and OL: 4 versus 11; P<0.001).

Median changes in estimated glomerular filtration rate (GFR; ml/min/1.73m²) were similar by age strata within study arms: -15 and -11 (RPV-YN and -OL) versus -5 and -3 (EFV-YN and -OL). In the YN stratum only, EFV subjects had more Grade 2–4 transaminase elevations (7% versus 13%; P<0.007).

Conclusions: In both age strata at week 96, no significant differences in overall virological and immunological responses were observed for RPV+FTC/TDF versus EFV+FTC/TDF. RPV+FTC/TDF had a more favourable AE profile in older subjects compared to EFV+FTC/TDF. In older and younger subjects with baseline VL<100,000 c/ml, VF rates were low and similar by study arms, but in overall analysis (regardless of baseline VL) VFs were higher for RPV+FTC/TDF.

ABSTRACT P02
Antiviral Therapy 2012; 17 Suppl 2:A25
Differential responses to HIV-1 infection and to first-line ART by mitochondria from peripheral blood lymphocytes and monocytes: the ANRS EP45 ‘Aging’ study

S. Perrin1,2, J. Cremer1,2, P. Roll1,2, O. Faucher3, J. Reyne1, P. Dellamonica4, J. Micallef3, E. Jouve3, C. Tamalet1, C. Solas3, I. Arnoux2, C. Nicolin-Brunet4, L. Espinos6, A. Robaglia-Shlupp1,2, I. Poizat-Martin4, P. Cau1,2
1 Aix Marseille University, Marseille, France; 2AP-HM, Marseille, France; 3CHRU Gui-de-Chauliac, Montpellier, France; 4CHU l’Archet, Nice, France

Background: The ANRS EP45 ‘Aging’ study investigates cellular mechanisms involved in accelerated aging exhibited by HIV-infected and treated patients. Data reported are focused on mitochondria, an organelle known to be involved in cell senescence.
Methods: 49 HIV-1-infected patients never treated with antiretroviral therapy (ART-naive), age- and sex-matched with 49 seronegative control subjects, as well as 81 HIV-1-infected and treated patients, were recruited by 3 AIDS centres (Marseille, Montpellier, Nice, France; http://clinicaltrials.gov/, NCT01038999). In more than 88% of treated patients, viral load was <40 copies/ml, and their CD4+ cell count >500/mm³. ROS (reactive oxygen species) production and ∆Ψm (inner membrane potential) were measured by flow cytometry in blood lymphocytes and monocytes (functional parameters). Three mitochondrial network quantitative morphological parameters were computed using confocal microscopy and image analysis. Three PBMC mitochondrial proteins (porin, subunits 2 and 4 of cytochrome C oxidase encoded by mtDNA or nuclear DNA, respectively) were analysed by western blot.

Results: Neither HIV-1 infection nor ART induced quantitative changes in the three PBMC mitochondrial proteins. HIV-1 infection leads to a 20% increase in basal ROS production by high-ROS lymphocytes and to a 21% ∆Ψm decrease by low-∆Ψm lymphocytes. Correlations between lymphocyte mitochondrial parameters and viral load confirmed the HIV-1 damaging effects. No significant variations were observed in monocyte mitochondria from naive patients. Discriminant analysis integrating functional or morphological parameters confirmed ART differential effects according to cell type. Whereas, first-line ART tend to rescue lymphocyte mitochondrial parameters altered by viral infection, slight changes were induced by ART combinations in monocytes. No statistical difference was found between the three ART regimens.

Conclusions: In patients considered to be stable, mitochondria exhibit minor modifications resulting either from HIV-1 infection direct or indirect effect, in lymphocytes, or from first-line ART, in monocytes.
ABSTRACT P03

Normal values and distribution of fat tissue in healthy adults

J Malouf1, F Torres2, S Di Gregorio1, L del Rio1, V Estrada1, A Marin1, S Herrera1, J Munoz1, P Domingo1

1Internal Medicine Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; 2Biostatistics and Data Management Platform, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clinic, Universitat de Barcelona, Barcelona, Spain; 3Department of Densitometry, CETIR Medical Group, Barcelona, Spain; 4Infectious Diseases Unit, Hospital Clinico San Carlos, Madrid, Spain

Aim: The aim of this study was to describe the distribution of the values of fat tissue in healthy adults. Methods: Whole body composition scan was performed to 3,387 subjects using three DXA scanners, (1) Lunar Prodigy Advance, (2) Lunar iDXA and (3) Hologic Discovery. Translational equations between scanners were developed, scanning 91 healthy volunteers in all scanners on the same day. Results: Demographic characteristics are summarized in Table 1. Bland Altman and Lin concordance analysis were performed after applying the translational equations to normalize the values acquired with the different scanners. Concordance results show good results for every compartment between scanners except for the trunk–leg ratio between iDXA and the other two scanners. Details exposed in Table 2. Distribution curves were similar for the three different scanners although iDXA gave different results for trunk–leg ratio and trunk–extremities ratio. Conclusion: Further statistical analysis has to be done before concluding this work and establish normal values and distribution of fat tissue. Nevertheless these are promising results that can help us indentify the abnormal fat tissue values in those patients with fat tissue redistribution.

ABSTRACT P04

Influence of age on indices of fat distribution in HIV-infected patients on antiretroviral treatment

P Domingo1, J Malouf1, F Torres2, E Negredo1, P Viciana3, J Luis Casado6, E Martinez2, V Estrada7, S Di Gregorio8, J Munoz1, A Marin1, L Del Rio1

1Internal Medicine Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; 2Biostatistics and Data Management Platform, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clinic, Universitat de Barcelona, Barcelona, Spain; Fundació Lluita contra la Sida, Hospital Germans Trias y Pujol, Barcelona, Spain; 3Infectious Diseases Unit, Hospital Universitari Virgen del Rocio, Sevilla, Spain; 4Infectious Diseases Unit, Hospital Universitario Ramón y Cajal, Madrid, Spain; 5Infectious Diseases Department, Hospital Clinic Universitari, Barcelona, Spain; 6Infectious Diseases Unit, Hospital Clinico San Carlos, Madrid, Spain; 7Department of Densitometry, CETIR Medical Group, Barcelona, Spain

Objective: To assess the impact of age on the indices of fat distribution in HIV-infected patients on antiretroviral therapy. Patients and methods: 3,042 HIV-infected patients on ART had a dual X-ray absorptiometry (DXA) performed from 1999 to 2012. BMI was body weight/height2. DXA scans were performed with Lunar Prodigy™ (n=1,079, 35.5%) and Hologic™ systems (n=1,963, 64.5%). Segmental fat was estimated following the instructions of manufacturers. Values are expressed as medians (95% CI) unless otherwise specified. The Fisher’s exact test was used to compare categorical and an ANOVA adjusting by centre, BMI and gender was used to compare the DXA scans between age groups. Results: There were 2,818 (92.6%) patients younger than 60 year and 224 (7.4%) were aged ≥60 years. Females were 688 (24.4%) in younger group and 42 (18.8%) in the older one (P=0.056). Patients’ age groups in the young patients were as follows: 17–30 years: 168 (6.0%), 30–40 years: 709 (25.2%). 40–50 years: 1,405 (49.9%), 50–60 years: 536 (19.0%). BMI strata by age group are as shown in Table 1. After adjusting by centre, BMI and gender, whole body fat was not different between groups, whereas trunk fat was significantly greater for the older (10,058.25 [9,695.01 to 10,421.50] versus 8,961.37 [8,828.37 to 9,094.37] grams; P<0.001), leg fat was inferior in the older group (3,696.70 [3,407.29 to 3,986.11] versus 3,807.37 [3,588.08 to 4,026.66] grams; P<0.001).

14th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV A27
Table 1. Demographic characteristics (Abstract P03)

<table>
<thead>
<tr>
<th></th>
<th>Prodigy</th>
<th>iDXA</th>
<th>Hologic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=542)</td>
<td>(n=466)</td>
<td>(n=2,379)</td>
<td>(n=3,387)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Female</td>
<td>431 (79.5%)</td>
<td>246 (52.8%)</td>
<td>787 (33.1%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>Mean (sd)</td>
<td>43.0 (18.6)</td>
<td>54.0 (14.8)</td>
<td>46.1 (14.8)</td>
</tr>
<tr>
<td>n (%)</td>
<td>&gt;17–≤30</td>
<td>191 (35.2%)</td>
<td>38 (8.2%)</td>
<td>265 (11.1%)</td>
</tr>
<tr>
<td></td>
<td>&gt;30–≤40</td>
<td>119 (22.0%)</td>
<td>52 (11.2%)</td>
<td>663 (27.9%)</td>
</tr>
<tr>
<td></td>
<td>&gt;40–≤50</td>
<td>46 (8.5%)</td>
<td>86 (18.5%)</td>
<td>798 (33.5%)</td>
</tr>
<tr>
<td></td>
<td>&gt;50–≤60</td>
<td>70 (12.9%)</td>
<td>127 (27.3%)</td>
<td>274 (11.5%)</td>
</tr>
<tr>
<td></td>
<td>&gt;60–≤70</td>
<td>62 (11.4%)</td>
<td>113 (24.2%)</td>
<td>167 (7.0%)</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>54 (10.0%)</td>
<td>50 (10.7%)</td>
<td>212 (8.9%)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>Mean (sd)</td>
<td>161.6 (8.6)</td>
<td>163.7 (10.2)</td>
<td>167.8 (9.9)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Mean (sd)</td>
<td>63.5 (13.1)</td>
<td>70.1 (13.0)</td>
<td>69.0 (12.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Mean (sd)</td>
<td>24.4 (4.3)</td>
<td>26.1 (3.8)</td>
<td>24.5 (3.4)</td>
</tr>
<tr>
<td>n (%)</td>
<td>≤20</td>
<td>90 (16.6%)</td>
<td>17 (3.6%)</td>
<td>244 (10.3%)</td>
</tr>
<tr>
<td></td>
<td>&gt;20–≤25</td>
<td>234 (41.2%)</td>
<td>187 (40.1%)</td>
<td>1,166 (49.0%)</td>
</tr>
<tr>
<td></td>
<td>&gt;25–≤30</td>
<td>158 (29.2%)</td>
<td>184 (39.5%)</td>
<td>769 (32.3%)</td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td>60 (11.1%)</td>
<td>78 (16.7%)</td>
<td>200 (8.4%)</td>
</tr>
</tbody>
</table>

Table 2. Lin concordance results (Abstract P03)

<table>
<thead>
<tr>
<th></th>
<th>Prodigy versus iDXA</th>
<th>Prodigy versus Hologic</th>
<th>iDXA versus Hologic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lin1 (95% LL)</td>
<td>Bias ±2 so</td>
<td>Lin1 (95% LL)</td>
</tr>
<tr>
<td>Arms-fat</td>
<td>0.908 (0.903)</td>
<td>388.3 [56.63–720.0]</td>
<td>0.981 (0.980)</td>
</tr>
<tr>
<td>Legs-fat</td>
<td>0.970 (0.969)</td>
<td>647.1 [1–197–1491]</td>
<td>0.977 (0.976)</td>
</tr>
<tr>
<td>Total-fat</td>
<td>0.964 (0.962)</td>
<td>1,882 [664–1,448]</td>
<td>0.935 (0.931)</td>
</tr>
<tr>
<td>Total-tissue</td>
<td>1.000 (1.000)</td>
<td>1,166 [100.0–1166]</td>
<td>0.984 (0.983)</td>
</tr>
<tr>
<td>Trunk-fat</td>
<td>0.985 (0.985)</td>
<td>1,954 [-1,091–1,920]</td>
<td>0.902 (0.892)</td>
</tr>
<tr>
<td>Trunk-extremities ratio</td>
<td>0.960 (0.958)</td>
<td>-1.57 [-368–0.054]</td>
<td>0.981 (0.980)</td>
</tr>
<tr>
<td>Trunk–legs ratio</td>
<td>0.115 (0.082)</td>
<td>0.112 [-2.80–3.028]</td>
<td>0.989 (0.988)</td>
</tr>
</tbody>
</table>

1Lin’s concordance and 95% lower limit. 2Bland-Altman bias ± 2 standard deviations (sd).

4,899.10 [4,793.13 to 5,005.06] grams; P<0.001). Fat mass ratio or trunk/leg fat ratio (3.30 [3.10 to 3.50] versus 2.23 [2.16 to 2.30]), and trunk/appendicular fat ratio (2.06 [1.97 to 2.16] versus 1.50 [1.46 to 1.53]), were significantly higher in the older group of patients (P<0.001, in both cases).

Conclusions: Our data suggest that patient’s age is a factor contributing to fat redistribution in HIV-infected patients on ART.

