Abstracts presented at the 9th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV
19–21st July 2007, Sydney, Australia
ORGANIZING COMMITTEE

Co-chairs for 2007
Jacqueline Capeau Faculty of Medicine Saint Antoine, INSERM, Paris, France
Andrew Carr St Vincent’s Hospital, Sydney, Australia
Ian Weller Royal Free and University College Medical School, London, UK
David Cooper University of New South Wales, Sydney, Australia
Stefan Mauss Center for HIV and Hepatogastroenterology, Düsseldorf, Germany
Kathleen Mulligan University of California at San Francisco, San Francisco, CA, USA
Morrie Schambelan University of California at San Francisco, San Francisco, CA, USA

SCIENTIFIC COMMITTEE

Georg Behrens Medical School of Hannover, Hannover, Germany
Judith Currier University of California, Los Angeles, CA, USA
Michael Dubé Division of Infectious Diseases, University of Indianapolis, IN, USA
Julian Falutz Immune Deficiency Treatment Center, Montreal General Hospital, Montreal, Canada
Steven Grinspoon Massachusetts General Hospital, Boston, MA, USA
Carl Grunfeld University of California Medical Center, San Francisco, CA, USA
Donald Kotler Columbia University, New York, NY, USA
Jens Lundgren University of Copenhagen, Hvidovre, Denmark
Esteban Martinez IDIPAPS – Hospital Clinic, University of Barcelona, Barcelona, Spain
Veronica Miller The George Washington University, Washington, DC, USA
Graeme Moyle Chelsea and Westminster Hospital, London, UK
Robert Munk New Mexico AIDS INFO NET, Arroyo Seco, NM, USA
David Nolan Centre for Clinical Immunology & Biomedical Statistics, Perth, Australia
William Powderly University College Dublin, Dublin, Ireland
Peter Reiss University of Amsterdam, Amsterdam, The Netherlands
Willy Rozenbaum Hôpital Tenon, Université Pierre et Marie Curie, Paris, France
Pablo Tebas Medizinische Universitätsklinik, Freiburg University, Freiburg, Germany
Sharon Walmsley University Health Network, Toronto, Canada
Kevin Yarasheski Washington University, St Louis, MO, USA

PLENARY SPEAKERS

Corinne Bagnis Pitié-Salpêtrière Hospital, Paris, France
Shabir Banoo Management Sciences for Health, Pretoria, South Africa
Scott Friedman Mount Sinai School of Medicine, New York, NY, USA
David James Garvan Institute of Medical Research, Sydney, Australia
Jonathan Shaw Monash University, Melbourne, Australia

ORGANIZING SECRETARIAT

International Medical Press 36 St Mary at Hill
London EC3R 8DU, UK
Tel: +44 20 7398 0700
Fax: +44 20 7398 0701
www.intmedpress.com
E-mail: Lipodystrophy@intmedpress.com
## ABSTRACT CONTENTS

<table>
<thead>
<tr>
<th>PAGE</th>
<th>TITLE AND PRESENTING AUTHOR</th>
<th>ABSTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>ORAL PRESENTATIONS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Plenary Lectures</strong></td>
<td></td>
</tr>
</tbody>
</table>
| L3   | Pathogenesis of hepatic fibrogenesis  
**SL Friedman** | PL-01 |
| L3   | Adverse event monitoring in a resource-poor setting  
**SL Banoo** | PL-02 |
| L3   | Clinical significance of metabolic syndrome  
**J Shaw** | PL-03 |
| L3   | Insulin signalling within adipocytes  
**D James** | PL-04 |
| L3   | Assessment of drug-induced nephrotoxicity in HIV patients  
**CI Bagnis** | PL-05 |
|      | **Session I**                |          |
| L4   | Incidence of hypersensitivity reactions associated with nevirapine-containing HAART in patients with prior treatment experience may differ from that in treatment-naive patients: the ATHENA cohort study  
**F Wit** | O-01 |
| L5   | Nevirapine increases high density lipoprotein-cholesterol by stimulation of apolipoprotein AI synthesis  
**P Reiss** | O-02 |
| L5   | Effects of efavirenz on lipid metabolism in APOE*3*Leiden hCETP double-transgenic mice: evidence for antagonism of LXR pathway  
**A Bellamine** | O-03A |
| L6   | Molecular mechanism for efavirenz effects on lipid metabolism  
**A Bellamine** | O-03B |
| L6   | Dyslipidaemia in vertically infected children and youth on protease inhibitor (PI)-containing antiretroviral therapy (ART): preliminary results of PACTG 1045  
**K Mulligan** | O-04 |
|      | **Session II**               |          |
| L7   | Design and outcomes of an antiretroviral pharmacovigilance programme in South Africa  
**U Mehta** | O-05 |
| L7   | Metabolic changes in a Thai treatment-naive population starting double-boosted protease inhibitor therapy  
**J van der Lugt** | O-06 |

9th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV
<table>
<thead>
<tr>
<th>PAGE</th>
<th>TITLE AND PRESENTING AUTHOR</th>
<th>ABSTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8</td>
<td>Effects of tipranavir/r (200/100 or 500/100 mg BID) in comparison with lopinavir/r (400/100 mg BID) on changes in body composition and metabolic parameters in ARV-naive patients over 48 weeks</td>
<td>O-07</td>
</tr>
<tr>
<td></td>
<td>A Carr</td>
<td></td>
</tr>
<tr>
<td>L9</td>
<td>Further data on the effects of tesamorelin (TH9507), a growth hormone-releasing factor analogue, on body composition and metabolic parameters in HIV-infected patients with abdominal fat accumulation</td>
<td>O-08</td>
</tr>
<tr>
<td></td>
<td>S Grinspoon</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Session III</strong></td>
<td></td>
</tr>
<tr>
<td>L10</td>
<td>Does diabetes mellitus (DM) confer an equivalent risk of coronary heart disease (CHD) to pre-existing CHD in HIV-positive individuals?</td>
<td>O-09</td>
</tr>
<tr>
<td></td>
<td>SW Worm</td>
<td></td>
</tr>
<tr>
<td>L10</td>
<td>The rate at which therapy-naive patients develop metabolic syndrome when treated and its association with different components of antiretroviral therapy: the Swiss HIV Cohort Study</td>
<td>O-10</td>
</tr>
<tr>
<td></td>
<td>J Young</td>
<td></td>
</tr>
<tr>
<td>L11</td>
<td>Effect of alternate treatment protocols on the incidence of electrocardiographic abnormalities among HIV-infected adults in the SMART trial</td>
<td>O-11</td>
</tr>
<tr>
<td></td>
<td>A Carr</td>
<td></td>
</tr>
<tr>
<td>L11</td>
<td>Subclinical coronary atherosclerosis, HIV-infection and antiretroviral therapy: results from the multicentre AIDS cohort study</td>
<td>O-12</td>
</tr>
<tr>
<td></td>
<td>LA Kingsley</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Session IV</strong></td>
<td></td>
</tr>
<tr>
<td>L12</td>
<td>Macrophage recruitment in adipose tissue from HIV-infected patients under ART: concomitant presence of classically activated pro-inflammatory M1 and alternatively activated M2 macrophages</td>
<td>O-13</td>
</tr>
<tr>
<td></td>
<td>J Capeau</td>
<td></td>
</tr>
<tr>
<td>L12</td>
<td>The effect of antiretroviral therapy on genes involved with glucose and lipid metabolism</td>
<td>O-14</td>
</tr>
<tr>
<td></td>
<td>M Shahmanesh</td>
<td></td>
</tr>
<tr>
<td>L13</td>
<td>Zidovudine/lamivudine persistently contributes to peripheral insulin resistance by a body composition-independent mechanism demonstrated by repeated clamp studies during 2 years of first-line ART with zidovudine/lamivudine/lopinavir/ritonavir</td>
<td>O-15</td>
</tr>
<tr>
<td></td>
<td>MGA van Vonderen</td>
<td></td>
</tr>
<tr>
<td>L14</td>
<td>Pioglitazone with or without exercise training reduces liver lipid content and improves insulin sensitivity in HIV patients with impaired glucose tolerance (IGT)</td>
<td>O-16</td>
</tr>
<tr>
<td></td>
<td>KE Yarasheski</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Session V</strong></td>
<td></td>
</tr>
<tr>
<td>L14</td>
<td>Effects of 4 weeks of atazanavir, lopinavir/ritonavir or placebo on endothelial function and insulin sensitivity in healthy men</td>
<td>O-17</td>
</tr>
<tr>
<td></td>
<td>MP Dubé</td>
<td></td>
</tr>
<tr>
<td>L15</td>
<td>Control of HIV viral replication is associated with rapid improvement in endothelial function sustained over 24 weeks: AS152s, a substudy of AS142</td>
<td>O-18</td>
</tr>
<tr>
<td></td>
<td>JS Currier</td>
<td></td>
</tr>
<tr>
<td>PAGE</td>
<td>TITLE AND PRESENTING AUTHOR</td>
<td>ABSTRACT</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>L15</td>
<td>Relationship of body composition, antiretroviral use, and HIV disease factors to endothelial dysfunction in HIV-infected subjects</td>
<td>O-19 MP Dubé</td>
</tr>
<tr>
<td>L16</td>
<td>Relationship of fat distribution with adipokines in HIV infection: the FRAM study</td>
<td>O-20 C Grunfeld</td>
</tr>
</tbody>
</table>

Session VII

| L17  | Proteinuria, creatinine clearance and immune activation in HIV-infected subjects: a secondary analysis of treatment-naive studies ACTG 384, A5095 and A5001 | O-21 SK Gupta |
| L17  | Important changes in bone metabolism soon after commencing HAART | O-22 E Bonnet |
| L18  | Uridine supplementation with Mitocnol antagonizes zidovudine-induced mitochondrial myopathy and hyperlactataemia in vivo | O-23 D Lebrecht |
| L19  | Racial differences in long-term changes in metabolic parameters in antiretroviral-naive persons initiating HAART | O-24A C Grunfeld |
| L19  | Racial differences in long-term changes in body composition in antiretroviral-naive persons initiating HAART | O-24B C Grunfeld |

POSTER PRESENTATIONS

Mitochondrial Disorders

<p>| L23  | The effect of antiretroviral therapy on genes involved with mitochondrial function | P-01 M Shahmanesh |
| L23  | Mitochondrial impairment in mononuclear cells of hyperlactatemic patients on HAART | P-02 G Garrabou |
| L24  | Risk factors for case fatality: do we need a new case definition for severe hyperlactataemia in HIV-infected patients exposed to NRTIs? | P-03 A Arenas-Pinto |
| L24  | The risk of developing NRTI-induced peripheral neuropathy decreases over time: evidence for special susceptibility from the Delta trial | P-04 A Arenas-Pinto |
| L25  | Acute inhibition of mitochondrial respiration by Efavirenz in hepatic cells: a new mechanism of damage following bioenergetic stress. | P-05 JV Esplugues |
| L25  | Single-dose and cumulative pharmacokinetics of the food supplement Nucleomax® and mechanism for enhanced bioavailability of uridine | P-06 ME Weinberg |
| L26  | Uridine supplementation with Mitocnol antagonizes zidovudine-induced mitochondrial myopathy and hyperlactataemia in vivo | P-07 D Lebrecht |</p>
<table>
<thead>
<tr>
<th>PAGE</th>
<th>TITLE AND PRESENTING AUTHOR</th>
<th>ABSTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>L26</td>
<td>Adipocyte Biology Effect of atazanavir and lopinavir on resistin expression in primary human macrophages A Bellamine</td>
<td>P-08</td>
</tr>
<tr>
<td>L27</td>
<td>Body Composition The effect of antiretroviral therapy on genes involved with glucose and lipid metabolism M Shahmanesh</td>
<td>P-09</td>
</tr>
<tr>
<td>L27</td>
<td>Gender independent Th1/2 cytokine dysbalance associated with lipodystrophy in HIV-patients GMN Behrens</td>
<td>P-10</td>
</tr>
<tr>
<td>L27</td>
<td>Sex differences in the correlations between baseline anthropometric measurements and fat distribution in HIV-infection-associated adipose redistribution syndrome (HARS) K Mulligan</td>
<td>P-11</td>
</tr>
<tr>
<td>L28</td>
<td>Factors associated with low limb fat in a cohort of zidovudine-treated subjects G Moyle</td>
<td>P-12</td>
</tr>
<tr>
<td>L28</td>
<td>Hepatic lipid and adipose tissue distribution in HIV-infected men DP Kotler</td>
<td>P-13</td>
</tr>
<tr>
<td>L29</td>
<td>Relationship of fat distribution with adipokines in HIV infection: the FRAM study C Grunfeld</td>
<td>P-14</td>
</tr>
<tr>
<td>L29</td>
<td>Evolution of body composition in HIV-infected lipodystrophic men treated with antiretroviral therapy E Bonnet</td>
<td>P-15</td>
</tr>
<tr>
<td>L30</td>
<td>Follow-up of lipodystrophy and metabolic alterations in the ANRS APPROCO-COPILOTE cohort studying HIV-infected patients initiated with protease inhibitors in 1997 and 1998: relation to adiponectin, leptin and triglycerides levels and to TNF polymorphisms J Capeau</td>
<td>P-16</td>
</tr>
<tr>
<td>L30</td>
<td>Long-term subcutaneous tissue changes among antiretroviral naive persons initiating three nucleoside regimens C Grunfeld</td>
<td>P-17</td>
</tr>
<tr>
<td>L31</td>
<td>Validation of a simple classification for facial lipoatrophy in HIV-infected adults J Fontdevila</td>
<td>P-18</td>
</tr>
<tr>
<td>L32</td>
<td>Effects of tipranavir/r (500/200 or 500/100 mg BID) in comparison with lopinavir/r (400/100 mg BID) on changes in body composition and metabolic parameters in ARV-naive patients over 48 weeks A Carr</td>
<td>P-19</td>
</tr>
<tr>
<td>L32</td>
<td>Lipoatrophy (LA) and lipohypertrophy (LH) are independently associated with depression and health-related quality-of-life (HRQOL); lipoatrophy is associated with adherence HM Crane</td>
<td>P-20</td>
</tr>
<tr>
<td>PAGE</td>
<td>TITLE AND PRESENTING AUTHOR</td>
<td>ABSTRACT</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>L32</td>
<td>Impact of lipoatrophy on quality of life in HIV-infected individuals receiving antiretroviral therapy (ART) R Rajagopalan</td>
<td>P-21</td>
</tr>
<tr>
<td>L33</td>
<td>The impact of tesamorelin (TH9507), a growth hormone releasing factor analogue, on body image and health-related quality of life in HIV-infected patients with abdominal fat accumulation RR Turner</td>
<td>P-22</td>
</tr>
<tr>
<td>L33</td>
<td>Induction therapy with recombinant human growth hormone (r-hGH) improves anthropometric parameters in patients (pts) with HIV adipose redistribution syndrome (HARS) D Kotler</td>
<td>P-23</td>
</tr>
<tr>
<td>L34</td>
<td>A randomized comparison of the safety of continued zidovudine plus lamivudine (Combivir, CBV) versus switching to tenofovir DF plus emtricitabine (Truvada, TVD) each plus efavirenz (EFV) in stable HIV-infected persons: results of a planned 24-week analysis G Moyle</td>
<td>P-24</td>
</tr>
<tr>
<td>L34</td>
<td>Autologous fat grafts are safe and durable in HIV-infected adults with facial lipoatrophy J Fontdevila</td>
<td>P-25</td>
</tr>
<tr>
<td>L35</td>
<td>Effectiveness and long-term durability of autologous fat transplant for HIV-related face lipoatrophy G Orlando</td>
<td>P-26</td>
</tr>
</tbody>
</table>