ABSTRACT P05

Antiviral Therapy 2012; 17 Suppl 2:A28

IGF-1, IGFBP3, IGF-1/IGFBP3, interleukins -4 and -6 in HIV-infected patients on antiretroviral therapy according to fat mass distribution

P Freitas1,2, E Lau1,3, AC Santos2,3, AJ Madureira2,4, J Pereira1, A Sarmento1,6, JL Medina2, D Carvalho1,2

1Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal; 2Faculty of Medicine, Centro Hospitalar São João, Porto, Portugal; 3Department of Clinical Epidemiology, Predictive Medicine and Public Health, Centro Hospitalar São João, Porto, Portugal; 4Nuclear Medicine Department, Centro Hospitalar São João, Porto, Portugal; 5Radiology Department, Centro Hospitalar São João, Porto, Portugal; 6Infectious Diseases Department, Centro Hospitalar São João, Porto, Portugal

Introduction: Combined antiretroviral therapy (cART) in the treatment of HIV-1 infection has been associated
with lipodystrophy, characterized by abnormal adipose tissue redistribution and insulin resistance, which can be associated with impaired expression of insulin-like growth factor-1 (IGF-1) and expression of pro-inflammatory cytokines, such as interleukin-4 (IL-4) and interleukin-6 (IL-6).

**Aims:** To compare IL-4, IL-6, IGF-1, IGF binding protein-3 (IGFBP-3) plasma levels and IGF-1/IGFBP-3 ratio in patients with and without lipodystrophy defined by fat mass ratio (FMR= % trunk fat mass/% lower-limb fat mass by DXA) and according to 4 groups of body composition (without lipodystrophy; with isolated central fat accumulation; with isolated peripheral lipoatrophy; mixed forms of lipodystrophy).

**Methods:** Cross-sectional study of 253 HIV-1 patients on cART. We evaluated anthropometric parameters, insulin resistance (HOMA) and body composition (assessed by DXA and at abdominal level by CT scanner).

**Results:** Of the total of the patients, 40.4% had lipodystrophy. Those with lipodystrophy had higher HIV infection duration (8.6 versus 7.6 years; \( P < 0.033 \)), longer cART duration (8.0 versus 5.8 years; \( P < 0.001 \)), higher IGFBP3 levels (6.8 versus 3.5 ng/ml; \( P < 0.001 \)), lower IGF-1/IGFBP-3 ratio (33.4 versus 42.4; \( P < 0.01 \)) and higher HOMA (3.72 versus 2.67; \( P < 0.001 \)). When taking into account the 4 groups of body composition, 12.6% had no lipodystrophy, 26.5% had isolated central fat accumulation, 32.8% isolated peripheral lipoatrophy and 28.1% mixed forms of lipodystrophy. Patients with isolated peripheral lipoatrophy had higher infection duration; mixed forms of lipodystrophy had longer cART duration and higher HOMA and IGFBP-3 levels. There were no statistically significant correlations between IGF-1, IGFBP-3 and IGF-1/IGFBP3 ratio and the different groups of body composition. Interleukins were evaluated in a subgroup of 84 patients, of which 46.4% had lipodystrophy. These patients had higher HIV infection duration (8.3 versus 6.1 years; \( P < 0.001 \)) and longer cART duration (7.8 versus 4.7 years; \( P < 0.001 \)). No differences were found in IL-4 and IL-6 serum levels between patients with or without lipodystrophy. When taking into account the 4 groups of body composition, 7% had no lipodystrophy, 25.6% had isolated central fat accumulation, 30.2% isolated peripheral lipoatrophy and 37.2% mixed forms of lipodystrophy. There were no statistically significant associations between IL-4 and IL-6 concentrations and body fat distribution in these subgroups analysis. No significant correlations of IL-4 and IL-6 levels and body fat distribution or HOMA were found.

**Conclusion:** In this group of HIV-infected patients under cART there were no significant correlations between IGF-1, IGFBP3 and IGF-1/IGFBP-3 ratio, according to body fat distribution or HOMA, despite the fact that lipodystrophic patients had higher levels of IGF-BP3, lower IGF-1/IGFBP3 ratio and higher HOMA. We couldn’t also find significant correlations between IL-4 and IL-6 levels and body fat distribution or insulin resistance.

**ABSTRACT P06**

**Antiviral Therapy 2012; 17 Suppl 2:A29**

**Gender-different associations of androgens to body fat mass distribution in HIV-infected patients**

P Freitas\(^1,2,\) E Lau\(^1,2,\) AC Santos\(^2,3,\) AJ Madureira\(^3,4,\) J Pereira\(^5,\) A Sarmento\(^2,6,\) JL Medina\(^1,\) D Carvalho\(^1,2\)

\(^1\)Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João, Porto, Portugal; \(^2\)Faculty of Medicine, Centro Hospitalar São João, Porto, Portugal; \(^3\)Department of Clinical Epidemiology, Predictive Medicine and Public Health, Centro Hospitalar São João, Porto, Portugal; \(^4\)Nuclear Medicine Department, Centro Hospitalar São João, Porto, Portugal; \(^5\)Radiology Department, Centro Hospitalar São João, Porto, Portugal; \(^6\)Infectious Diseases Department, Centro Hospitalar São João, Porto, Portugal.

**Introduction:** Combined antiretroviral therapy (cART) in the treatment of HIV-1 infection has been associated with lipodystrophy, characterized by fat redistribution and insulin resistance. Visceral adipose tissue (VAT) has been inversely correlated with testosterone and sex hormone binding globulin (SHBG).

**Objectives:** To compare total testosterone (TT), free testosterone (Tf), dehydroepiandrosterone-sulfate (DHEA-S) and androstenedione in patients with and without lipodystrophy defined by fat mass ratio (FMR= % of the trunk fat mass/ % of the lower limbs fat mass) and according to 4 different groups of body composition (without lipodystrophy; with isolated central fat accumulation; with isolated peripheral lipoatrophy; mixed forms of lipodystrophy).

**Methods:** Cross-sectional study of 253 HIV-1-infected patients on cART. We evaluated anthropometric parameters, insulin resistance (HOMA) and body composition (assessed by DXA and by CT scanner at abdominal level).
Results: Patients with lipodystrophy had longer duration of cART and higher HOMA; lipodystrophic men showed lower SHBG levels (47.6 versus 74.5 nmol/l; \( P=0.004 \)). Men with isolated central fat accumulation had lower TT levels. Women with mixed forms of lipodystrophy had lower DEHA-S levels, while men had lower concentrations of SHBG. Both had higher HOMA. In total sample, TF was inversely correlated with total fat; in men it was also inversely correlated with subcutaneous abdominal tissue (SAT). In men, negative correlations were found between TT and visceral adipose tissue (VAT), total abdominal fat mass and HOMA. Also, other significant negative correlations were found between: DHEA-S and VAT/SAT ratio; androstenedione and total abdominal fat mass and SAT; and between SHBG and total abdominal fat mass, SAT, VAT and VAT/SAT ratio. In women, SHBG was negatively correlated with total abdominal fat mass, VAT and SAT.

Conclusion: In this group of HIV-infected patients under cART, androgens (TT, TF, DHEA-S and androstenedione) levels were differently associated with body fat distribution according to gender.

ABSTRACT P07

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Lipodystrophy and ectopic adipose tissue are associated with activated immune phenotype in HIV-infected patients on virologically suppressive ART

K Luzi1, GM Bellestri1, S Zona2, AR Domingues da Silva1, F Bai1, G Orlando2, F Carli2, A d’Arminio Monforte1, G Marchetti1, G Guaraldi2

1Department of Medicine, Surgery and Dentistry, Clinic of Infectious and Tropical Diseases, University of Milano, Milan, Italy; 2Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy; 3Servizio di Doenças Infecciosas, Hospital de Joaquim Urbano, Porto, Portugal

Objective: The aim of the study was to describe the association between clinical lipodystrophy (LD) and ectopic fat measurements with peripheral activated/differentiated T-cell phenotype and IL-7/IL-7R system. Visceral and epicardial fat measurements were explored in the association to T2DM and CVD risks.

Methods: Cross-sectional study including 87 HIV+ patients on suppressive antiretroviral therapy, evaluated for clinical LD, visceral/total adipose tissue ratio (VAT/TAT), epicardial adipose tissue (EAT), insulin resistance (HOMA-IR) and coronary calcium score (CAC>10). T-lymphocytes (T-ly) activation (CD8/HLA-DR/CD38), differentiation (CD4/CD8/CCR7/CD45RA) and IL-7/IL7R system (CD4/CD8/CD127; IL-7; CD4/CD8/pStat-5) were assessed by cytometry.

Results: Both lipoatrophy and central fat accumulation were associated with CD8+CD38+T cells (lipoatrophy: \( \beta=5.63; P=0.005 \)); central fat accumulation: \( \beta=12.8; P=0.003 \) and CD8+CD127+T cells (lipoatrophy \( \beta=12.8; P=0.003 \); central fat accumulation \( \beta=9.45; P=0.016 \)) after adjusting for sex and age. CD8+CD38+DR+T cells were associated with VAT/TAT (\( \beta=0.26; P=0.011 \)) but not with EAT (\( \beta=0.23; P=0.839 \)). CD8+CD127+ T cells were associated with EAT (\( \beta=-0.22; P=0.043 \)) but not with VAT/TAT (\( \beta=-0.12; P=0.27 \)). VAT/TAT was associated with both HOMA-IR and CAC, on the contrary, EAT was associated only with CAC.

Conclusions: CD8+CD38+T cells and CD8+CD127+T cells homeostasis alteration is associated with lipodystrophy and central fat accumulation linked with subclinical cardiometabolic diseases.

ABSTRACT P08

Antiviral Therapy 2012; 17 Suppl 2:A30

Body composition changes in ageing HIV-infected patients: the complex interplay between low muscle mass, lipodystrophy and osteopenia

G Guaraldi1, S Zona1, E Garlassi2, G Orlando1, F Carli1, C Stentarelli1, AR Domingues da Silva2, M Menozzi3, A Santoro1, C Mussini1

1Infectious Diseases Clinic, University of Modena and Reggio Emilia, Modena, Italy; 2Servizio di Doenças Infecciosas, Hospital de Joaquim Urbano, Porto, Portugal

Background: Body composition is a key determinant of ageing phenotype. HIV patients (pts) on ART are frequently affected by lipodystrophy (LD) and osteopenia/osteoporosis (O/O), and in the aging process they experience a decline in fat free mass index (FFMi=FFM/h²) similar to uninfected individuals. In an ageing HIV-infected cohort we aimed to describe the interaction between anthropometric changes of FFMi, leg fat % (surrogate for lipatrophy), VAT/TAT (surrogate for lipohypertrophy) and lumbar BMD (surrogate for O/O).

Methods: Observational prospective study including HIV+ men older than 50 years or HIV+ post-menopausal women. Measured changed in: FFMi, leg fat %, BMD (using DXA) and in VAT/TAT (using abdominal CT) were performed at least 1 year apart. The interplay of anthropometric variable changes was analysed using a multivariable log-linear model and was depicted with a log linear graphical model. In
these analyses, higher P-values describe a better fitness of results.

**Results:** 195 pts (25 women) were analysed. Median follow-up period was 3.2 years (IQR 1.9–4.3). Median CD4+ =500 cell/ml (IQR 346–680).

A grapho model was built to demonstrate that: FFMI change was related with age; VAT change was associated with age, sex, and leg fat % change; leg fat % change was associated with VAT change and sex; and lumbar BMD was associated with male sex.

**Discussion:** This study contributes to describing the complex interaction between lipodystrophy evolution and anthropometric changes occurring with aging. A reciprocal interaction was found between changes in leg fat % and VAT, the latter resulted associated with sex and age. FFMI change was found associated with age.

**ABSTRACT P09**

*Antiviral Therapy* 2012; 17 Suppl 2:A31

**Urinary eicosanoids in the Metabolic Abnormalities, Telmisartan, and HIV Infection (MATH) Trial**

T Huluang1, CH Tseng2, G Milne3, S Sanchez1, JE Lake2

1Vanderbilt University School of Medicine, Nashville, TN, USA; 2University of California–Los Angeles, Los Angeles, CA, USA

**Objectives:** Eicosanoids are arachidonic acid breakdown products; their metabolites can be quantified in urine as *in vivo* measures of oxidant stress and vascular health. We have previously reported abnormal eicosanoids in HIV-infected persons, including sex differences and associations with anthropometrics. Telmisartan is an angiotensin receptor blocker with PPAR-gamma agonist activity and potential metabolic and anti-inflammatory benefits. The MATH trial assessed effects of 24 weeks of telmisartan on metabolic parameters in HIV-infected patients with lipohypertrophy on suppressive antiretroviral therapy. This analysis assessed the effects of telmisartan on urine eicosanoids (MATH) subjects.

**Methods:** Thirty-five HIV-infected volunteers (15 women; 20 men) enrolled and completed 24 weeks of open-label oral telmisartan 40 mg daily.Visceral and subcutaneous abdominal adipose tissue (VAT and SAT) were quantified by lumbar computed tomography. Urine F2-isoprostane (F2-isoP), prostaglandin E2 (PGE-M), prostacycline (PGI-M) and thromboxane B2 (TxB2) metabolites were quantified at baseline and 24 weeks using gas or liquid chromatography-mass spectroscopy, and normalized to mg creatinine (cr). Median (interquartile range) 24-week changes were compared using the Wilcoxon signed rank test. Spearman correlations assessed relationships between laboratory and clinical variables.