### Cardiovascular Disease

<p>| L36  | Efavirenz and atazanavir induce leukocyte-endothelial cell interactions in the microvasculature JV Esplugues | P-27 |
| L36  | Coronary artery disease in HIV-infected patients RG Micheletti | P-28 |
| L37  | Rosiglitazone inhibits CIMT progression but may reverse plaque area in low-moderate risk HIV patients KW Johns | P-29 |
| L37  | The anti-inflammatory agent salsalate improves HIV-related endothelial dysfunction: a pilot study SK Gupta | P-30 |
| L38  | Association of antiretroviral therapy with fibrinogen levels in HIV infection C Grunfeld | P-31 |
| L38  | Lack of association between antiretroviral therapy and predictors of endothelial function and cardiovascular disease (CVD) risk among HIV-infected persons on long-term HAART K Yarasheski | P-32 |
| L39  | All-cause death and markers of early atherosclerosis in a cohort of HIV-infected subjects from nutrition for healthy living (NFHL) A Mangili | P-33 |</p>
<table>
<thead>
<tr>
<th>PAGE</th>
<th>TITLE AND PRESENTING AUTHOR</th>
<th>ABSTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>L40</td>
<td>Framingham risk score (FRS) analysis in treated HIV patients: modelling differential effects on risk reduction of lipid-lowering therapy versus stopping cigarette smoking.</td>
<td>P-34</td>
</tr>
<tr>
<td>L40</td>
<td>Effect of alternate treatment protocols on the incidence of electrocardiographic abnormalities among HIV-infected adults in the SMART trial</td>
<td>P-35</td>
</tr>
<tr>
<td>L40</td>
<td>Clinically evident facial lipoatrophy is associated with a higher cardiovascular risk</td>
<td>P-36</td>
</tr>
<tr>
<td>L41</td>
<td>The rate at which therapy-naive patients develop metabolic syndrome when treated and its association with different components of antiretroviral therapy: the Swiss HIV Cohort Study</td>
<td>P-37</td>
</tr>
<tr>
<td>L41</td>
<td>The role of virological and immunological parameters on the diagnosis of metabolic syndrome in HIV-associated lipodystrophy</td>
<td>P-38</td>
</tr>
<tr>
<td>L42</td>
<td>Cardiovascular disease risk analysis in treated HIV males: does use of combined Framingham risk score (FRS) and metabolic syndrome (MetS) diagnosis improve the identification of patients at increased CVD risk?</td>
<td>P-39</td>
</tr>
<tr>
<td>L42</td>
<td>Heart for HAART. A novel screening programme for cardiovascular risk in HIV-infected populations</td>
<td>P-40</td>
</tr>
<tr>
<td>L43</td>
<td>Myeloperoxidase level does not predict future cardiovascular events in HIV-infected subjects</td>
<td>P-41</td>
</tr>
<tr>
<td>L43</td>
<td>Hypertriglyceridaemia and small dense LDL-cholesterol in HIV-infected patients with myocardial infarction</td>
<td>P-42</td>
</tr>
<tr>
<td>L44</td>
<td>Factors affecting the short term nutritional response to HAART in Rwandan women</td>
<td>P-43</td>
</tr>
<tr>
<td>L44</td>
<td>Adverse effects of standard first-line antiretroviral therapy on black South African patients</td>
<td>P-44</td>
</tr>
<tr>
<td>L45</td>
<td>Antiretroviral treatment related adverse events (AEs) in the TREAT Asia HIV Observation Database (TAHOD)</td>
<td>P-45</td>
</tr>
<tr>
<td>L45</td>
<td>Differential willingness to accept adverse event (AE) risks among ART-naive HIV-positive African Americans (AA)</td>
<td>P-46</td>
</tr>
<tr>
<td>PAGE</td>
<td>TITLE AND PRESENTING AUTHOR</td>
<td>ABSTRACT</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>L46</td>
<td>Insulin Resistance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The acute effects of HIV protease inhibitors on glucose production in healthy HIV-negative men</td>
<td>P-47</td>
</tr>
<tr>
<td></td>
<td>GA Lee</td>
<td></td>
</tr>
<tr>
<td>L46</td>
<td>Zidovudine/lamivudine persistently contributes to peripheral insulin resistance by a body composition-independent mechanism demonstrated by repeated clamp studies during 2 years of first-line ART with zidovudine/lamivudine/lopinavir/ritonavir</td>
<td>P-48</td>
</tr>
<tr>
<td></td>
<td>MGA van Vonderen</td>
<td></td>
</tr>
<tr>
<td>L46</td>
<td>A randomized double-blind control study of benfluorex versus placebo in HIV-infected patients with insulin resistance or impaired glucose tolerance</td>
<td>P-49</td>
</tr>
<tr>
<td></td>
<td>I Poizot-Martín</td>
<td></td>
</tr>
<tr>
<td>L47</td>
<td>Correlation of HDL-cholesterol and insulin resistance in HIV-patients with lipodystrophy</td>
<td>P-50</td>
</tr>
<tr>
<td></td>
<td>GMN Behrens</td>
<td></td>
</tr>
<tr>
<td>L47</td>
<td>Lipid Metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hatha/Ashtanga yoga intervention modestly improves cardiovascular disease (CVD) risk parameters in dyslipidaemic HIV+ subjects with central adiposity.</td>
<td>P-51</td>
</tr>
<tr>
<td></td>
<td>KE Yarasheski</td>
<td></td>
</tr>
<tr>
<td>L48</td>
<td>Resistance to highly potent statin therapy in patients with HIV metabolic syndrome</td>
<td>P-52</td>
</tr>
<tr>
<td></td>
<td>KW Johns</td>
<td></td>
</tr>
<tr>
<td>L48</td>
<td>Adherence to dyslipidaemia guidelines in patients taking protease inhibitors at an inner-city academic medical centre</td>
<td>P-53</td>
</tr>
<tr>
<td></td>
<td>M Díaz-Linares</td>
<td></td>
</tr>
<tr>
<td>L49</td>
<td>Changes in lipid parameters during treatment with lopinavir/ritonavir (LPV/r) plus zidovudine/lamivudine (ZDV/3TC) induction followed by maintenance on LPV/r monotherapy compared with efavirenz (EFV) + ZDV/3TC through 96 weeks</td>
<td>P-54</td>
</tr>
<tr>
<td></td>
<td>BA da Silva</td>
<td></td>
</tr>
<tr>
<td>L50</td>
<td>Evolution of the lipid profile in patients treated with tenofovir DF and protease inhibitors. Data from the PROTECTION cohort study</td>
<td>P-55</td>
</tr>
<tr>
<td></td>
<td>R Sánchez-de la Rosa</td>
<td></td>
</tr>
<tr>
<td>L50</td>
<td>Evaluation of the impact of highly active antiretroviral therapy (HAART) on lipid profiles — data from the 24-week interim analysis of the Gemini Study: saquinavir/r (SQV/r) twice daily versus lopinavir/r (LPV/r) twice daily plus emtricitabine/tenofovir (FTC/TDF) once daily in ARV-naive HIV-1-infected patients</td>
<td>P-56</td>
</tr>
<tr>
<td></td>
<td>C Guittari</td>
<td></td>
</tr>
<tr>
<td>L51</td>
<td>Comparison of the effects of darunavir/ritonavir and atazanavir/ritonavir on lipid and glucose-related laboratory parameters in healthy volunteers</td>
<td>P-57</td>
</tr>
<tr>
<td></td>
<td>F Tomaka</td>
<td></td>
</tr>
<tr>
<td>L52</td>
<td>Heart Positive 4: fuel selection for oxidation in the fasted state is markedly abnormal in HIV patients – implications for a uniquely dysregulated form of energy metabolism</td>
<td>P-58</td>
</tr>
<tr>
<td></td>
<td>RV Sekhar</td>
<td></td>
</tr>
<tr>
<td>PAGE</td>
<td>TITLE AND PRESENTING AUTHOR</td>
<td>ABSTRACT</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>L52</td>
<td>Heart Positive 2: increased resting energy expenditure in HIV patients on HAART is related to fat redistribution and insulin resistance</td>
<td>RV Sekhar P-59</td>
</tr>
<tr>
<td>L53</td>
<td>Long-term trends in plasma lipids and glucose in antiretroviral-naive HIV-infected patients starting highly active antiretroviral therapy</td>
<td>E Martinez P-60</td>
</tr>
<tr>
<td>L54</td>
<td>Dyslipidaemia in an urban HIV-infected population</td>
<td>St Hodder P-61</td>
</tr>
<tr>
<td>L54</td>
<td>Heart Positive 3: Low cholesterol ester transfer protein (CETP) concentrations are associated with the lack of an inverse relationship between plasma triglyceride and HDL-C concentrations in HIV patients on HAART</td>
<td>RV Sekhar P-62</td>
</tr>
<tr>
<td>L55</td>
<td>Correlation between in vitro and in vivo effects of HIV protease inhibitors on the hepatocyte and adipocyte metabolome</td>
<td>A Bellamine P-63</td>
</tr>
<tr>
<td>L55</td>
<td>Nevirapine increases high density lipoprotein-cholesterol by stimulation of apolipoprotein AI synthesis</td>
<td>P Reiss P-64</td>
</tr>
<tr>
<td>L56</td>
<td>Molecular mechanism for efavirenz effects on lipid metabolism</td>
<td>A Bellamine P-65</td>
</tr>
<tr>
<td>L56</td>
<td>Effects of efavirenz on lipid metabolism in APOE<em>3</em>Leiden hCETP double-transgenic mice: evidence for antagonism of LXR pathway</td>
<td>A Bellamine P-66</td>
</tr>
<tr>
<td></td>
<td><strong>Other Toxicities</strong></td>
<td></td>
</tr>
<tr>
<td>L56</td>
<td>Impact of patient-selected self-injection devices on the development of injection site reactions associated with Enfuvirtide use</td>
<td>M Gottlieb P-67</td>
</tr>
<tr>
<td>L57</td>
<td>A randomized study to evaluate injection site reactions (ISR) using three different mechanisms for delivery of enfuvirtide (ENF): a 27-gauge needle, a 31-gauge needle and a needle-free device</td>
<td>MA Boyd P-68</td>
</tr>
<tr>
<td>L57</td>
<td>Lack of evidence of metabolic abnormalities and mitochondrial toxicity with enfuvirtide; a double-blind, placebo-controlled, cross-over study with random sequence assignment in healthy adult volunteers</td>
<td>E Martinez P-69</td>
</tr>
<tr>
<td>L58</td>
<td>HAART-induced viral suppression compensates potential negative effects of TDF on renal function</td>
<td>F Ravera P-70</td>
</tr>
<tr>
<td>L58</td>
<td>Renal safety profile of TDF in combination with protease inhibitors (PI) in a clinical setting. Results from the PROTECTION cohort</td>
<td>P Viciana P-71</td>
</tr>
<tr>
<td>L59</td>
<td>Low long-term incidence of tenofovir associated renal dysfunction as measured by creatinine clearance</td>
<td>CM Tsoukas P-72</td>
</tr>
<tr>
<td>PAGE</td>
<td>TITLE AND PRESENTING AUTHOR</td>
<td>ABSTRACT</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>L59</td>
<td>Cystatin C underestimates glomerular filtration rate in HIV-infected individuals</td>
<td>P-73</td>
</tr>
<tr>
<td></td>
<td>S Mauss</td>
<td></td>
</tr>
<tr>
<td>L60</td>
<td>Adverse reactions on switching from tenofovir/lamivudine (3TC) to the fixed-dose combination (FDC) of tenofovir/emtricitabine (FTC)</td>
<td>P-74</td>
</tr>
<tr>
<td></td>
<td>M Harris</td>
<td></td>
</tr>
<tr>
<td>L60</td>
<td>Effectiveness and safety profile of TDF+ddI+EFV. Results from the DIDITEN cohort.</td>
<td>P-75</td>
</tr>
<tr>
<td></td>
<td>C Miralles</td>
<td></td>
</tr>
<tr>
<td>L61</td>
<td>Effect of nucleoside reverse transcriptase inhibitors (NRTIs) on CD4 recovery for individuals on long-term, fully suppressive antiretroviral therapy (ART)</td>
<td>P-76</td>
</tr>
<tr>
<td></td>
<td>H Byakwaga</td>
<td></td>
</tr>
<tr>
<td>L62</td>
<td>Updated clinical characteristics and clinical risk factor analysis for suspected hypersensitivity (HSR) to abacavir (ABC) comparing ABC once daily (QD) versus ABC twice daily (BID)</td>
<td>P-77</td>
</tr>
<tr>
<td></td>
<td>JE Hernandez</td>
<td></td>
</tr>
<tr>
<td>L62</td>
<td>One-year bone mineral density changes in antiretroviral-naive HIV-infected patients treated by a triple, versus a single-agent regimen, with Lopinavir/ritonavir in the Monark Trial</td>
<td>P-78</td>
</tr>
<tr>
<td></td>
<td>P Ngo Van</td>
<td></td>
</tr>
<tr>
<td>L63</td>
<td>HIV proteins modulate osteogenesis in a phase-specific manner</td>
<td>P-79</td>
</tr>
<tr>
<td></td>
<td>EJ Cotter</td>
<td></td>
</tr>
<tr>
<td>L63</td>
<td>Liver Disease &amp; Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic effects of atazanavir plus ritonavir (ATV-r)-based combinations in patients with hepatitis virus coinfection: relationship with pre-existing liver damage</td>
<td>P-80</td>
</tr>
<tr>
<td></td>
<td>JA Pinedo</td>
<td></td>
</tr>
<tr>
<td>L64</td>
<td>Association of hyperlipidaemia with advanced liver fibrosis in HIV+ patients</td>
<td>P-81</td>
</tr>
<tr>
<td></td>
<td>F Blanco</td>
<td></td>
</tr>
<tr>
<td>L64</td>
<td>Metabolic syndrome and progression of liver fibrosis in HIV/HCV-coinfected patients on HAART</td>
<td>P-82</td>
</tr>
<tr>
<td></td>
<td>F Blanco</td>
<td></td>
</tr>
</tbody>
</table>
ORAL PRESENTATIONS
ABSTRACT PL-01
*Antiviral Therapy* 2007; 12 Suppl 2:L3