**Results:** Baseline urine PGE-M was 8.07 (4.45, 11.46) ng/mg cr and increased significantly on telmisartan (+1.58 [-0.12, +5.94] ng/mg cr; P=0.008). Increase from baseline was greatest in men (+4.08 ng/mg cr, P=0.03 versus +1.03 in women, P=0.11; between-group P=0.25). Week 24 PGE-M was significantly higher in men than women (17.02 ng/mg cr versus 9.13; P=0.04). PGE-M increases were greater and statistically significant in subjects losing VAT (+3.18 ng/mg cr [P=0.001] versus VAT gain +1.03 [P=0.36]; between-group P=0.59) and in subjects gaining SAT (+5.01 ng/mg cr [P=0.03] versus SAT loss +1.24 [P=0.06]; between-group P=0.19). PGE-M change correlated with systolic blood pressure change (rho=0.45; P=0.006). Baseline F2-isoP was 1.19 (0.93, 2.18) ng/mg cr, and tended to be higher in women than men (2.18 versus 1.10 ng/mg cr, P=0.08). There was no significant overall change in F2-isoP (+0.14 ng/mg cr, P=0.78), but there were differences by sex (men +0.35 ng/mg cr, P=0.06; women -0.15, P=0.19; between-group P=0.03). There were no significant changes in PGI-M or TxB2.

**Discussion/conclusions:** Urine PGE-M increased with 24 weeks of telmisartan in antiretroviral-treated, HIV-infected subjects with central adiposity, with men and persons losing VAT and gaining SAT having the greatest increases. Associations with favourable adipose tissue redistribution suggest that increased PGE-M reflects a beneficial response in HIV-infected persons with baseline fat maldistribution. However, the increase in F2-isoP in men would suggest increased oxidant stress in these subjects. Limitations include the single-arm design, lack of adherence measures, and lack of data on anti-inflammatory use. These pilot results identified F2-isoP and prostaglandin E2 as potential biological mediators and/or biomarkers for inclusion in future studies in HIV-infected populations.

**ABSTRACT P10**

*Antiviral Therapy* 2012; 17 Suppl 2:A31

**Effect of recombinant human growth hormone (rhGH) and rosiglitazone (rosi) on liver fat in people with HIV-associated abdominal obesity and insulin resistance**

Q He1, ES Engelson1,2, DP Kotler1,2, JB Albu1,2, YL Chiu3, MJ Glesby3

1St Luke’s-Roosevelt Hospital Center, New York, NY, USA; 2Columbia University College of Physicians and Surgeons, New York, NY, USA; 3Weill Cornell Medical College, New York, NY, USA

**Objectives:** Liver fat is related to both insulin resistance and increased visceral fat content in HIV+ and uninfected...
individuals. Growth hormone reduces visceral adipose tissue (VAT) volume but may worsen glucose homeostasis. We conducted a substudy in a trial of rhGH and rosi to determine their effects on liver fat and to characterize associations between liver fat, VAT and glucose metabolism.

Methods: This was a substudy of a randomized, double-blind, placebo-controlled, multicentre trial using a 2×2 factorial design in which HIV-infected subjects with abdominal obesity by anthropometric criteria and insulin resistance (QUICKI≤0.33) but not diabetes. Participants were randomized to rhGH 3 mg daily, rosi 4 mg twice daily, combination rhGH + rosi, or double placebo (control) ×12 weeks. Liver fat was measured as intrahepatocellular lipid (IHCL) by magnetic resonance spectroscopy (MRS) at baseline and week 12 in a subset. The current analysis includes VAT measured by MRI and changes in 2-h oral glucose tolerance test (OGTT) parameters (fasting glucose, fasting insulin, glucose and insulin area under the curve [AUC], QUICKI).

Results: Of 69 subjects who had baseline MRI, 40 also had MRS. Thirty-one with MRI and MRS at baseline and week 12 are included in this analysis. There was no difference between treatment groups at baseline in age, percent liver fat, VAT volume, nor any OGTT parameter by 1-way ANOVA. There was significant correlation at baseline between liver fat (range 4–78%) and all indicators of glucose metabolism (P≤0.05) except fasting insulin (P=0.2). At baseline, VAT correlated with liver fat (P=0.02) and glucose AUC (P=0.04), with a trend for fasting glucose (P=0.08) but no correlation with insulin or QUICKI (all P>0.6). Since there was no significant rhGH × rosi interaction for change in IHCL by 2-way ANOVA, groups were pooled. There was a trend (P=0.056) toward decreased IHCL (-29%) in the rhGH group but no change in the rosi group (P=0.71). Change in fasting glucose differed between treatment groups (P<0.02) with post hoc comparison indicating an increase in the rhGH group compared with the double placebo group. There was no correlation between change in liver fat and changes in VAT (P=0.4) or glucose metabolism (P range 0.25–0.83).

Conclusions: Liver fat correlated significantly with both VAT and glucose metabolism at baseline, but changes in liver fat did not correlate with changes in VAT and glucose metabolism over 12 weeks. rhGH decreased liver fat but rosi had no effect. These results suggest an independent effect of growth hormone on liver fat.

ABSTRACT P11

Antiviral Therapy 2012; 17 Suppl 2:A32

Anthropometric differences between HIV-infected subjects starting antiretroviral therapy (ART) from the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) Cohort and a representative cohort of US adults from the National Health and Nutrition Examination Survey (NHANES)

BE Atkinson1, S Krishnan2, AC Collier1

1Harborview Medical Center, Seattle, WA, USA; 2Harvard School of Public Health, Boston, MA, USA; 3University of Washington, Seattle, WA, USA

Objective: Overweight and abnormal body shapes increase metabolic disease risk. Anthropometric comparisons between HIV-infected and HIV-uninfected persons are limited.

Methods: ALLRT is a prospective longitudinal cohort of HIV-infected subjects randomized to ART in ACTG trials. NHANES is a cohort representative of the US population (approximately 0.6% HIV prevalence). Waist, thigh, arm circumferences and body mass index (BMI) were compared between ART-naive ALLRT participants (2003–2007) and NHANES (2003–2006) using linear regression adjusted for age, race, height, smoking history and diabetes. We then evaluated anthropometrics from ALLRT subjects with virological suppression (HIV RNA<400 copies/ml) at 48 weeks.

Results: ALLRT had more males (83% versus 48%). At ART initiation and after 48 weeks, ALLRT males had significantly smaller mean anthropometrics and mean BMI than NHANES. ALLRT females also had smaller baseline anthropometrics than NHANES. After 48 weeks, ALLRT females had mean BMI, waist and thigh circumferences similar to NHANES. Among the virally suppressed ALLRT subjects, anthropometrics and BMI were higher at 48 weeks compared to ART initiation (P<0.05; Table 1).

Conclusions: Significant anthropometric differences exist between HIV-infected ART-naive persons and the general US population, indicating the profound impact of untreated HIV on body shape and size. The similarity of waist circumferences and obesity prevalence at 48 weeks of plasma viral suppression in females, may contribute to increased metabolic disease risk, though this remains to be tested in this cohort.
Table 1. Mean (95% CI) BMI (kg/m²) and anthropometrics (cm) adjusted for age, race, height, history of smoking and diabetes (Abstract P11)

<table>
<thead>
<tr>
<th></th>
<th>NHANES 2003–2006 (HIV-)</th>
<th>At ART initiation</th>
<th>After 48 weeks of ART HIV RNA&lt;400 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean [95% CI]</td>
<td>N</td>
</tr>
<tr>
<td>Males BMI ≥30 (%)</td>
<td>4,494</td>
<td>27.5 [27.3, 27.7]</td>
<td>1,457</td>
</tr>
<tr>
<td>Circumferences:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist ≥30 (%)</td>
<td>29</td>
<td>9.9 [99.1, 100.7]</td>
<td>1,390</td>
</tr>
<tr>
<td>Arm ≥30 (%)</td>
<td>4,494</td>
<td>34.2 [33.9, 34.4]</td>
<td>1,153</td>
</tr>
<tr>
<td>Thigh ≥30 (%)</td>
<td>4,494</td>
<td>54.3 [53.9, 54.7]</td>
<td>349</td>
</tr>
<tr>
<td>Females BMI ≥30 (%)</td>
<td>4,856</td>
<td>28.3 [28.0, 28.5]</td>
<td>302</td>
</tr>
<tr>
<td>Circumferences:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist ≥30 (%)</td>
<td>36</td>
<td>97.9 [97.1, 98.9]</td>
<td>292</td>
</tr>
<tr>
<td>Arm ≥30 (%)</td>
<td>4,856</td>
<td>32.7 [32.4, 33.0]</td>
<td>226</td>
</tr>
<tr>
<td>Thigh ≥30 (%)</td>
<td>4,856</td>
<td>53.5 [53.0, 53.9]</td>
<td>71</td>
</tr>
</tbody>
</table>

P-values from adjusted models comparing ALLRT to NHANES: *P<0.0001; †P<0.05; ‡P<0.1.

ABSTRACT P12

Antiviral Therapy 2012; 17 Suppl 2:A33

Predictors of prevalence and reduction of VAT in HIV-infected patients

B Hayward1, S Stanworth2, M Stepanians2, A Mangili1

1EMD Serono, Inc., Rockland, MA, USA; 2PROMETRIKA, LLC, Cambridge, MA, USA

Objectives: Tesamorelin is indicated for the reduction of excess visceral adipose tissue (VAT) in HIV-infected patients with lipodystrophy and was studied in 806 HIV-positive individuals in two Phase III randomized, placebo-controlled trials. Distinguishing abdominal obesity from excess VAT can be challenging in this population. While CT was used to longitudinally follow changes in VAT in the research setting and waist circumference (WC) correlated with CT-measured VAT, additional clinical tools are warranted to facilitate the diagnosis of VAT in the clinical setting and recognize those likely to respond to therapy with tesamorelin.

Methods: This is a retrospective analysis of pooled Phase III data. Framingham Risk Score (FRS) and Metabolic Syndrome (MSX), two validated disease risk scores that have previously been applied to HIV-infected cohorts, were calculated. VAT was stratified by quartiles. We applied χ² test for binary and ANOVA for continuous variables. Multivariate regression was used to determine baseline predictors of VAT loss at 26 weeks.

Results: Participants with an FRS ≥10% at baseline had significantly more VAT than those with FRS <10% (221 versus 173 cm²; P<0.0001) despite similar BMI (28.5 versus 29.2 kg/m²; P=0.1233) and similar WC (105.1 versus 104.5 cm; P=0.4639). Similarly, those who had MSX at baseline had significantly more VAT compared to those without MSX (209 versus 163 cm²; P<0.0001). BMI was significantly different between those with and without MSX (30.3 versus 28.0 kg/m²; P<0.0001) and a larger percentage of those with MSX were obese (50% versus 24%; P<0.0001). FRS at baseline increased linearly across VAT quartiles (Q1: 4.8% versus Q2: 5.9% versus Q3: 7.3% versus Q4: 8.2%) and more participants had MSX in the upper quartile of VAT at baseline compared to the lower quartile (Q4: 63% versus Q1: 33%; P<0.0001). BMI was similar between the quartiles of baseline VAT (Q1: 28.5 versus Q2: 28.1 versus Q3: 29.2 versus Q4: 30.1 kg/m²). In regression analysis, predictors of VAT at baseline were age, gender, high DBP, triglycerides >150, weight, high WC, waist-to-hip ratio, PI-based HAART, duration of HIV infection and ART. There were no significant predictors of change in VAT after 26 weeks of therapy except BMI.

Conclusion: Calculating FRS and determining the presence of MSX in HIV-infected patients with excess abdominal fat may be practical clinical tools to identify individuals with VAT, either to complement or to replace CT-based imaging or anthropometric measures when they are not available. Additionally, several clinical parameters, including PI use and duration of both...
HIV infection and ARV exposure, could help identify patients most likely to exhibit excess VAT. However, which patients will most likely benefit from treatment with tesamorelin to reduce HIV-associated excess abdominal fat was not evident in the current study.
ABSTRACT P13

*Antiviral Therapy* 2012; 17 Suppl 2:A35

**Effect of the change in the Framingham Risk Score (FRS) calculator on the cardiovascular disease (CVD) risk profile in treated HIV men**

*J Falutz¹, AO Rosengren¹, CM Tsoukas¹, J Cox¹, A Giannakis¹, J Szabo¹, H Turner¹, N Gilmore¹*

¹McGill University Health Centre, Montreal QC, Canada

**Objectives:** The FRS is routinely used to assess CVD risk in HIV disease. The recent FRS calculator update has resulted in more persons being eligible for lipid-lowering treatment (LLRx). It is unknown how this will affect the CVD risk profile of treated HIV patients (pts) and the number of HIV pts requiring LLRx. We calculated the FRS in treated HIV patients using the 2006 Canadian Lipid guidelines FRS calculator and compared this to the 2009 guidelines using the updated calculator.

**Methods:** We retrospectively analysed charts of pts whose FRS was calculated since January 2010 using the 2006 guidelines (clinically evident atherosclerosis, FRS ≥ 20%, type II diabetes [T2DM]); 2) receiving LLRx; and 4) HAART-naive, as the 2009 guidelines includes only treated HIV as a unique indication for lipid profile evaluation. Results are reported as mean ± SD and the difference between groups was calculated using a two-sided t-test and Fischer’s exact test.

**Results:** An FRS was available on 123 subjects of who 52 were excluded (females – 15, HAART-naive – 5, atherosclerosis – 3, FRS ≥ 20% – 5, T2DM – 3 and receiving LLRx – 21). The remaining 71 males’ mean age was 49.9 ± 4.2 (range 24–771). Their mean CD4 count was 595 ± 320 (range 36–1,738), and the HIV RNA was undetectable in 94%. By the 2006 FRS calculator 49 pts (69%) were categorized as low risk, 6 (27%) were reassigned to high-risk category, using the 2009 calculator. Of 22 initially moderate-risk pts, 6 (27%) were reassigned to high-risk category, representing a significant increase in pts in either the moderate- or high-risk FRS category (P=0.036).

**Conclusion:** Applying the updated FRS calculator resulted in significantly higher number of treated HIV males who increased their FRS risk category and who met criteria to begin LLRx. These findings should prompt more aggressive assessment of lipid profiles on treated HIV patients.

ABSTRACT P14

*Antiviral Therapy* 2012; 17 Suppl 2:A35

**Intramyocardial lipid in HIV-infected adults and healthy controls**

*N Schmidt¹, J Purdy¹, D Thiara¹, H Duarte¹, C Liu², C Sibley², DA Bluemke², C Hadigan³*

¹National Institutes of Health, Bethesda, MD, USA; ²The Johns Hopkins Hospital, Baltimore, MD, USA

**Objectives:** Lipid accumulation in myocardial tissue has been identified in diabetes and insulin resistance and is associated with impaired myocardial function. Given prior observations of abnormal lipid deposition, we sought to measure intramyocardial lipid using novel magnetic resonance spectroscopy (MRS) techniques in a cohort of HIV-infected people with a broad range of cardiac risk factors and ARV exposure compared to healthy volunteers.

**Methods:** We conducted a prospective cross-sectional study of 48 HIV-infected adults and 13 age/sex/race-matched controls. Participants with known coronary artery disease were excluded. We measured intramyocardial lipid with MRS of the intraventricular septum, as well as MRS of hepatic lipid, abdominal visceral and subcutaneous fat volumes, serum lipids, glucose, insulin, CD4 T-cell count, viral load, and echocardiography. Clinical history and past antiretroviral exposure was characterized for all subjects.

**Results:** There was no difference between patients and controls in intramyocardial or hepatic lipid content. Intramyocardial lipid content was not associated with ejection fraction, serum lipids, CD4 count or HIV viral load. Both subcutaneous (r=0.37; P=0.006) and visceral (r=0.36; P=0.009) fat
volume were significantly positively correlated with intramyocardial lipid. These associations remained significant in multivariate analysis that adjusted for age, BMI and HIV status. HIV-infected subjects on protease inhibitors (n=19) tended to have higher intramyocardial lipid than subjects not on a protease inhibitor (n=25; heart fat% 2.18 versus 1.40; P=0.18), but this was not statistically significant. Increased fasting insulin was associated with increased intramyocardial lipid in controls (r=0.81; P=0.003), but not in HIV. (See Table 1)

Conclusions: These preliminary data demonstrate that both increased subcutaneous and visceral fat are independently associated with increased intramyocardial lipid, but intramyocardial lipid is not increased in HIV per se. Some patient groups such as those on protease inhibitors may be at increased risk. Further investigation with larger sample size is warranted.

ABSTRACT P15

Antiviral Therapy 2012; 17 Suppl 2:A36

Metabolic syndrome (MetS) status after 96 weeks of antiretroviral therapy (ART) among HIV-infected individuals with MetS at ART initiation

S Krishnan1, JT Schouten2, B Atkinson3, T Brown4, D Wohl5, DL Jacobson6

1Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, USA; 2Department of Surgery, University of Washington School of Medicine, Seattle, WA, USA; 3Harborview Medical Center, Seattle, WA, USA; 4Division of Endocrinology and Metabolism, Johns Hopkins University, Baltimore, MD, USA; 5AIDS Clinical Trials Unit, University of North Carolina, Chapel Hill, NC, USA

Objective: To determine if HIV-infected individuals with MetS at ART initiation continue to exhibit MetS after 96 weeks of ART.

Method: MetS was assessed at ART initiation and after 96 weeks of ART in ART-naive, HIV-infected individuals from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort. Based on the Adult Treatment Panel (ATP) III criteria, MetS diagnosis required at least three of following: impaired glucose tolerance, hypertension, increased waist circumference, increased triglycerides or low HDL-cholesterol.

Prevalence of MetS and the individual criteria were compared at two time points using McNemar’s test.

Results: At ART initiation, 450 (20%) individuals had MetS: 55% age >40 years; 73% male; 47% white, non-Hispanic; 27% black, non-Hispanic; 24% Hispanic; 17% CD4≤50 cells/mm3; 25% CD4 ≥350 cells/mm3. After 96 weeks of ART, 239 (58%) of 411 cases in follow-up continued to exhibit MetS. For those with MetS at ART initiation and week 96, the proportion with ≥4 criteria was higher at week 96 versus at ART initiation (48% versus 40%; P<0.03). Similarly, the proportion with high triglycerides was higher at week 96 (87% versus 69%; P<0.0001) and the proportion with high glucose was higher at week 96 (59% versus 42%; P<0.0001). Similar differences (P<0.05) between ART initiation and week 96 were observed among 195 of 239 cases with an HIV-1 viral load <50 copies/ml at week 96. Among the 172 cases with MetS at ART initiation but not at week 96, the proportion with low HDL was higher at ART initiation versus week 96 (95% versus 26%; P<0.0001); the proportion with other criteria also decreased at week 96 (P<0.0001).

Conclusion: While more than half of the individuals with MetS at ART initiation continued to have MetS after 96 weeks of ART, 42% with MetS at
ART initiation no longer met criteria for MetS. Factors associated with continuing MetS and with improvement in MetS status need to be assessed.

ABSTRACT P16

Antiviral Therapy 2012; 17 Suppl 2:A37

Flow-mediated vasodilation does not independently predict coronary artery calcium scores in HIV-infected adults

AC Ross1,2, GA McComsey3, S Liu4, R Lyles4, S Zona5, P Raggi5, G Orlando5, F Carli5, S Cocchi5, G Guaraldi5

1Emory University School of Medicine, Atlanta, GA, USA; 2Children’s Healthcare of Atlanta, Atlanta, GA, USA; 3Case Western Reserve University, Cleveland, OH, USA; 4Emory University School of Public Health, Atlanta, GA, USA; 5University of Modena and Reggio Emilia, Modena, Italy

Background: HIV+ patients are at an increased risk of cardiovascular disease (CVD). There are several non-invasive cardiovascular tests currently used to estimate CVD risk, including measures of endothelial function by flow-mediated vasodilation (FMD), and that of atherosclerosis by CT-measured coronary artery calcium (CAC) score. No study has investigated the relationship between FMD and CAC, and the predictive value of FMD in HIV-atherosclerosis.

Methods: HIV+ patients were selected from a large, on-going, Italian, single-site, observational cohort assessing metabolic and CVD outcomes. Subjects were included if they had at least one CAC score and ≥1 FMD test performed at the same time or prior to ART initiation no longer met criteria for MetS. Factors associated with continuing MetS and with improvement in MetS status need to be assessed.

Table 1. MetS at ART initiation and after 96 weeks of ART (table shows column percents; Abstract P15)

<table>
<thead>
<tr>
<th>Number of MetS criteria</th>
<th>MetS at ART initiation (n=450)</th>
<th>MetS at ART initiation and week 96 (n=239)</th>
<th>Follow-up at week 96 (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ART initiation</td>
<td>Week 96</td>
<td>ART initiation</td>
</tr>
<tr>
<td></td>
<td>ART initiation</td>
<td>MetS at ART initiation and no MetS at week 96 (n=172)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>–</td>
<td>–</td>
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</tr>
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<td>–</td>
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</tr>
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</tr>
<tr>
<td>5</td>
<td>6</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>High blood pressurea</td>
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<td>76</td>
<td>74</td>
</tr>
<tr>
<td>High triglyceridesa</td>
<td>70</td>
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</tr>
<tr>
<td>High glucosea</td>
<td>40</td>
<td>42</td>
<td>59</td>
</tr>
<tr>
<td>Low HDLa</td>
<td>94</td>
<td>93</td>
<td>72</td>
</tr>
<tr>
<td>High waist circumferencea</td>
<td>62</td>
<td>70</td>
<td>69</td>
</tr>
</tbody>
</table>

Based on the ATP III criteria for MetS. ART, antiretroviral therapy; HDL, high-density lipoprotein; MetS, metabolic syndrome.

CAC. A proportional odds model was constructed with the FMD test score that was obtained farthest in time from the CAC score. The model was first analysed unadjusted except for the time lag between FMD and CAC. The model was then adjusted for traditional risk factors (age, sex, LDL, smoking and diabetes status) and HIV factors (HIV duration, cumulative ART use, ΔCD4 count [current-nadir], HIV-1 RNA). FMD% was considered in a continuous fashion, whereas CAC scores were considered categorically (0, 1–99, >99).

Results: 466 subjects were analysed. Median age was 46 years, BMI 24 kg/m², LDL-cholesterol 112 mg/dl, HIV duration 172 months, CD4 count 508 cells/mm³, with cumulative duration of ART of 106 months. 73% of the subjects were male, 29% smokers, 6.8% with diabetes, 97% on ART (71% PI), 89% HIV-1 RNA <1,000 copies/ml. FMD and CAC were separated by a median (range) of 334 (1–1,527) days with 45% >1 year apart. FMD% median (range) was 8.3% (26.4%–41.6%). 64%, 26% and 10% of subjects had a CAC score of 0, 1–99 and >99, respectively. In the model adjusted for time lag, time lag <1 versus >1 year separation was significant (P=0.03). The odds ratio (OR; confidence interval, CI) of FMD predicting CAC when obtained <1 year apart was 1.07 (1.02, 1.012; P<0.01), and the OR (CI) of FMD predicting CAC when obtained >1 year from one another decreased to 1.03 (1.00, 1.06; P=0.03). However, when adjusted for traditional CVD risk factors, FMD was no longer significant regardless of the time that separated the two tests (P=0.87). Only age, sex and HIV duration were significant (P<0.01, P<0.01, P=0.04, respectively).

Conclusions: FMD predicts CAC scores in HIV+ patients. However, traditional CVD risk factors and HIV duration were the only factors independently associated with CAC.

14th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV A37
ABSTRACT P17

*Antiviral Therapy* 2012; 17 Suppl 2:A39

**Ezetimibe in addition to rosuvastatin for improvement of lipid parameters in HIV-positive patients not reaching lipid targets with rosuvastatin alone**

**KW Johns**, **MT Bennett**, **GP Bondy**

1Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada; 2University of British Columbia, Division of Cardiology, Department of Medicine, Vancouver, BC, Canada; 3Director, HIV Metabolic Clinic, St. Paul’s Hospital, Vancouver, BC, Canada; 4University of British Columbia, Departments of Medicine and Pathology, Faculty of Medicine, Vancouver, BC, Canada

**Background:** HIV-positive patients on highly active antiretroviral therapy are subject to adverse effects that include lipid elevations, which may persist despite therapy with potent lipid-lowering agents. This prospective pilot study sought to determine whether patients not reaching lipid treatment targets with rosuvastatin 10 mg would show a greater improvement in their fasting lipid profile when ezetimibe was added to their ongoing rosuvastatin therapy (R+E) compared to those treated with an increased dose of rosuvastatin (Rosu 20). To our knowledge, this is a novel investigation within the HIV-positive population.

**Methods:** The study design was a 12 week, prospective, randomized, open-label clinical trial comparing the effect of ezetimibe in addition to ongoing rosuvastatin therapy to an increased dose (20 mg) of rosuvastatin on the lipid profile of HIV-positive patients. Subjects were deemed eligible if they had an apolipoprotein B (apoB) of >0.80 g/l despite therapy with rosuvastatin 10 mg daily for a minimum of 3 months. The primary endpoint was the difference in apoB change from baseline to week 12 between groups. Secondary outcomes included within-group changes in apoB, between-group differences in changes in other lipid parameters and safety. Eligible, consenting subjects were randomized using a computer-generated list that employed blocks of 4, 6 or 8. Two-way, two-sample *t*-tests were used for between-group analyses and two-way, paired *t*-tests were used for within-group analyses.