**Pathogenesis of hepatic fibrogenesis**

*SL Friedman*

Mount Sinai School of Medicine, New York, NY, USA

The understanding of hepatic fibrosis or the liver’s scarring response has emerged as a major focus of current research in hepatology, and has begun to yield meaningful progress in predicting the risk of fibrosis in chronic liver disease, assessing its severity non-invasively, and establishing antifibrotic therapies. Hepatic stellate cells (HSC) are the primary source of extracellular matrix in normal and fibrotic liver. These resident perisinusoidal cells undergo an ‘activation’ or transdifferentiation in progressive stages yielding a cell type that is highly proliferative, fibrogenic and contractile. Activation of HSCs is the central event of fibrogenesis. Exciting progress has been made in understanding the molecular basis of this process. There have been major advances in defining pathways of activation, mediators and mechanisms of fibrosis resolution. These advances in pathogenesis have led to rational new approaches to antifibrotic therapies, including: 1) treating the underlying liver disease etiology; 2) hepatoprotection to reduce liver cell injury and oxidant stress; 3) downregulating stellate cell activation; 4) inhibiting cytokine driven pathways of stellate cell proliferation, contractility and fibrogenesis; 5) stimulating stellate cell apoptosis; and 6) directly degrading scar matrix. Clinical trials are underway attacking a number of these pathways, primarily in patients with HCV and NASH.

Another major advance in understanding the natural history of chronic liver disease, especially, viral hepatitis and NASH, has been the recognition that fibrosis progression can be predicted based on genetic markers, and varies tremendously between patients, independent of viral load or genotype in HCV. Large scale studies have begun to identify host genetic polymorphisms that predict risk of fibrosis progression. Fibrosis is also greatly accelerated in patients with HIV/HCV coinfection, but is slowed by HAART therapy. The development of accurate, non-invasive markers of liver fibrosis has become an urgent priority in order to allow the evaluation of antifibrotic and antiviral drugs in clinical trials. Interest is accelerating in new modalities, as well as refining existing methods including serum assays, elastography (Fibroscan), proteomics and Ultrasound/CT/MRI. In particular, Fibroscan is as an outstanding test to diagnose cirrhosis, and ongoing studies are assessing its utility in tracking disease over time in lieu of liver biopsy, particularly in HIV/HCV coinfection and NASH.

Ultimately, advances in the understanding of the molecular biology of hepatic fibrosis are critical to the development of effective, targeted antifibrotic therapy that may benefit millions of patients with chronic liver disease worldwide.

ABSTRACT PL-02
*Antiviral Therapy* 2007; 12 Suppl 2:L3

**Adverse event monitoring in a resource-poor setting**

*SL Banoo*

Management Sciences for Health, Pretoria, South Africa

Not available.

ABSTRACT PL-03
*Antiviral Therapy* 2007; 12 Suppl 2:L3

**Clinical significance of metabolic syndrome**

*J Shaw*

Monash University, Melbourne, Australia

Not available.

ABSTRACT PL-04
*Antiviral Therapy* 2007; 12 Suppl 2:L3

**Insulin signalling within adipocytes**

*D James*

Garvan Institute of Medical Research, Sydney, Australia

Not available.

ABSTRACT PL-05
*Antiviral Therapy* 2007; 12 Suppl 2:L3

**Assessment of drug-induced nephrotoxicity in HIV patients**

*CI Bagnis*

Pitié-Salpêtrière Hospital, Paris, France

Several lines of evidence point to renal disease becoming an important complication of HIV infection and therapy. The kidney is particularly exposed to toxic nephropathy because of the increasing number of drugs used for the purpose of treating what has become a chronic disease. Very few drugs exhibit severe intrinsic nephrotoxic properties, but renal risk factors such as age (the number of HIV patients over the age of 65 has grown 10x over the past ten years), pre-existing chronic renal failure (glomerular filtration rate is below 60 ml/min/1.73 m² in as much as 10% of HIV patients) and diabetes mellitus or hypertension are highly prevalent in HIV patients.
Drug-induced toxic nephropathy may manifest as acute or chronic renal failure, an isolated decrease in glomerular filtration rate or a selective defect in tubular functions, a nephrotic range albuminuria or a low level tubular proteinuria together with or without leucocyturia or haematuria. All segments of nephron may be involved. Diagnosis relies on close monitoring of renal parameters at diagnosis of HIV infection, before any therapeutic change and once a year or more often depending on initial screening and current treatment. Renal biopsy is the only gold-standard tool to perform appropriate diagnosis, define prognosis and tailor therapy.

Patients with low CD4 cell count and high viral load are especially at high risk for acute renal failure often enhanced by the high prevalence of antiretroviral medication errors in this setting.

Lastly it seems critical to bear in mind that chronic kidney disease has emerged in the past few years as one of the top five major cardiovascular risk factors, putting chronic kidney disease on the front scene as a major comorbidity impacting outcome and survival.

There is no need to be a nephrologist to appropriately screen for renal disease, monitor renal parameters, carefully adapt drug dosage when mandatory and thus allow preservation of renal function in HIV patients.

**ABSTRACT O-01**

*Antiviral Therapy* 2007; 12 Suppl 2:L4

Incidence of hypersensitivity reactions associated with nevirapine-containing HAART in patients with prior treatment experience may differ from that in treatment-naive patients: the ATHENA cohort study

**F Wit**, **A Kesselring**, **L Gras**, **C Richter**, **M van der Ende**, **K Brinkman**, **J Lange**, **F de Wolf** and **P Reiss**

1Center for Poverty-Related Communicable Diseases and Academic Medical Center, Department of Infectious Diseases, Tropical Medicine and AIDS, Amsterdam, Netherlands; 2HIV Monitoring Foundation, Amsterdam, Netherlands; 3Rijnstate ziekenhuis, Department of Internal Medicine, Arnhem, Netherlands; 4Erasmus Medical Center, Department of Internal Medicine, Rotterdam, Netherlands; 5Onze Lieve Vrouwe Gasthuis, Department of Internal Medicine, Amsterdam, Netherlands

**Background:** Current recommendations that nevirapine (NVP) should not be initiated in females with CD4 counts greater than 250/μl or in males with CD4 counts greater than 400/μl are based on findings in treatment-naive patients. The incidence rate is unknown for treatment-experienced patients with low pre-ART CD4 counts and current CD4 counts above the mentioned threshold, who switch to NVP-containing regimens. Whether current guidelines are applicable in such patients is unclear.

**Methods:** All patients in the ATHENA cohort who ever used NVP were included. We identified patients who discontinued NVP because of NVP-induced HSR within 18 weeks after first starting NVP. We grouped patients according to CD4 counts at the start of NVP-based HAART, being either high (>250/μl for females and >400/μl for males) or low. Treatment-experienced patients were also subdivided according to the last available pre-ART CD4 count using the same criteria: treatment-naive, low current CD4 (NL), treatment-naive, high current CD4 (NH); pretreated, low pre-ART CD4 and low current CD4 (PLL); pretreated, low pre-ART CD4 and high current CD4 (PLH); pretreated, high pre-ART CD4 and low current CD4 (PLL); pretreated, high pre-ART CD4 and high current CD4 (PHH). Risk factors for developing HSR were assessed using multivariate logistic regression.