**Results:** Forty-three subjects (20 Rosu 20, 23 R+E) completed the trial. Average age of participants was 56.7 years, 90.6% were male and 81.4% were Caucasian. There were no differences at baseline between groups in terms of age or clinical characteristics of HIV. More patients in the R+E group had a history of hypertension and more were current smokers, whereas more patients in the Rosu 20 group self-identified as past smokers. Significant improvements in apoB were seen within both R+E (-0.17 g/l; *P*<0.001) and Rosu 20 (-0.13 g/l; *P* =0.03) treatment groups, but these did not differ between groups (*P* =0.54). Significant between-group differences were observed in the changes in total cholesterol (-1.00 mmol/l versus -0.51 mmol/l; *P* =0.04) and triglycerides (-0.63 mmol/l versus +0.04 mmol/l; *P* =0.03), both in favour of the R+E group. Two patients, both in the Rosu 20 group, experienced mild myalgias, but neither discontinued the study medication due to these events.

**Conclusions:** This pilot study is the first to investigate the efficacy of rosuvastatin in combination with ezetimibe in HIV-positive patients. Significance of the findings may have been limited by sample size. However, the addition of ezetimibe to ongoing therapy with rosuvastatin was safe and effective at improving certain lipid parameters as compared to rosuvastatin alone.

ABSTRACT P18

*Antiviral Therapy* 2012; 17 Suppl 2:A39

**Efficacy and safety outcomes for rilpivirine (RPV) versus efavirenz (EFV) plus emtricitabine/tenofovir DF (FTC/TDF) in treatment-naive, HIV-1 infected adults with baseline viral load ≤100,000 copies/ml: pooled 48-Week ECHO and THRIVE analysis**


1Anthony Mills MD Inc, Los Angeles, CA, USA; 2Hanover Medical School, Hanover, Germany; 3Erasmus Medisch Centrum, Rotterdam, Netherlands; 4Chelsea & Westminster Hospital, London, UK; 5Barts and The London HIV Service, London, UK; 6Community Research Initiative of New England, Boston, MA, USA; 7Tibotec Inc, Titusville, FL, USA; 8Tibotec BVBA, Beerse, Belgium; 9Gilead Sciences Inc, Foster City, CA, USA; 10Gilead Sciences Inc, Stockley Park, UK

**Background:** At week 48, RPV+FTC/TDF demonstrated high virological response and non-inferiority to EFV+FTC/TDF overall and by baseline HIV-1 RNA (BLVL) above or below 100,000 copies/ml in the pooled ECHO and THRIVE studies. However, there were more virological failures (VF) at higher BLVL. An
analysis of efficacy, safety and resistance outcomes for RPV subjects receiving FTC/TDF with BLVL ≤100,000 copies/ml is particularly relevant given the majority of FTC/RPV/TDF use is in this population globally.

**Methods:** ECHO and THRIVE subjects with BLVL ≤100,000 copies/ml who received FTC/TDF with either RPV (n=288) or EFV (n=256) were included in this 48-week post-hoc, pooled analysis of efficacy, safety and resistance outcomes.

**Results:** Of the 544 subjects, 75% were male, 59% White race, 26% Black race, median age 36 years, median BLVL 4.5 log_{10} copies/ml and median CD4 279 cells/mm³.

At week 48, RPV+FTC/TDF was non-inferior to EFV+FTC/TDF with higher virological response (VR) of 90% versus 85% (VL<50 copies/ml, ITT-TLOVR; 95%CI: 5% [-0.8%, 10.5%]) in subjects with BLVL≤100,000 copies/ml. In both treatment arms, VR was ~20% lower with self-reported adherence ≤95% versus >95% and VR rates were low for RPV+FTC/TDF and EFV+FTC/TDF (4.2% and 2.3%). There were fewer discontinuations due to adverse events (AEs) with RPV+FTC/TDF versus EFV+FTC/TDF (2% versus 6%) and similar mean CD4 count increases observed (+202 cells/mm³ versus +195, respectively).

The proportions of VF subjects who had emergent NNRTI and N(t)RTI resistance associated mutations (RAMs) were 4/14 and 5/14 for RPV and 2/6 and 0/6 for EFV, respectively.

**Conclusions:** In subjects with BLVL≤100,000 copies/ml, RPV+FTC/TDF demonstrated non-inferior virological efficacy to EFV+FTC/TDF with low VR rates at week 48. Overall, RPV+FTC/TDF had an improved safety profile versus EFV+FTC/TDF with significantly less grade 2–4 AEs, treatment-related neurological and psychiatric AEs, dizziness, abnormal dreams/nightmares grade 3+ laboratory abnormalities, grade 2+ total cholesterol and low density lipoprotein (LDL-cholesterol).

**Methods:** Pooled 96-week data from the randomized, double-blind, Phase III ECHO and THRIVE studies were used to analyse the efficacy and safety outcomes in women specifically, and compared to men, for RPV+FTC/TDF (n=550) and EFV+FTC/TDF (n=546).

**Results:** Analysis included 236 women and 860 men of whom were 45%/18% Blacks, 33%/70% Whites and 16%/28% Hispanics, respectively, with median baseline CD4 count of 243/258 cells/mm³ and HIV-1 RNA (VL) of 4.9/5.0 log_{10} copies/ml.

At week 96, in women RPV+FTC/TDF was non-inferior to EFV+FTC/TDF overall (VL<50 copies/ml, SNAPSHOT: 77% versus 74%) and for baseline VL≤100,000 copies/ml (81% versus 79%). This was similar in men overall (77% RPV+FTC/TDF versus 78% EFV+FTC/TDF) and for baseline VL≤100,000 copies/ml (84% versus 81%, respectively). Overall, there was higher virological failures (VFs) for RPV+FTC/TDF (14% RPV+FTC/TDF versus 6% EFV+FTC/TDF), that was more pronounced with baseline VL>100,000 copies/ml (22% versus 11%, respectively) compared with baseline VL≤100,000 copies/ml (7% versus 5%, respectively). Similar, low VFs (<3%) were observed in the second year in both genders. Similar mean CD4 count increases observed for women (+229 RPV+FTC/TDF versus +214 EFV+FTC/TDF).

RPV+FTC/TDF had significantly improved safety and tolerability profile: less grade 2–4 treatment-related
AEs, AEs leading to discontinuation, treatment-related neurologic AEs, dizziness and rash with more neutral lipid profile. Nausea occurred more commonly in women versus men, but there were lower rates of any treatment-related psychiatric AEs, abnormal dreams/nightmares, and diarrhoea observed with women versus men.

Women compared to men on RPV+FTC/TDF had more limb fat gain, but similar BMD decreases. Minimal serum creatinine change with both genders for RPV+FTC/TDF and EFV+FTC/TDF.

Conclusions: In women, sustained 96-week, non-inferior virological efficacy was observed with RPV+FTC/TDF versus EFV+FTC/TDF. While RPV+FTC/TDF had a safety advantage there were more VFs in the first year and similar, low VFs in the second year. Overall, safety and tolerability findings with RPV+FTC/TDF were generally similar across genders with exception of minor differences in the incidences of specific AEs – higher incidence of nausea and lower rates of any treatment-related psychiatric AEs and abnormal dreams/nightmares in women compared to men.

ABSTRACT P20

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Myopathy in HIV-1-infected patients receiving raltegravir-containing antiretroviral therapy

P Monteiro1, I Perez1, J Pich1, JM Gatell1, E Martinez1

1Infectious Diseases Unit, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain

Objective: To evaluate the incidence and risk factors for myopathy in HIV-1-infected patients who were prescribed a raltegravir-containing antiretroviral therapy.

Design: A retrospective analysis of a prospective cohort in a referral hospital involving all consecutive patients who were prescribed a raltegravir-containing antiretroviral regimen, between June 2005 and December 2010.

Methods: Myopathy was defined as a creatine kinase elevation of at least threefold from the upper normal limit (UNL; grade 2, WHO classification) or any muscular complaint while receiving raltegravir. Blood analysis at each visit included at least creatine kinase, aspartate aminotransferase and lactate dehydrogenase as well as plasma HIV-1 RNA and CD4 cell count.

Results: There were 475 patients who had been exposed to raltegravir for a median of 11.5 (IQR 8.2–15.2) months. An increase of creatine kinase ≥3-fold UNL was detected in 53 (11.2%) patients, representing an incidence of 3.8/100 person-years.

Symptoms were reported by 7 patients (1.5%), but they showed either grade 1 (n=3) or 2 (n=4) creatine kinase increases. Median duration of raltegravir therapy before myopathy diagnosis was 5.9 (IQR 3.3–9.3) months. Evidence of prior creatine kinase elevations (RH 3.30; 95% CI, 1.59 ±6.86; P=0.001), abnormal baseline creatine kinase (RH 3.24; 95% CI, 1.63 ±6.45; P=0.001) and male gender (RH 4.17; 95% CI, 1.33 ±1.27; P=0.0019) were identified as independent risk factors for myopathy.

Conclusions: Although approximately 1 of 10 patients on raltegravir therapy developed myopathy as defined in this study, symptoms were uncommon and not severe and myopathy occurred in patients with easily identifiable risk factors.

ABSTRACT P21

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Lack of clinically significant pharmacokinetic interactions between quinine and ritonavir in healthy adult participants

S Wason1, R Faulkner1, MW Davis1

1URL Pharma, Inc., Philadelphia, PA, USA

Objective: Quinine is metabolized primarily by cytochrome P450 3A4 (CYP3A4) and is also a substrate for P-glycoprotein (P-gp). Ritonavir is metabolized primarily by CYP3A4 and is a potent inhibitor of CYP3A4 and P-gp. Soyinka et al. (2010) identified a potential drug–drug interaction between quinine and ritonavir. We evaluated the potential for a pharmacokinetic interaction between ritonavir and quinine following coadministration of multiple doses of ritonavir and a single standard therapeutic dose of quinine sulphate minitablets in healthy adult participants.

Methods: Phase I open-label study; 80 eligible participants were randomized to four study groups (20 participants each). Participants in each group received a dose of quinine 648 mg in the morning on day 1. After a 3-day washout period, participants received ritonavir 100 mg twice daily (12-h intervals) on days 4–19. On day 18, all participants received a dose of quinine sulphate minitablets in healthy adult participants.

Results: Ritonavir plasma concentration–time profiles for steady-state ritonavir 100 mg twice daily alone
and in combination with quinine were similar. Quinine coadministration did not significantly alter ritonavir median $T_{\text{max}}$ (3.39 versus 3.0 h) or mean $C_{\text{max}}$ (1.8 ±0.51 versus 2.1 ±0.88 μg/ml), but appeared to marginally enhance ritonavir absorption (mean AUC$_{0-12}$: 9.2 ±2.21 versus 11.1 ±3.96 μg∙h/ml), respectively. There was no statistically significant difference in plasma quinine concentration–time profiles for quinine alone and with steady-state ritonavir 100 mg twice daily. Concomitant ritonavir did not significantly alter quinine median $T_{\text{max}}$ (2 versus 2.5 h), or mean $C_{\text{max}}$ (4.3 ±1.07 versus 3.9 ±0.88 μg/ml) or AUC$_{0-\infty}$ (78.9 ±26.78 versus 68.4 ±22.29 μg∙h/ml), respectively.

Conclusion/Discussion: No clinically significant drug–drug interaction was identified when a single 648-mg dose of quinine sulphate minitablets was coadministered with ritonavir 100 mg twice daily for 16 days in healthy adult participants. The potential for slightly increased ritonavir exposure and slightly decreased quinine exposure exists during ritonavir–quinine coadministration; however, they are unlikely to be clinically significant although caution should be exercised.

**ABSTRACT P22**

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Clinically significant drug interaction between colchicine and ritonavir in healthy adults

*S Wason,1 JL DiGiacinto 2,3, MW Davis1*

1URL Pharma, Inc., Philadelphia, PA, USA; 2Salamandra, LLC, Bethesda, MD, USA; 3Consultant, URL Pharma, Inc., Philadelphia, PA, USA

**Objective:** To determine the effect of multiple-dose ritonavir, a potent inhibitor of CYP3A4 and P-gp, on the pharmacokinetics of single dose of colchicine (0.6 mg) in healthy adults under fasted conditions and to assess the safety and tolerability of a single colchicine dose administered alone and in combination with multiple-dose ritonavir.

**Methods:** This was an open-label, non-randomized, two period drug–drug interaction study. Twenty-four (24) healthy male and female volunteers (mean age of 23 years) received 0.6 mg of colchicine on day 1 under fasting conditions. After a 14-day washout period, volunteers received ritonavir 100 mg twice daily (at 12-h intervals) on days 15–18, a sufficient duration to achieve steady-state. On day 19, after an overnight fast, volunteers received another dose of colchicine 0.6 mg administered concomitantly with 100-mg ritonavir (a.m. dose) and then received the final 100 mg ritonavir on the evening of day 19. Serial blood samples were collected on days 1 and 19 to determine colchicine plasma concentrations at pre-dose (within 1 h prior to dosing) and post-dose administration at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72 and 96 h. The following colchicine pharmacokinetic parameter values were calculated ($n$=18): $C_{\text{max}}$, $T_{\text{max}}$, AUC$_{0-t}$, AUC$_{0-\infty}$, $t_{1/2}$, CL/F and Varea/F.