**Results:** In patients that ever used NVP (n=3,752), HSR occurred in 231 (6.2%). We found no difference in HSR rate between the NL and PLL groups (5.2% versus 4.4%, P=0.44). Similarly, NH patients had a HSR rate comparable to the HSR rate in PHH patients (8.4% versus 10.8%, P=0.33). The HSR rate in the PLH group (6.2%) was higher than in the PLL group (4.4%, P=0.057), but lower when compared with the rate in the PHH group (10.8%, P=0.003). Using PLH as the reference group, the multivariate adjusted odds ratios (OR) for developing HSR were significantly lower for NL (OR 0.54; 95%CI 0.35–0.82) and PLL (OR 0.55; 95%CI 0.38–0.78). Other independent risk factors include female gender and Asian race. Having an undetectable viral load at the start of NVP use was also associated with reduced risk for developing HSR (OR 0.52; 95%CI 0.38–0.71). Using NL as the reference group, PLH patients with a detectable viral load at the start of NVP use had a significantly higher risk for HSR (OR 1.87; 95%CI 1.11–3.12), whereas PLH patients with undetectable viral load did not (OR 1.03; 95%CI 0.66–1.61).

**Conclusions:** Treatment-experienced patients with low pre-ART CD4 counts, high current CD4 counts and undetectable viral load have a similar risk for developing HSR when they switch to NVP compared with treatment-naive patients with low CD4 counts. This suggests that NVP may be safely initiated in such patients. However, in similar patients with a detectable viral load, it is prudent to continue adhering to current guidelines.
ABSTRACT O-02

*Antiviral Therapy* 2007; 12 Suppl 2:

Nevirapine increases high density lipoprotein-cholesterol by stimulation of apolipoprotein AI synthesis


1Academic Medical Center, Amsterdam, the Netherlands; 2IATEC bv, Amsterdam, the Netherlands; 3Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; 4Royal Free & University College Medical School, London, UK; 5Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, USA

**Objectives:** Combination therapy for HIV-1 infection including protease inhibitors (PI), but not non-nucleoside reverse transcriptase inhibitors (NNRTI) is associated with increased cardiovascular (CVD) risk. Whereas many PI are associated with atherogenic lipid changes, NNRTI exert more favourable changes, notably increases in HDLc. We therefore investigated the mechanism by which the NNRTI nevirapine (NVP) increases HDLc.

**Methods:** Thirteen HIV-1-infected patients with plasma HIV-1 RNA <50 copies/ml on AZT/3TC/abacavir for ≥ 6 months added NVP at usual dose for 24 weeks. Before (week 0), and 6 and 24 weeks later patients received a primed bolus infusion of stable isotope L-[1-13C]-valine for 12 h to study apolipoprotein A-I (apoAI) kinetics. Using SAAM-II modelling, absolute production rates (APR) and fractional catabolic rates (FCR) of apoAI were calculated. All HDLc-modulating enzymes were assessed.

**Results:** See Table 1. Other HDLc-modulating enzymes, including hepatic lipase, lecithin:cholesterol acyl transferase and phospholipid transfer protein remained unchanged.

**Conclusions:** NVP increased apoAI and HDLc by selectively promoting apoAI production without affecting HDL catabolism. This may contribute to why the increased CVD risk with PI-based therapy has not been found with treatment including NNRTI. Moreover, in view of the recent disappointing results of HDL increasing strategies with the CETP inhibitor torcetrapib targeting HDL degradation, our findings may lead to the identification of more promising novel targets for increasing HDLc

ABSTRACT O-03A

*Antiviral Therapy* 2007; 12 Suppl 2:

Effects of efavirenz on lipid metabolism in APOE*3*Leiden hCETP double-transgenic mice: evidence for antagonism of LXR pathway

**OP Flint**, **A Bellamine**, **MA Noor**, **JWA van der Hoorn**, **HMG Princen** and **RA Parker**

1Pharmaceutical Research and Development, Bristol-Myers Squibb Co, Princeton, NJ, USA; 2TNO Biosciences, Leiden, The Netherlands

**Introduction:** In HAART, efavirenz (EFV) has been associated with increases in plasma HDL-cholesterol (HDL-C). We observed that EFV does not directly inhibit the activity of the plasma cholesterol ester transfer protein (CETP), and proposed an alternative hypothesis that EFV down-regulates CETP expression through antagonism of the lipid transcription factor, LXR. We tested this hypothesis in vivo by administering EFV with a potent LXR agonist, T0901317, and measuring lipid metabolism and plasma CETP levels and activity in a transgenic mouse model APOE*3*Leiden hCETP.

**Methods:** Forty-two male APOE*3*Leiden hCETP transgenic mice were randomized and dosed orally once daily with vehicle, EFV (25, 50 or 75 mg/kg), T0901317 (10 mg/kg), or the combination of EFV (75 mg/kg) plus T0901317 (10 mg/kg) for 2 weeks. Total plasma cholesterol, HDL-c, triglycerides, plasma CETP protein and activity were determined.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Week 0*</th>
<th>Week 6†</th>
<th>Week 24†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDLc, mmol/l</td>
<td>1.1 (1.0–1.4)</td>
<td>4 (-5–12)</td>
<td>19 (8–31)</td>
</tr>
<tr>
<td>ApoA1, g/l</td>
<td>1.2 (1.1–1.4)</td>
<td>-4 (-19–11)</td>
<td>14 (5–23)</td>
</tr>
<tr>
<td>Large HDL particles, μmol/l</td>
<td>4.6 (2.2–5.0)</td>
<td>17 [-6–40]*</td>
<td>42 (28–110)*</td>
</tr>
<tr>
<td>CETP activity, %</td>
<td>84% (81–91)</td>
<td>10 (2–18)</td>
<td>14 (6–23)*</td>
</tr>
<tr>
<td>APR, mg/kg/day</td>
<td>721.6 (646.8–817.5)</td>
<td>-7 [-31–16]</td>
<td>17 (2–31)*</td>
</tr>
<tr>
<td>FCR, pools/day</td>
<td>0.18 (0.15–0.20)</td>
<td>-6 [-19–8)</td>
<td>2 [-9–13]</td>
</tr>
</tbody>
</table>

*Median (IQR); †Estimated mean (95%CI); ‡P<0.01; §0.01≤P<0.05; ¶ change from wk6 to wk24 0.01≤P<0.05

Table 1. (Abstract 0-02)
EFV abrogated T0901317 increase in total cholesterol (8.1–12.7 mM) and CETP protein (14.7–18.0 μg/ml) and activity (0.72–0.95 μmol/ml/h). EFV, T0901317 or their combination decreased HDL-C (-55%, -43% and -68%, respectively). Plasma triglycerides were increased with T0901317 (47-fold), but not with EFV alone or in combination. (P<0.05 for the reported data).

**Conclusion:** In this double transgenic mouse model, EFV prevented the marked up-regulation of plasma CETP levels induced by a potent LXR agonist. EFV also blocked some of the increases in plasma lipids observed with the LXR agonist. The demonstration of in vivo functional antagonism by EFV of a major LXR response gene, CETP, which is known to regulate human lipoprotein CE/TG exchange and affect HDL-C levels, suggests a potential molecular mechanism for the influence of EFV on human lipid profiles.

**ABSTRACT O-03B**

*Antiviral Therapy 2007; 12 Suppl 2:i6*

**Molecular mechanism for efavirenz effects on lipid metabolism**

**O Flint, A Bellamine, M Noor and R Parker**

Research and Development, Bristol-Myers Squibb Co, Princeton, NJ, USA

**Background:** Efavirenz (EFV) therapy is associated with elevated HDL-cholesterol (HDL-C). Cholesterol ester transfer protein (CETP) is secreted from liver and adipose tissue and regulates HDL levels by mediating cholesterol ester exchange among lipoproteins. EFV is not a direct inhibitor of CETP activity, but decreases expression of some lipogenic genes in vitro. We identified CETP as an additional EFV-suppressed gene, and proposed that decreased liver X receptor (LXR) activity could explain the gene regulation pattern.

**Methods:** LXR activity was measured by cell-based LXR-Gal4/luciferase and SRE-promoter-Luc reporter transactivation in HEK293 or hepatoma lines with T-0901317 or 24,25-epoxycholesterol (synthetic and natural LXR agonists), and a ligand-binding assay using recombinant LXR-α and -β. Lipid synthesis was assayed in HepG2 and 3T3-L1 cells along with mRNA for CETP and other LXR target genes by RT-PCR.

**Results:** In hepatoma and 3T3-L1 cells, EFV (1–10 μM, 6–48 h) reduced mRNA for the LXR target genes CETP (60%), SREBP1c (90%), and FAS (50% at 10 μM) at 10 μM, but not LXR itself. LXR agonist-induced lipid synthesis and gene expression in HepG2 cells were blocked by EFV (1–10 μM) with effects dependent on agonist concentration. In transactivation assays, EFV (EC50 ~7 μM) antagonized effects of the synthetic and natural agonists, and in binding assays, EFV directly displaced 3H-24,25-epoxycolesterol from purified LXR-α and -β (EC50 ~11 μM).

**Conclusions:** At levels approaching its Cmax, EFV antagonizes LXR transcriptional activity in cells and displaces binding of natural and synthetic LXR agonists in vitro. These effects provide a possible mechanism for EFV suppression of lipogenic gene expression including the important LXR target gene CETP in liver and adipose cell lines. These findings support a hypothesis for EFV-mediated elevation of HDL-C through LXR antagonism and reduction in CETP expression and activity.

**ABSTRACT O-04**

*Antiviral Therapy 2007; 12 Suppl 2:i6*

**Dyslipidaemia in vertically infected children and youth on protease inhibitor (PI)-containing antiretroviral therapy (ART): preliminary results of PACTG 1045**

**GM Aldrovandi1, JC Lindsey2, D Jacobson3, B Heckman3, A Zadzilka3, E Sheeran4, J Moye5, P Borum6, WA Meyer III7, D Hardin8, E DeCarlo9 and K Mulligan10**

1Children’s Hospital of Los Angeles, Los Angeles, CA, USA; 2Harvard School of Public Health, Boston, MA, USA; 3Frontier Science and Technology Research Foundation, Amherst, NY, USA; 4Social and Scientific Systems, Inc., Silver Spring, MD, USA; 5National Institute of Child Health and Human Development, NIH, Bethesda, MD, USA; 6University of Florida, Gainesville, FL, USA; 7Quest Diagnostics, Inc., Baltimore, MD, USA; 8The Ohio State University, Columbus, OH, USA; 9National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA; 10University of California San Francisco, San Francisco, CA, USA

**Aim:** To determine the prevalence of lipid and glucose abnormalities and their association with ART among vertically infected youth.

**Methods:** HIV+ subjects, 7–24 (median 12) years, stratified by sex, race/ethnicity and Tanner stage, were randomly selected at 37 sites and enrolled in groups on PI±12 months (PI; n=161 [90M/71F]) or non-PI containing ART (NoPI; n=79 [37M/42F]). Matching seronegative controls (HIVneg; n=146 [84M/62F]) were recruited in the same clinics. Measurements included fasting lipids, insulin and glucose, a 2-h oral glucose tolerance test, fat distribution by DXA and ART and medical histories. Medians were compared with HIVneg by Wilcoxon rank sum tests.

**Results:** The PI group tended to have longer total exposure to ART (10.0 versus 9.0 years; P=0.055 versus NoPI). There were no differences in current CD4 and HIV RNA, but subjects on PI had lower nadir CD4 and higher peak HIV RNA (P<0.001 versus NoPI). Lopinavir/r and nelfinavir were the most commonly used PIs at the time of study. Both HIV+ groups had lower z-scores for height and weight, as well as total, trunk and limb fat, compared
with HIVneg. Triglycerides (TG) were significantly higher in both HIV+ groups. The PI group, but not NoPI, had higher total, LDL and non-HDL cholesterol and lower HDL cholesterol than HIVneg. A greater proportion of subjects on PI had abnormal values for each lipid parameter. Fasting insulin and HOMA-IR were higher in both HIV+ groups (insulin 10.0, 10.5 and 7.0 mIU/ml in PI, NoPI, and HIVneg, and P<0.025 for both groups versus HIVneg; HOMA-IR 2.0, 2.3 and 1.5, respectively, P=0.049 and 0.019 versus HIVneg). Fewer than 5% of subjects in any group had abnormal 2 h glucose.

Conclusion: In this large study of randomly selected youth, there was a high prevalence of lipid abnormalities among those on PI. Insulin and HOMA-IR were higher in both PI and NoPI, but the prevalence of glucose intolerance was relatively low. Dyslipidemia and insulin resistance may accelerate lifetime risk of cardiovascular disease in vertically infected youth with extensive exposure to ART.

ABSTRACT O-05

Antiviral Therapy 2007; 12 Suppl 2:L7

Design and outcomes of an antiretroviral pharmacovigilance programme in South Africa

U Mehta1,2, DN Durrheim3, K Cohen1, M Osler1, T Kredo1, A Boulle3 and G Maartens4

1Division of Clinical Pharmacology, University of Cape Town, South Africa; 2Hunter New England Population Health, Australia; 3School of Public Health, University of Cape Town, South Africa

Background: Access to antiretroviral (ARV) therapy is expanding on a large scale in Africa. The safety profile of these agents in routine public health programmes needs to be established. We report on the initial findings of a pharmacovigilance reporting system for antiretrovirals (ARVs).

Method: A passive stimulated reporting system of serious suspected adverse drug reactions (ADRs) was introduced at HIV/AIDS treatment facilities in the Western Cape province of South Africa using a specifically designed ADR form, which included simple case definitions of target events and a monthly zero reporting form. The system aimed to identify signals of new (ADRs) and potential risk factors contributing to serious ADRs. The performance of this system is reviewed 2 years after its initiation.

Results: During the 24-month study period (15 March 2005 to 15 March 2007), 611 reports were received where the contribution of drug therapy could not be excluded, 18 (3%) in paediatric patients and 585 (96%) in adults (>16 years). Two signals of possible new ADRs associated with efavirenz: haemolytic anaemia and cerebellar ataxia. One report of a congenital anomaly and two reports of spontaneous abortions in the first trimester were reported with efavirenz exposure. Lactic acidosis or symptomatic hyperlactataemia (LASH) were the most frequently reported events (n=298, 49%) with all but three in patients taking stavudine-based regimens. LASH ADRs tended to be reported more frequently in women compared to non-LASH ADRs (238/293 [81%] versus 209/292 [72%], P=0.031), and in patients with a higher body mass (≤60 kg: 53/153 [35%]; 61–75 kg: 132/241 [55%]; >75 kg: 82/132 [62%], P<0.001). Cases of LASH were also reported in patients on the stavudine 30 mg twice daily dose. The median time to detection of LASH ADRs was 336 days (IQR 267–436.5). Peripheral neuropathy was more commonly reported in older patients (median of 39 years [IQR 33–45] versus 35 years [IQR 30–41], P<0.001) and lipodystrophic changes were more commonly reported in women (63/447 [14%] versus 4/134 [3%], P=0.001).

Conclusion: This passive stimulated ADR reporting system has been useful in detecting signals, and guiding clinical care and drug policy in the province and nationally.

ABSTRACT O-06

Antiviral Therapy 2007; 12 Suppl 2:L7

Metabolic changes in a Thai treatment-naive population starting double-boosted protease inhibitor therapy

J van der Lugt1,2, K Ruxrungtham1,3, S Autar1,2, S Ubolyam1, J Lange1,2,4, D Cooper5, P Phanuphak1,3, D Burger6, F Wit3,4 and P Reiss2,4

1HIV Netherlands Australia Thailand (HIV-NAT) Research Collaboration, Thai Red Cross AIDS Research Center Bangkok; 2International Antiretroviral Therapy Evaluation Center, Amsterdam, The Netherlands; 3Department of Medicine, Faculty of Medicine, Chulalongkorn University, Thailand; 4Department of Internal medicine, Academic Medical Center, University of Amsterdam, The Netherlands; 5National Center in HIV Epidemiology and Clinical Research, University of New South Wales; 6Radboud University Medical Center, Nijmegen, The Netherlands

Table 1. (Abstract O-04)

<table>
<thead>
<tr>
<th></th>
<th>PI</th>
<th>No PI</th>
<th>HIVneg</th>
<th>P-value versus HIVneg</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG, mg/dl</td>
<td>134</td>
<td>82</td>
<td>67</td>
<td>&lt;0.001 0.004</td>
</tr>
<tr>
<td>% ≥150</td>
<td>45</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total chol, mg/dl</td>
<td>174</td>
<td>153</td>
<td>153</td>
<td>&lt;0.001 0.479</td>
</tr>
<tr>
<td>% ≥200</td>
<td>29</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>99</td>
<td>89</td>
<td>89</td>
<td>0.002 0.323</td>
</tr>
<tr>
<td>% ≥130</td>
<td>19</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>44</td>
<td>46</td>
<td>49</td>
<td>&lt;0.001 0.112</td>
</tr>
<tr>
<td>% &lt;40 M/50F</td>
<td>46</td>
<td>38</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Non HDL-C, mg/dl</td>
<td>130</td>
<td>109</td>
<td>105</td>
<td>&lt;0.001 0.952</td>
</tr>
<tr>
<td>% ≥160</td>
<td>24</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Objective: To assess changes in body fat distribution, lipid and glucose metabolism, after initiation of therapy with ritonavir-boosted lopinavir (LPV/r) plus (hard gel) saquinavir (SQV) in treatment-naive patients.

Methods: Forty-eight treatment-naive patients were randomized to LPV/r 400/100 mg + SQV 1,000 mg twice daily (bid) (Group A), LPV/r 400/100 mg + SQV 600 mg bid (Group B), LPV/r 266/66 mg + SQV 1,000 mg bid (Group C) or LPV/r 266/66 mg + SQV 600 mg bid (Group D) and followed for 24 weeks. Fasting high-density lipoprotein (HDL), directly measured low-density lipoprotein (LDL-c), total cholesterol (TC), triglycerides (TG), insulin and glucose levels were measured at week 0, 4, 12 and 24. DEXA and abdominal CT at L4 were done at week 0, 12 and 24. Data were analysed using repeated-measures linear regression.