**Results:** Coadministration of a single 0.6 mg colchicine dose with steady-state ritonavir, as compared to colchicine alone, resulted in 170% increase in colchicine $C_{\text{max}}$, 245% increase in AUC$_{0-t}$ and a 239% increase in AUC$_{0-\infty}$. $T_{\text{max}}$ was not affected. Colchicine CL/F decreased by 70% following the coadministration of 100 mg of ritonavir twice daily, as compared to colchicine alone. Colchicine 0.6 mg alone, and with ritonavir, was well tolerated, with no apparent increase in the incidence of AEs during colchicine–ritonavir concomitant therapy. The most common AEs following colchicine administration, with or without ritonavir, were nausea and rhinorrhea ($n$=2 for each). All AEs were mild to moderate in intensity and did not result in study withdrawal.

**Conclusion:** Colchicine is a substrate for both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) transporter. Clinically significant drug interactions between colchicine and CYP3A4 and P-gp inhibitors can cause an increase in colchicine systemic exposures that can precipitate colchicine-related toxicities. The study findings indicate a clinically significant drug–drug interaction with the concomitant administration of single-dose colchicine and multiple-dose ritonavir that results in significant increases in systemic colchicine exposures. Colchicine doses should be adjusted when administered with ritonavir, as described in the FDA-approved colchicine prescribing information, to avoid the risk of colchicine-related toxicities.
Background: HIV infection is an independent risk factor of atherosclerosis development and cardiovascular damage. Since vessel wall mesenchymal stem cells (MSCs) are involved in the regulation of vessel structure homeostasis, we have investigated the role of Tat in MSC survival and differentiation.

Methods: Arterial segments of femoral arteries from three male heart-beating donors (mean age 39 years) were employed for cell isolation. Adipogenic differentiation was induced in confluent cells cultured, full-length HIV-1 Tat was added, PPARγ transcription factor activity was detected, MSCs were analysed to assay the expression of endothelial specific markers, apoptosis analysis was performed and the mRNA expression of specific cellular genes involved in endothelial and adipogenic differentiation was determined.

Results: The survival of subconfluent MSCs was impaired when Tat was employed at high concentrations (200–1,000 ng/ml), whereas lower Tat amounts (1–100 ng/ml) did not promote apoptosis. Tat enhanced the MSC differentiation to adipogenesis by the activity up-regulation of PPARγ. Tat-related modulation was tackled by treatment with some antagonists of Tat-specific receptors, SU5416 and RGD Fc. Tat inhibited the MSCs differentiation to endothelial cells down-regulating VEGF-induced endothelial markers, Flt-1, KDR and vWF. The MSC treatment with Tat-derived peptides, corresponding to cysteine-rich, basic and RGD domains, indicated that these Tat regions are involved in the inhibition of endothelial marker expression.

Conclusions: Since Tat is present in a free form in the blood and tissues, high levels of HIV replication as detectable in naive patients, might determine the derangement in the vessel wall homeostasis with a polarization of MSC differentiation, because the vessel wall derived-MSCs increased the differentiation to adipogenesis, whereas the differentiation to endotheliogenesis is consistently tackled. MSC differentiation dysregulation might also explain the fat tissues observed in atherosclerotic vessel degeneration. Tat-related impairment of MSC differentiation might play an important role in vessel damage and atherosclerosis lesions observed in HIV-infected patients.

ABSTRACT P24
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Effect of second generation antipsychotics on metabolic variables in HIV-infected adults on long-term antiretroviral therapy

M Ferrara1, A Umlauf2, C Fitzsimons3, JM Meyer4, NA Duarte5, G Guaraldi3, JH Atkinson2, I Grant4, RJ Ellis4, CHARTER Study Group

1University of Modena and Reggio Emilia, Psychiatry, Modena, Italy; 2HIV Neurobehavioral Research Program (HNRP), University of California San Diego (UCSD), Psychiatry, San Diego, CA, USA; 3University of Modena and Reggio Emilia, Metabolic Clinic, Infectious Disease, Modena, Italy; 4HIV Neurobehavioral Research Program (HNRP), University of California San Diego (UCSD), Neurosciences, San Diego, CA, USA

Background: Psychiatric disorders are common among HIV-infected adults, but there are no published data on the metabolic side effects of concurrent use of second-generation antipsychotics (SGAs) with antiretroviral therapy (ART).

Methods: A cross-sectional study was conducted in participants consecutively recruited at the UCSD HIV Neurobehavioral Research Program examining the use of SGAs and ART in relation to metabolic outcomes, including body mass index (BMI), serum lipids, diabetes mellitus (DM) diagnosis and mean arterial pressure (MAP). Potentially confounding covariates examined included demographics, psychiatric diagnoses, biomarkers of HIV disease status, type of antiretroviral regimen and hepatitis C coinfection. DSM-IV psychiatric diagnoses were obtained using standardized diagnostic assessments. Metabolic outcome variables and covariates were compared using t-tests, χ² or Fisher’s exact tests. Univariate and linear and logistic multivariable models explored metabolic outcomes for participants taking concomitant SGA (SGA+) or not (SGA-).
multivariable models adjusted for relevant covariates showed higher triglycerides ($P=0.01$), higher odds of DM (OR 2.28, 95% CI 1.29, 4.02; $P=0.004$) and numerically higher BMI ($P=0.06$) in the SGA+ group. SGA+ participants had higher MAP ($P=0.004$) than SGA- participants.

**Conclusions:** Use of SGAs in HIV-infected adults taking ART was independently associated with worse metabolic parameters, which might accelerate mortality and morbidity through vascular disease. Further research is needed to investigate possible mechanisms behind, and treatment of the metabolic complications of concurrent SGA and ART use.

**ABSTRACT P25**

*Antiviral Therapy* 2012; 17 Suppl 2:A44

**Habitual nutrient intake in HIV-infected youth and associations with HIV-related factors**

LA Stricker¹, M Ndurangu¹, A Nucci², TR Ziegler², V Tanapricha³, GA McComsey³, JK Frediani², EC Millson², L Seaton⁴, AC Ross²,⁴

¹Georgia State University, Atlanta, GA, USA; ²Emory University School of Medicine, Atlanta, GA, USA; ³Case Western Reserve University, Cleveland, OH, USA; ⁴Children’s Healthcare of Atlanta, Atlanta, GA, USA

**Background:** Few studies have evaluated habitual nutrient intake among HIV-infected youth in the United States, even though diet may influence immune function and thus HIV-related outcomes. We determined micro- and macro-nutrient intake in HIV-infected youth in Atlanta and Georgia, and investigated relationships between nutrient intake and HIV-related parameters.

**Methods:** HIV-infected subjects and healthy controls (1–25 years) were prospectively enrolled. Concomitant demographic, clinical and laboratory data were collected. Food and nutrient intake was assessed via 24-h dietary recalls performed one-on-one with a trained investigator every 3 months for 1 year. Nutrient intake was determined from pooled food recall data using NDS-R software and directed by research nutritionists. Nutrient intake was compared to Dietary Reference Intakes (DRI) and Acceptable Macronutrient Distribution Ranges (AMDR). Analysis utilized non-parametric and parametric tests and Pearson correlations to evaluate associations.

**Results:** Subjects with ≥2 food recalls were analysed (175 HIV+ and 43 HIV- matched controls). The two groups were similar in age, race, sex, body mass index and kilocalorie intake (HIV+: mean [SD] age = 17.4 ±4.8 years; 95% black; 54% male). Neither group met the DRI for mean daily intake of vitamins A, D, E, calcium, magnesium, sodium, and potassium (all $P<0.01$). HIV+ subjects did not meet recommendations for pantothenic acid or folate (both $P<0.01$) and had lower %DRI than controls for vitamins A, E, pantothenic acid, magnesium, calcium, folate and potassium ($P<0.04$). Carbohydrate and protein intakes were within the AMDR for both groups; however, % kilocalories from fat was above normal and higher in HIV+ subjects ($P=0.02$). Both groups consumed less fibre, and more saturated and trans fat than recommended intakes. Caucasian HIV+ subjects had significantly greater vitamin D and calcium %DRI than black HIV+ subjects ($P=0.03$). Female HIV+ subjects had lower %DRI for folate, pantothenic acid, vitamin D, calcium, potassium and kilocalories than males (all $P<0.01$). Mean daily caloric intake was negatively correlated with current ($ρ=-0.12; P=0.024$) and nadir CD4 counts ($ρ=-0.11; P=0.04$), respectively. Zinc, riboflavin and magnesium %DRI, were each positively correlated with current CD4 count (all $P<0.02$), while vitamin A %DRI correlated with nadir CD4 count ($ρ=0.10; P=0.05$). In HIV+ subjects not on antiretroviral therapy ($n=56$), HIV-1 RNA levels were negatively correlated with protein intake ($ρ=-0.30; P=0.05$).

**Conclusions:** HIV+ youth have inadequate intake of several essential vitamins and minerals compared to DRIs and lower habitual dietary intake of a variety of micronutrients compared to HIV- controls. HIV+ youth consumed higher than recommended amounts of dietary fat and lower than recommended amounts of dietary fibre. Intake of some nutrients was associated with HIV-related factors, including CD4 counts. Further investigation is warranted to determine whether nutrient intake data correlate with plasma nutrient concentrations in HIV+ youth and the potential impact of nutritional status on immune function and HIV progression in this patient population.
ABSTRACT P26
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Cellular and biochemical effects induced by ARVs in CHO-IR cells

K Anwar1, A Phulukdaree1, T Little1, AA Chuturgoon1, TS Pillay2

1Department of Chemical Pathology & Medical Biochemistry, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa; 2Division of Chemical Pathology, Department of Clinical Laboratory Sciences, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Background: Protease inhibitors (PIs) and nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs) are the major components of highly active antiretroviral therapy (HAART) and cause various metabolic disorders in HIV patients. The primary side effects induced are insulin resistance and lipodystrophy of which the precise mechanistic basis remains unknown. The aims of this study were to analyse the role of regulatory pathways in insulin signalling, such as NF-kB and to profile the metabolic effects of ARVs. We have previously shown that these drugs inhibit insulin signalling at a proximal level. Sodium salicylate (NaSal) and berberine chloride (BBR) are used to reverse the side effects induced by the PIs and NRTIs.

Methods: Chinese hamster ovary cells transfected with the human insulin receptor (CHO-IR) pretreated with inhibitor of IkB kinase (IKK16), BBR and nasal were incubated with indinavir, nelfinavir, stavudine or tenofovir and then stimulated with insulin (10 ng/ml) and probed for phosphorylated insulin-receptor (IR) substrate-1, IR-β, mitogen-activated protein kinase (MAPK), Akt and glycogen synthase kinase (GSK)-3α/β by western blotting. Metabolites in the cell culture media were assessed using nuclear magnetic resonance (NMR).

Results: Phosphorylation of MAPK was reduced by both NRTIs and PIs. Both indinavir and nelfinavir caused a significantly decreased phosphorylation of IRβ, IRS-1 and Akt. Cells treated with IKK16 showed a reversal of the effects of indinavir only, by increasing the phosphorylation at IR-β subunit, IRS-1 and MAPK. NaSal and BBR treatments on its own showed increased phosphorylation at IR beta. BBR increased phosphorylation at IR-β and Akt by inhibiting the effect of indinavir. NaSal also showed improvement in phosphorylation at IR-β after dephosphorylation by nelfinavir. Tenofovir and stavudine both showed no significant change in phosphorylation at IR-β and IRS-1, however, reduced phosphorylation was observed at the level of MAPK and Akt and increased phosphorylation at ser21/9 GSKα/β. NaSal decreased the effect of tenofovir at Akt and BBR showed increased phosphorylation at MAPK in the presence of stavudine. Metabolic profiling indicated a significant change in 19 metabolites following treatment with PIs including β-hydroxy butyrate, phosphocholine phosphatidylycholine, isoleucine, GSH, valine, glycerol, threonine and lactic acid. A change in four metabolites was observed in supernatant of cells following treatment with NRTIs including threonine, isoleucine and methionine.

Discussion/conclusions: This study confirms that the mechanism by which indinavir induces insulin resistance via activation of the NF-kB pathway. Other PIs and NRTIs investigated also cause significant inhibition of MAPK phosphorylation, which may influence cell growth and proliferation. NaSal and BBR displayed affirmative effects on the insulin signalling by reversing the drug-induced inhibition at IR beta, MAPK and Akt. Metabolomic data indicates that lipid, protein and carbohydrate metabolism is affected by PIs to a greater extent than with NRTIs in vitro.