Results: Six patients were excluded from the DEXA/CT analysis because they had no scans performed. Another patient was lost to follow up after 1 week. Baseline values did not differ significantly among groups. HIV RNA and CD4 change at week 24 did not differ significant by ITT analysis. TC, HDL-c, LDL-c and TG, but not glucose and insulin, increased significantly in all arms. Increases in TC, HDL-c and LDL-c, but not TG, were significantly greater in group A than in groups C and D. Body weight, and trunk, total limb, and intra-abdominal fat increased significantly in group A only. Changes were less marked in the other groups.

Conclusion: Therapy-naive patients treated with LPV/r + SQV only, at least in the first 6 months, did not show evidence of limb fat loss, but rather overall fat gain in both peripheral and central compartments and dyslipidaemia, particularly in the highest dose group. The latter suggests that metabolic and body composition changes on this PI combination may be exposure-related.

Table 1. (Abstract O-06)

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>Slope</th>
<th>P-value</th>
<th>P-value A versus rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>166</td>
<td>+57</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>157</td>
<td>+45</td>
<td>&lt;0.0001</td>
<td>0.35</td>
</tr>
<tr>
<td>C</td>
<td>166</td>
<td>+21</td>
<td>0.032</td>
<td>0.0041</td>
</tr>
<tr>
<td>D</td>
<td>196</td>
<td>+34</td>
<td>0.0001</td>
<td>0.052</td>
</tr>
<tr>
<td>LDL-c, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>88</td>
<td>+30</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>82</td>
<td>+24</td>
<td>0.0002</td>
<td>0.46</td>
</tr>
<tr>
<td>C</td>
<td>91</td>
<td>+10</td>
<td>0.11</td>
<td>0.015</td>
</tr>
<tr>
<td>D</td>
<td>112</td>
<td>+16</td>
<td>0.007</td>
<td>0.054</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>56</td>
<td>+6.0</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>53</td>
<td>+0.0</td>
<td>0.97</td>
<td>0.0018</td>
</tr>
<tr>
<td>C</td>
<td>58</td>
<td>+0.0</td>
<td>0.96</td>
<td>0.0025</td>
</tr>
<tr>
<td>D</td>
<td>56</td>
<td>-0.4</td>
<td>0.80</td>
<td>0.0008</td>
</tr>
<tr>
<td>Limb fat, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>6.9</td>
<td>+0.59</td>
<td>0.0038</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>6.0</td>
<td>+0.38</td>
<td>0.078</td>
<td>0.44</td>
</tr>
<tr>
<td>C</td>
<td>7.5</td>
<td>+0.42</td>
<td>0.063</td>
<td>0.54</td>
</tr>
<tr>
<td>D</td>
<td>6.6</td>
<td>+0.38</td>
<td>0.062</td>
<td>0.42</td>
</tr>
<tr>
<td>HDL-c, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>46</td>
<td>+15</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>52</td>
<td>+7</td>
<td>0.014</td>
<td>0.040</td>
</tr>
<tr>
<td>C</td>
<td>52</td>
<td>+6</td>
<td>0.046</td>
<td>0.014</td>
</tr>
<tr>
<td>D</td>
<td>53</td>
<td>+6</td>
<td>0.017</td>
<td>0.011</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>124</td>
<td>+100</td>
<td>0.0003</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>104</td>
<td>+81</td>
<td>0.0085</td>
<td>0.63</td>
</tr>
<tr>
<td>C</td>
<td>108</td>
<td>+75</td>
<td>0.014</td>
<td>0.53</td>
</tr>
<tr>
<td>D</td>
<td>113</td>
<td>+75</td>
<td>0.0055</td>
<td>0.49</td>
</tr>
<tr>
<td>Trunk fat, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>6.2</td>
<td>+0.72</td>
<td>0.0024</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>4.8</td>
<td>+0.20</td>
<td>0.40</td>
<td>0.10</td>
</tr>
<tr>
<td>C</td>
<td>5.4</td>
<td>+0.38</td>
<td>0.14</td>
<td>0.29</td>
</tr>
<tr>
<td>D</td>
<td>5.4</td>
<td>-0.07</td>
<td>0.74</td>
<td>0.0098</td>
</tr>
<tr>
<td>Abdominal fat, cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>54</td>
<td>+7.6</td>
<td>0.023</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>33</td>
<td>+3.6</td>
<td>0.31</td>
<td>0.40</td>
</tr>
<tr>
<td>C</td>
<td>33</td>
<td>-3.9</td>
<td>0.28</td>
<td>0.015</td>
</tr>
<tr>
<td>D</td>
<td>40</td>
<td>-3.4</td>
<td>0.35</td>
<td>0.020</td>
</tr>
</tbody>
</table>

BL, baseline value; slope, change from baseline at week 24; P-value A versus rest, comparison of slope from group A with each of the other groups.

ABSTRACT O-07

Antiviral Therapy 2007; 12 Suppl 2:18

Effects of tipranavir/r (500/200 or 500/100 mg BID) in comparison with lopinavir/r (400/100 mg BID) on changes in body composition and metabolic parameters in ARV-naive patients over 48 weeks

A Carr1, R Zajdenverg2, C Workman3, J Gatell4, P Cahn5, A Ritzhaupt6, W Zhang7 and R Chaves6

1St Vincent’s Hospital, Sydney, Australia; 2Projeto Praça Onze – UFRJ Hospital Escola São Francisco de Assis, Rio de Janeiro, Brazil; 3AIDS Research Initiative, Darlinghurst, Australia; 4Hospital Clinic de Barcelona, Barcelona, Spain; 5Fundacion Huesped, Buenos Aires, Argentina; 6Boehringer Ingelheim GmbH, Biberach an der Riss, Germany; 7Boehringer Pharmaceuticals Inc. Ridgefield, CT, USA

Objectives: Protease inhibitor (PI)-based antiretroviral therapy is associated with progressive lipoatrophy, relative central fat accumulation and insulin resistance.

Methods: We evaluated changes in body composition and metabolism in 140 ARV-naive patients randomized to tenofovir-lamivudine with tipranavir/ritonavir (500/200 [TPV/r200] or 500/100 mg [TPV/r100] twice daily) or lopinavir/ritonavir (400/100 mg [LPV/r] twice daily) in a metabolic sub study. Body composition (DEXA for total and regional fat; L4–5 abdominal CT for subcutaneous
and visceral adipose tissue (SAT; VAT) and fasting metabolic parameters (including lipids, glucose, insulin, adiponectin and leptin) were assessed at baseline and week 48. The primary analysis was the change in limb fat in TPV/r100 versus LPV/r and TPV/r200 versus LPV/r (Wilcoxon rank-sum test \( P=0.025 \) two-sided).

**Results:** Baseline mean limb fat mass was higher in both TPV/r groups versus LPV/r, although medians were comparable (Kruskal–Wallis test, \( P=0.907 \)). At week 48, limb fat increased by 1.17 kg with LPV/r as compared with 0.83 kg with TPV/r200 (\( P=0.163 \)) and 0.41 kg with TPV/r100 (\( P=0.072 \)). VAT decreased in all groups: -3 cm\(^2\) with LPV/r as compared with -9 cm\(^2\) with TPV/r200 (\( P=0.036 \)) and -6 cm\(^2\) with TPV/r100 (\( P=0.402 \)). No significant between-group change in glucose sensitivity was observed as measured by fasting glucose, insulin or HOMA-IR. Of interest, plasma adiponectin levels increased, but significantly less with LPV/r (+1,360 ng/ml; \( P<0.0001 \)) than with TPV/r200 (6,010 ng/ml; \( P<0.0001 \)) or TPV/r100 (+4,497 ng/ml; \( P=0.002 \)). In contrast, there was much less change in plasma leptin levels.

**Conclusions:** After 48 weeks, subcutaneous fat increased with both TPV/r and LPV/r. TPV/r treatment was not associated with increased insulin resistance or increased VAT, in contrast to previous studies with other PIs.

**ABSTRACT O-08**

*Antiviral Therapy* 2007; 12 Suppl 2:±9

Further data on the effects of tesamorelin (TH9507), a growth hormone-releasing factor analogue, on body composition and metabolic parameters in HIV-infected patients with abdominal fat accumulation

J Falutz\(^1\), S Allas\(^2\), J-C Mamputu\(^2\), D Potvin\(^2\), D Kotler\(^3\) and S Grinspoon\(^4\)

\(^1\)Montreal General Hospital, McGill University Health Center, Montreal, Canada; \(^2\)Theratechnologies, Inc. Montreal, Canada; \(^3\)St. Lukes Hospital Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, Canada; \(^4\)Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

**Background:** We previously reported that 26-week treatment with tesamorelin resulted in significant decreases in visceral adipose tissue (VAT) and improvements in lipids. Here we report further data, which have not previously been presented, on the time course for changes in VAT and metabolic parameters, and the relationship of baseline VAT and change in IGF-I to change in VAT with tesamorelin.

**Methods:** Patients on ART with abdominal fat accumulation were randomized to tesamorelin 2 mg (\( n=273 \)) or placebo (\( n=137 \)) subcutaneously daily for 26 weeks. The percent change from baseline in VAT was the primary end-point. Secondary endpoints included changes in triglycerides, TC/HDL-C ratio and IGF-I.