ABSTRACT P27
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Analysis of glucose, insulin, HOMA-IR and triglycerides after 48 weeks of LPV/r therapy among subjects enrolled in three prospective randomized clinical trials

R D’Amicoq1, C Wegzyn1, W Richterq, CW Lin1, J Beron1, L Fredrick1, B Sager1, M Guion1, M Norton1

1Abbott, Abbott Park, IL, USA; 2Research Institute for Lipid Metabolism and Hemorrhology, Windach, Germany; 3Abbott AG, Baar, Switzerland

Aim: The potential for development of insulin resistance (IR) in patients receiving LPV/r was raised in HIV treatment guidelines including the 2011 DHHS and 2010 IAS–USA versions. There are conflicting data for this association. Studies in healthy volunteers demonstrate a transient effect of LPV/r on IR while studies in HIV-infected individuals demonstrate minimal impact of LPV/r on insulin, glucose or HOMA-IR levels after 48 weeks of antiretroviral therapy (ART).

This retrospective analysis compared baseline (BL) and
week 48 (WK48) insulin resistance parameters and triglyceride levels in subjects receiving LPV/r either as mono-, dual- or triple ART.

Methods: Fasting glucose, insulin, HOMA-IR and triglyceride (TG) levels were measured from plasma samples of 529 antiretroviral-naive subjects in three randomized, prospective, multicentre studies. Of the 529 subjects, 486 subjects with BL and WK48 data were included: LPV/r monotherapy (n=70), LPV/r+AZT/3TC (n=40), LPV/r+FTC/TDF (n=280) and LPV/r+RAL (n=96). Within-group median changes from BL to WK48 were evaluated using the Wilcoxon signed-rank test.

Results: 80% of subjects were male, 77% were White, and 9% were Hispanic. At BL, 37% of subjects had CD4+ T-cell counts <200 cells/μl and 33% of subjects had plasma HIV-1 RNA ≥100,000 copies/ml. There was no significant increase in fasting glucose, insulin or HOMA-IR levels from BL to WK48 within any treatment group. However, a significant increase in TG was observed from BL to WK48 within all treatment groups. Results were similar when 66 subjects receiving lipid-lowering or anti-glycaemic agents pre- or post-BL were excluded. Using regression analysis, LPV/r-associated increases in TG did not appear to be associated with increased insulin resistance (Table 1).

Conclusions: In this analysis, there was no evidence for the development of insulin resistance in HIV-infected subjects receiving LPV/r-based regimens. These findings challenge hypotheses associating LPV/r therapy and insulin resistance.

Table 1. (Abstract P27)

<table>
<thead>
<tr>
<th>Glucose, mg/dl</th>
<th>LPV/r monotherapy</th>
<th>LPV/r+AZT/3TC</th>
<th>LPV/r+RAL</th>
<th>LPV/r+FTC/TDF</th>
<th>LPV/r total</th>
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<tbody>
<tr>
<td>Median BL (IQR)</td>
<td>83.8 (77.5–95.5)</td>
<td>86.5 (79.3–93.7)</td>
<td>86.8 (81.1–97.0)</td>
<td>88.3 (81.1–95.5)</td>
<td>88.0 (81.1–95.5)</td>
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<tr>
<td>Median WK48 (IQR)</td>
<td>82.0 (77.5–93.7)</td>
<td>85.6 (75.7–91.9)</td>
<td>88.7 (83.0–97.0)</td>
<td>90.1 (82.9–98.5)</td>
<td>88.3 (81.1–97.3)</td>
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<tr>
<td>Median Δ from BL</td>
<td>-1.8</td>
<td>-0.9</td>
<td>+1.9</td>
<td>+1.8</td>
<td>+0.3</td>
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<tr>
<td>Insulin, μU/ml</td>
<td></td>
<td></td>
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<tr>
<td>Median BL (IQR)</td>
<td>7.2 (6.2–12.4)</td>
<td>8.2 (6.2–12.4)</td>
<td>4.7 (2.6–8.6)</td>
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<td>Median WK48 (IQR)</td>
<td>8.2 (5.2–12.4)</td>
<td>7.2 (4.2–14.4)</td>
<td>4.9 (2.3–11.0)</td>
<td>7.8 (6.0–11.2)</td>
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<td>Median Δ from BL</td>
<td>+1.0</td>
<td>-1.0</td>
<td>+0.3</td>
<td>0.0</td>
<td>+0.4</td>
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<td>HOMA-IR, mmol/l*μU/ml</td>
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<tr>
<td>Median BL (IQR)</td>
<td>1.6 (1.2–2.7)</td>
<td>1.7 (1.2–2.4)</td>
<td>1.0 (0.5–1.9)</td>
<td>1.7 (1.1–3.1)</td>
<td>1.6 (1.0–2.7)</td>
</tr>
<tr>
<td>Median WK48 (IQR)</td>
<td>1.4 (0.9–2.5)</td>
<td>1.6 (0.9–2.8)</td>
<td>1.1 (0.5–2.8)</td>
<td>1.9 (1.2–2.7)</td>
<td>1.6 (0.9–2.7)</td>
</tr>
<tr>
<td>Median Δ from BL</td>
<td>-0.2*</td>
<td>-0.1</td>
<td>+0.1</td>
<td>+0.2</td>
<td>+0.1</td>
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<tr>
<td>Triglycerides, mg/dl</td>
<td></td>
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<tr>
<td>Median BL (IQR)</td>
<td>83.0 (62.0–122.0)</td>
<td>92.0 (71.0–145.0)</td>
<td>111.0 (81.0–165.0)</td>
<td>110.0 (81.0–160.0)</td>
<td>104.0 (77.0–157.0)</td>
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<tr>
<td>Median WK48 (IQR)</td>
<td>136.0 (92.0–221.0)</td>
<td>164.5 (101.0–235.0)</td>
<td>175.0 (115.0–287.0)</td>
<td>172.0 (117.0–239.0)</td>
<td>169.0 (112.0–241.0)</td>
</tr>
<tr>
<td>Median Δ from BL</td>
<td>+53.0*</td>
<td>+72.5*</td>
<td>+64.0*</td>
<td>+62.0*</td>
<td>+65.0*</td>
</tr>
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*P<0.05 for median change from BL to WK48.
ABSTRACT P28

_Antiviral Therapy_ 2012; 17 Suppl 2:A47

**Modifications of lipids fractions or the creatinine concentration in HIV-infected patients treated with monotherapy**

_I-M Rios-Holgado1, A Fernandez-Rodriguez1, A Martin-Aspas1, R Perez-Cano1, F Guerrero1, M-J Marquez1, J-A Giron-Gonzalez1_

1Hospital Puerta del Mar, Universidad de Cadiz, Cadiz, Spain

**Introduction:** Protease inhibitor monotherapy is a recognized option in the treatment of HIV infection, either because of simplification of triple therapy, or by secondary effects induced by nucleoside analogues inhibitors of the reverse transcriptase. The objective was the analysis of the modifications of lipid fractions or the creatinine concentration in a sample of HIV-infected patients, treated with monotherapy.

**Patients and methods:** Forty six HIV patients (median age 47, interquartile range [IQR] 42–51 years; male sex 34 patients [74%]; drug users as risk factor 19 [41%], time from HIV diagnosis median 20, IQR 10–24 years; HCV coinfection 32 patients [70%], CDC stage C 16 [35%] in monotherapy treatment with either ritonavir-potentiated lopinavir [16, 35%] or darunavir [30 patients, 65%]) were studied. Causes of change to monotherapy treatment were simplification (27 cases, 59%) or nucleoside analogue secondary effects (19, 41%). All of them showed undetectable HIV load at the moment of change to monotherapy.

**Total cholesterol, HDL- and LDL-cholesterol and creatinine serum concentrations as well as HIV load and CD4 T-cell counts were analysed at the beginning of monotherapy and at the end of follow-up (median follow-up, 10 months, range 2–26 months). Data are shown as the median (IQR) of the calculated annual increase of these variables.**

**Results:** Every one of the patients maintained the undetectable HIV load at the end of the follow-up. At the end of the follow-up CD4 T-cell count decreased by a median of 35 cells/mm³ (IQR, -165, +30). Serum concentrations of the cholesterol fractions showed non-significant changes during the follow-up (total cholesterol, median +1,50 mg/dl [IQR, -37, +36]; HDL cholesterol, median + 0,7 mg/dl [IQR, -5, +23]; LDL cholesterol, median -7,20 mg/dl [IQR, -49, +13]). Finally, serum creatinine concentration showed similar values at the beginning and at the end of the study (median change 0,0 mg/dl [IQR, - 0,1, +0,2]). No significant differences were detected when patients in lopinavir- or darunavir-based monotherapy were compared.

**Conclusions:** Monotherapy with either lopinavir or darunavir is a safe alternative in patients with previously suppressed HIV replication. However, no beneficial effects of lipid fractions or renal function was detected when conventional therapy (based in three drugs combination) was changed to monotherapy.

ABSTRACT P29

_Antiviral Therapy_ 2012; 17 Suppl 2:A47

**Analysis of lipid levels and changes in body fat distribution in treatment-naive HIV-1-infected adults treated with rilpivirine (RPV) or efavirenz (EFV) over 96 weeks in pooled ECHO and THRIVE trials**

_M Sension1, J Arribas2, M Botes3, D Duiculescu4, E Florence5, C-C Hung6, P Tebas7, T Wilkin8, H Deckx9, S Vanveggel9, M Stevens8_

1Comprehensive Care Center, Fort Lauderdale, Fl, USA; 2Hospital Universitario La Paz, Madrid, Spain; 3MuelMed Hospital, Pretoria, South Africa; 4‘Titu Maiorescu’ University of Medicine and ‘Dr Victor Babes’ Hospital for Infectious and Tropical Diseases, Bucharest, Romania; 5Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium; 6National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; 7University of Pennsylvania, Philadelphia, PA, USA; 8Weill Medical College of Cornell University, New York, NY, USA; 9Janssen Infectious Diseases BVBA, Beerse, Belgium

**Aim:** In the Phase III, randomized, double-blind ECHO (NCT00540449) and THRIVE (NCT00543725) trials, RPV 25 mg qd had non-inferior efficacy compared to EFV 600 mg qd in treatment-naive, HIV-1-infected adults at week 96. The present pre-planned analyses compare changes in fasting lipid parameters. Changes in body fat distribution over 96 weeks and proportions of patients with ≥10% decrease in limb fat from baseline at week 96 (primary end point) were compared in the optional dual energy X-ray absorptiometry (DEXA) substudies.

**Methods:** In the main trials, changes in lipid parameters were assessed at each visit. In the DEXA substudies, body fat distribution was measured at baseline, week 48 and week 96 (or time of withdrawal for patients who discontinued >64 weeks).

**Results:** In the pooled trials, 1,368 patients received RPV or EFV. Background regimens were balanced between groups. Treatment-emergent dyslipidaemia did
not lead to discontinuation in either group. Lipid levels in the RPV group remained unchanged (total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C]) or showed a small decrease from baseline (triglycerides [TG]) through week 96. In contrast, these parameters were significantly increased (all \( P<0.0001 \)) in the EFV group. As the mean increase in high-density lipoprotein-cholesterol (HDL-C) with RPV was smaller than with EFV, no differences were seen between treatments in the TC/HDL-C ratio. The baseline-corrected proportion of patients with values above the National Cholesterol Education Program (NCEP) thresholds at any time point was lower for RPV than EFV for TC (22\% versus 52\%, \( P<0.0001 \)), LDL-C (21\% versus 44\%, \( P<0.0001 \)) and TG (40\% versus 55\%, \( P<0.0001 \)). EFV-treated patients were more likely to have HDL-C levels above the NCEP threshold (RPV 42\% versus EFV 53\%, \( P=0.0186 \)). The incidence of grade 3 or 4 lipid-related abnormalities was significantly lower for RPV than EFV. Lipid-modifying drug use remained low for both groups (RPV 3\% versus EFV 6\%, \( P=0.0062 \)).

In the pooled DEXA substudies (\( n=413 \)), background regimens were balanced between groups. Overall, limb fat increased similarly in both groups at week 96. Median (interquartile range) limb fat absolute change from baseline was +734 g (-132 to 2,103 g) with RPV (\( N=173 \)) versus +704 g (-388 to 2,093 g) with EFV (\( N=180 \); within group \( P<0.0001 \)). The proportions of patients with \( \geq 10\% \) decrease (RPV: 27/173 [15.6\%] versus EFV: 31/180 [17.2\%]) or \( \geq 20\% \) decrease (12/173 [6.9\%] versus 17/180 [10.0\%], respectively) in limb fat at week 96 were similar in both groups.

Conclusions: Over 96 weeks, RPV produced no increases in TC, LDL-C and TG in contrast to EFV. However, EFV increased HDL-C; therefore, there was no difference in the TC/HDL-C ratio between groups. Lipid abnormalities above NCEP thresholds were more common with EFV than RPV. Limb fat changes were small and similar in both groups.
ABSTRACT P30

Factors associated with increased liver fat in HIV-infected persons

R Kohli1, JE Forrester1, H Ji1, Y Zhao2, J Moy1, S Bhasin3, C Wanke1

1Tufts University School of Medicine, Boston, MA, USA; 2Philips Healthcare, Cleveland, OH, USA; 3Boston University School of Medicine, Boston, MA, USA

Background: Highly active antiretroviral therapy has been associated with metabolic complications including insulin resistance, changes in body fat distribution, and fatty liver disease. We examined liver fat in HIV-infected persons with insulin resistance and either central fat deposition or peripheral fat atrophy.

Methods: In this pilot study, HIV-infected subjects with insulin resistance (defined by fasting insulin ≥15 μU/ml and/or fasting glucose ≥100 but <126 mg/dl) and either isolated central fat deposition (waist cm >88 cm in women and >102 cm in men) or peripheral fat atrophy (triceps skinfold thickness <6 mm in men and <14 mm in women) underwent a frequently sampled oral glucose tolerance test and proton magnetic resonance spectroscopy to assess liver fat.

Results: We enrolled 10 subjects, 6 (60%) with central fat deposition and 4 (40%) with peripheral fat atrophy. Mean age was 45 years and 8 (80%) of subjects were male. Four (40%) subjects were Black and 6 (60%) were White. Subjects were infected with HIV for a median of 17.5 years; median CD4 count and HIV RNA was 372 cells/mm³ and <75 copies, respectively. Four (40%) subjects were coinfected with hepatitis C. Median BMI was 33.3 kg/m² and median fasting insulin was 34.5 μU/ml. Four (66%) subjects with central fat deposition and one (25%) with peripheral fat atrophy had elevated liver fat, defined as >5%. The correlation of liver fat with ALT and liver fat with waist circumference was r=0.58 (P=0.077) and r=0.51 (P=0.13), respectively. The correlation of liver fat with fasting insulin and liver fat with triglycerides was r=-0.28 (P=0.42) and r=-0.39 (P=0.26), respectively.

Conclusions: Traditional risk factors for fatty liver disease, including elevated triglycerides and insulin, were not associated with liver fat in our study sample. Our data suggest that, in HIV-infected persons, elevation in ALT may warrant evaluation for fatty liver disease. Further investigation is needed to identify factors associated with fatty liver disease in HIV-infected persons.
**ABSTRACT P31**

*Antiviral Therapy* 2012; 17 Suppl 2:A51

The other genome: a systematic review of studies of mitochondrial DNA (mtDNA) haplogroups and outcomes of HIV infection and antiretroviral therapy (ART)

A Hart¹, D Samuels¹, T Hulgan¹

¹Vanderbilt University, Nashville, TN, USA

**Background:** Mitochondria are near-ubiquitous organelles critical for cellular energy production and apoptosis. Mitochondrial toxicity is implicated in some treatment-limiting ART complications, and reports of mitochondrial dysfunction in untreated HIV infection also suggest ART-independent effects of HIV infection itself. Several studies have explored associations between maternal ancestry-specific patterns of mtDNA polymorphisms (haplogroups) and outcomes of HIV infection and/or ART complications, but findings have been inconsistent. We systematically reviewed published studies examining mtDNA haplogroups in HIV-infected persons to summarize reported outcome associations, and to highlight potential future research directions.

**Methods:** A systematic review was performed using PubMed and the search terms ‘([mitochondrial haplogroups OR mitochondrial genomics OR mitochondrial haplotypes] AND [HIV])’ without publication year restriction. Bibliographies were reviewed for additional publications. We included studies reporting associations between mtDNA haplogroups and any phenotype in HIV-infected adults or HIV/ART-exposed children.

**Results:** Of 38 studies initially identified, 14 met inclusion criteria. Another was identified through bibliography review providing a total of 15 articles published from 2005 to 2012. Studies included persons of either European or African descent, and sample sizes ranged from 29 to 1,833. Eleven different phenotypes were studied; most were ART-associated metabolic outcomes (for example, lipodystrophy, insulin resistance and dyslipidaemia). Eleven studies reported statistically significant mtDNA haplogroup associations; haplogroup H was associated with the most outcomes, including AIDS progression, cirrhosis (in hepatitis C coinfected subjects) and metabolic outcomes.

**Conclusions:** This review is the first to focus on the emerging area of mtDNA haplogroups in HIV infection and summarizes associations between mtDNA haplogroups and clinical outcomes. Although provocative, reported associations are inconclusive due to heterogeneous methods and outcomes, limited racial/ethnic groups, lack of replication and inadequate statistical power. The field will be advanced by: 1) combined analyses of existing data using uniform phenotype definitions and methods; 2) analyses within completed/ongoing studies to replicate reported associations and identify new ones; and 3) *in vitro* studies to define biological mechanisms of observed associations. Definitive conclusions cannot yet be drawn, but research in this area has the potential to explain outcome disparities across populations and impact patient management.
Prevalence and determinants of cognitive complaints in people with HIV

MJ Fuster1,2, JA Muñoz-Moreno3,4, D Dalmau1, MJ Ferrer1,4, B Clotet3,4,5, E Ortega1

1Sociedad Española Interdisciplinaria del SIDA (SEISIDA), Madrid, Spain; 2Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain; 3Fundació Lluita contra la SIDA, Badalona (Barcelona), Spain; 4Universitat Autònoma de Barcelona, Bellaterra (Barcelona), Spain; 5Institut per la Recerca de la SIDA IrsiCaixa, Badalona (Barcelona), Spain

Background: There are connections between impairment of the central nervous system functioning and HIV-related cognitive complaints. Since there are few studies exploring this aspect in the current era of combination antiretroviral therapies (cART), we decided to develop this work to determine its prevalence, as well as to study relationships with demographic and clinical variables.

Methods: We planned and carried out a cross-sectional observational multicentre study. A total of 791 people with HIV participated from different areas in Spain. We designed a self-reported questionnaire that measured variables involving cognitive complaints, quality of life and psychological health. A comparison of proportions and means was performed to analyse the relationship of cognitive complaint with the clinical data, psychological health and quality of life. Then, discriminant analysis was performed to study the determinants of cognitive complaint.

Results: Half of the people interviewed (49.9%) expressed cognitive complaints and (72.1%) important interference of these in their daily life. Memory and concentration were the most affected areas. The presence of cognitive complaint was significantly related to a greater infection period, a lower number of CD4, undetectable viral charge and worse quality of life. The discriminating analysis showed that the variables that allow for classification in people with HIV with cognitive complaint are depression, anxiety, older age, marital status (single people and widows) and low academic level of studies.

Conclusions: Prevalence of self-reported cognitive complaints is high in people with HIV in the current cART era. This fact is related to older age and disturbances in emotional status, although independent from the use of therapy. Cognitive complaints, but also neurocognitive functioning, should be both monitored in HIV infection.
ABSTRACT P33

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**Estimation of glomerular filtration rate using serum cystatin C and beta-trace protein in HIV patients**

A Rumman1, K Gee2, CA White3, WL Wobeser4

1 Division of Infectious Diseases, Department of Medicine, Queen's University, Kingston, ON, Canada; 2 Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada; 3 Division of Nephrology, Department of Medicine, Queen's University, Kingston, ON, Canada

**Aim:** Chronic kidney disease has emerged as a prominent cause of morbidity in HIV-infected patients. Due to the limitations of serum creatinine (SCr) in this population, cystatin C and beta-trace protein (BTP) have been proposed as alternative markers of renal function. In this cross-sectional study, we compared estimated glomerular filtration rates (eGFR) using SCr versus cystatin C and BTP. We also evaluated the prevalence of chronic kidney disease (CKD; eGFR < 60 ml/min/1.73 m2) and a panel of inflammatory markers.

**Methods:** Cystatin C was measured by nephelometric N-Latex Cystatin C kit. BTP was measured using a nephelometric Dade-Behring BN assay. Estimated GFR values were calculated using five equations: MDRD for SCr, CKD-EPI for SCr and cystatin C (adjusted for age, sex and race) and the White equations for BTP (adjusted for gender and urea or SCr).

**Results:** Thirty-two patients were included in the study, 8 on abacavir- or zidovudine-based regimens (ABC/AZT), 12 on tenofovir-based regimens (TDF) and 12 untreated (mean age 48.9 years, 75% male, mean CD4 435 cells/mm3, mean viral load 2.76 log10 copies/ml and 34% HCV-coinfected). Bland–Altman analysis showed only moderate agreement between SCr eGFR and cystatin C and BTP eGFR. Median eGFR derived from cystatin C and BTP equations was significantly lower compared to CKD-EPI SCr eGFR for all groups (TDF-based 80.3 and 91.4 versus 101.1 ml/min/1.73 m2; untreated 85.3 and 94.9 versus 101.5 ml/min/1.73 m2, respectively, P < 0.01; and ABC/AZT-based 97.3 and 93.5 versus 103.0 ml/min/1.73 m2, respectively, P < 0.05). SCr-based equations failed to identify any patients with possible CKD, whereas cystatin C and BTP equations identified 3 and 2 possible CKD patients, respectively. Serum lipopolysaccharide (LPS), an inflammatory marker, was significantly higher in the ABC/AZT group. Although eGFR did not vary significantly by HCV status, HCV+ patients had significantly higher mean cystatin C values (0.84 versus 0.96 mg/l, P < 0.05).

**Conclusions:** Cystatin C- and BTP-based equations yielded a lower estimate of GFR and classified a larger proportion of patient with CKD compared to conventional Scr-based equations. These novel biomarkers may be more sensitive for the early detection of HIV nephropathy and antiretroviral-therapy-induced renal dysfunction. The influence of extra-renal factors such as inflammation and HCV coinfection on these novel biomarkers remains unclear.

ABSTRACT P34

*Antiviral Therapy* 2012; 17 Suppl 2:A55

**Estimated glomerular filtration rates (eGFR) through 144 weeks on therapy in HIV-infected subjects receiving atazanavir/ritonavir and abacavir/lamivudine or simplified to unboosted atazanavir/abacavir/lamivudine**

B Young1, KE Squires2, K Tashima3, K Henry4, S Schneider5, A LaMarca6, HH Zhao7, LL Ross7, MS Shaefer8 for the ARIES study team

1 Rocky Mountain CARES, Denver, CO, USA; 2 Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, USA; 3 Miriam Hospital Brown University, Providence, RI, USA; 4 Hennipen County Medical Center, Minneapolis, MN, USA; 5 Living Hope Clinic Foundation, Long Beach, CA, USA; 6 Therafirst Medical Center, Ft Lauderdale, FL, USA; 7 GlaxoSmithKline, Research Triangle Park, NC, USA; 8 ViiV Healthcare, Research Triangle Park, NC, USA

**Objectives/aims:** Previous studies have suggested an increased risk of significant eGFR decline in subjects receiving boosted protease inhibitors, including atazanavir/ritonavir (ATV/r)-containing regimens. Renal function was evaluated for extension phase subjects in the open-label randomized ATV treatment simplification study ARIES, in which subjects received abacavir/lamivudine (ABC/3TC; 600 mg/300 mg once daily, fixed-dose combination) + atazanavir/ritonavir (300 mg/100 mg once daily) from baseline through randomization at week 36, then maintained or discontinued ritonavir for an additional 108 weeks.

**Methods:** The eGFR change from baseline and the incidence of renal dysfunction, defined as a ≥25% decline from baseline using the Modifications of Diet in Renal Disease (MDRD) formula, were determined for each group. The effect of atazanavir on renal...
dysfunction was assessed by multivariate Cox hazards model. Changes in eGFR over 144 weeks were evaluated using repeated mixed-effects models.

**Results:** 189/369 and 180/369 subjects were randomized to the ATV simplification and ATV/r continuation groups. The median baseline age and weight for females versus males, respectively, were 39 years, 71 kg versus 38 years, 76.4 kg. 31% (58/189) of the ATV simplification group were African–Americans (18 females; 40 males) compared to 32% (57/180; 17 females; 40 males) in the ATV continuation group (Table 1).

No significant difference in eGFR between treatment groups, by gender or gender by group was observed in repeated mixed-effects models. At week 144, only 3% of subjects in the ATV group and 5% in the ATV/r group had a ≥25% decrease in eGFR. In a stepwise Cox regression model for time to a ≥25% decrease in eGFR evaluating multiple variables, only baseline creatinine (P<0.0001) and baseline HIV RNA (P=0.0001) were significant. Lower baseline creatinine (P=0.0004), higher HIV RNA (P=0.0045) and lower CD4 (P=0.0391) were associated with a faster time to a ≥25% decrease in eGFR for subjects with weights below the median in a separate Cox regression model.

**Conclusions:** In combination with ABC/3TC, ATV or ATV/r-treated subjects had no statistically significant decline in eGFR from baseline. At 144 weeks, <5% of subjects had a ≥25% decrease in eGFR. Lower baseline creatinine levels and higher HIV RNAs were significantly associated with renal dysfunction, but body weight, gender and age were not.

<table>
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<th><strong>ABC/3TC+ATV/r (n=180)</strong></th>
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Table 1. (Abstract P34)