**Results:** Baseline age was 48±7 (SD) years, WC 104±10 cm, WHR 1.1±0.1 with no differences between treatment groups. Most of the VAT loss occurred within the first 13 weeks: -12.1% (\( P<0.001 \) versus placebo), with further loss by Week 26 (-5.2%, \( P<0.001 \) versus placebo, \( P<0.001 \) for time effect within the tesamorelin group). IGF-I increased from baseline at Week 13 (82%, \( P<0.001 \) versus placebo), with no further changes at Week 26 (81%, \( P<0.001 \) versus placebo). Adiponectin increased significantly at Week 26 (0.5±2.7 versus -0.1±1.3 μg/ml; \( P=0.03 \) versus placebo). In addition, there were significant but small correlations between changes from baseline in IGF-I and VAT at Weeks 13 (\( r=-0.29 \), \( P<0.001 \)) and 26 (\( r=-0.23 \), \( P<0.001 \)) in tesamorelin-treated patients. Finally, the change in VAT was greater among patients with larger VAT at baseline (Week 26: -35 cm\(^2\) for 75th, -25.8 cm\(^2\) for 50th and -17.6 cm\(^2\) for 25th percentile, \( P<0.001 \) versus placebo at all points).

**Conclusion:** These data provide more information as to the effects of tesamorelin on VAT and related metabolic parameters in HIV-infected patients with central fat accumulation. Significant changes in VAT were mainly achieved within the first 13 weeks of treatment, with further benefits over the following 13 weeks. These changes were observed in association with changes in IGF-I. The absolute reduction in VAT was related to the magnitude of VAT accumulation at baseline. Increased adiponectin may help improve metabolic parameters with use of tesamorelin.
ABSTRACT O-09

Antiviral Therapy 2007; 12 Suppl 2:1-10

Does diabetes mellitus (DM) confer an equivalent risk of coronary heart disease (CHD) to pre-existing CHD in HIV-positive individuals?

SW Worm1, S De Wit2, R Weber3, CA Sabin4, P Reiss5, W El-Sadr6, A D’Arminio Monforte1, O Kirk7, E Fontas8, F Dabis9, MG Law11, JD Lundgren1 and N Friis-Møller1 on behalf of the D:A:D study group

1Copenhagen HIV Programme (CHIP), Hvidovre University Hospital, Copenhagen, Denmark; 2Saint-Pierre Cohort, CHU Saint-Pierre Hospital, Brussels, Belgium; 3SHCS, Division of Infectious Diseases and Hospital Epidemiology, Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland; 4Royal Free Centre for HIV Medicine and Department of Primary Care and Population Sciences, Royal Free and University College, London, UK; 5ATHENA, HIV Monitoring Foundation, Academic Medical Center, Amsterdam, The Netherlands; 6CPCPR Columbia University/Harlem Hospital, New York, NY, USA; 7ICONA, L Sacco Hospital, University of Milan, Milan, Italy; 8EuroSIDA, CHIP, Hvidovre University Hospital, Copenhagen, Denmark; 9Nice Cohort, CHU Nice Hospital de l’Archet, Nice, France; 10INSERM E0338 & U593, ISPED, Université Victor Segalen Bordeaux 2, Bordeaux, France; 11AHOD, National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia

Background: NCEP guidelines operate with a concept of ‘CHD risk equivalent’ a disease state conferring similar risk of CHD as pre-existing CHD. In HIV, risk factors for diabetes mellitus (DM) may differ from those in the background population (e.g. ART-induced). It is unknown if DM should be considered a CHD risk equivalent in HIV.

Methods: The incidence of a composite CHD outcome (myocardial infarction, angioplasty, bypass or fatal cardiovascular event) was calculated according to the presence (+) or absence (-) of prior CHD and +/- DM at D:A:D baseline. Multivariable Poisson analyses compared the risk of CHD in these four groups after adjustment for gender, age, cohort, HIV transmission, ethnicity, family history of CHD, smoking and calendar year. Sensitivity analysis assessed the risk of CHD according to duration of DM: no DM, DM during follow-up of <2 years, DM during follow-up of ≥2 years and DM before baseline.

Results: The incidence rate for CHD per 100 PY in persons with -DM and -CHD, +DM and -CHD, +CHD and -DM, and +DM and +CHD were 0.32 (95% CI 0.29–0.35), 1.40 (1.02–1.71), 7.73 (6.03–9.42), and 8.48 (5.11–13.25), respectively. Using a prior CHD (+CHD, -DM) as a reference group, the relative rate (RR) of CHD associated with DM (+DM, -CHD) was 0.30 (Table 1). There was a trend towards increasing risk of CHD with longer duration of DM (Table 2).

Discussion: A history of CHD is a far stronger predictor of CHD than a diagnosis of DM in HIV. Prior CHD was a strong predictor of recurrence of CHD, regardless of whether the patient also had DM or not. Conversely, in patients without prior CHD, DM was an important risk factor for CHD, but not a CHD risk equivalent. A higher risk of CHD was observed with longer time since diagnosis of DM. Intensity of preventive interventions should be guided by estimates of absolute CHD risk from the Framingham equation or the D:A:D risk equation currently under development.

ABSTRACT O-10

Antiviral Therapy 2007; 12 Suppl 2:1-10

The rate at which therapy-naive patients develop metabolic syndrome when treated and its association with different components of antiretroviral therapy: the Swiss HIV Cohort Study

J Young1, T Glass1, R Weber2, E Bernasconi3, M Rickenbach4, HJ Furrer5, M Cavassini6, P Vernazza6, B Hirschel7, M Battegay1 and HC Bucher1

1University Hospital Basel, Switzerland; 2University Hospital Zurich, Switzerland; 3Regional Hospital Lugano, Switzerland; 4University Hospital Lausanne, Switzerland; 5University Hospital Bern, Switzerland; 6University Hospital St Gallen, Switzerland; 7University Hospital Geneva, Switzerland

Objectives: To estimate associations between components of antiretroviral therapy and the rate at which therapy-naive patients develop metabolic syndrome (MS) when treated.

Methods: In April 2000, a cardiovascular risk assessment became part of each biannual cohort visit. We consider progression to MS (under the 2005 International Diabetes Federation definition) using discrete time survival analy-
sis. Our model is hierarchical with 16 drug components and four drug classes as first and second levels, respectively, and it allows for residual effects not otherwise included in the model. Our model adjusts for age, sex, transmission by drug use; for BMI, CD4 count and viral load when starting therapy; for smoking status at each visit; and for variation in the time between visits.

**Results:** As of 31 December 2006, 1,218 patients with multiple visits and without MS at their first visit were followed for a median of 27 months; 242 (20%) developed MS at a rate of 7.5 cases per 100 patient years. Five-hundred and twenty-one patients (43%) used only PI-based therapy, 465 (38%) used only NNRTI-based therapy, and 232 (19%) used both. Among NRTIs, progression to MS appears relatively unlikely with the use of didanosine [odds ratio] 0.82, [95% CI] 0.64–1.05 [per 6 months use] and relatively likely with the use of stavudine (1.07, 0.88–1.31). Among PIs, MS appears relatively unlikely with the use of atazanavir, either as a single PI (0.37, 0.18–0.78) or boosted with ritonavir (0.76, 0.48–1.21), and relatively likely with the use of indinavir boosted with ritonavir (1.17, 0.83–1.65). MS appears relatively unlikely with both NNRTIs (efavirenz 0.90, 0.74–1.10; nevirapine 0.82, 0.62–1.10). These estimates from a hierarchical model are less exaggerated than estimates from a conventional model.

**Conclusions:** Each drug class has specific drugs that seem relatively unlikely to lead to MS.

### ABSTRACT O-11

*Antiviral Therapy 2007; 12 Suppl 2:L11*

**Effect of alternate treatment protocols on the incidence of electrocardiographic abnormalities among HIV-infected adults in the SMART trial**

**R Prineas**, **M Roediger**, **A Carr**, **W El-Sadr**, **S Esser**, **G Grandits**, **B Knysz** and **A Palfreeman**

*for the SMART Study Group and INSIGHT*

1University of Wake Forest School of Medicine, Division of Public Health Sciences, Winston-Salem, USA; 2University of Minnesota School of Public Health, Biostatistics, Minneapolis, USA; 3St Vincents Hospital, Sydney, Australia; 4Columbia University, New York, USA; 5Universitklinikum Essen, Essen, Germany; 6University of Minnesota, Biostatistics, Minneapolis, USA; 7Wroclaw University, Infectious Diseases, Wroclaw, Poland; 8Edith Cavell Hospital, Sexual Health, Peterborough, UK

**Objectives:** The SMART trial compared strategies of continuous antiretroviral therapy (ART) (viral suppression arm; VS) and CD4-guided ART (drug conservation arm; DC). On January 11, 2006 the trial was stopped due to increased risk of progression of HIV disease, death, and cardiovascular disease (CVD), in the DC arm. We compared the effects of VS and DC on incidence of electrocardiogram (ECG) abnormalities.

**Methods:** Twelve-lead ECGs, recorded at baseline and annually, were transmitted electronically and centrally analysed blinded to treatment. Incidence of Q wave abnormalities during mean follow-up of 16 months and one-year changes in measures of cardiac function were compared between study arms for participants who had a baseline and a follow-up ECG. Cox models estimated hazard ratios (HRs) (DC/VS) adjusted for demographics, clinical history, HIV-related parameters and ART status at baseline. Changes between treatment groups for heart rate and spatial QRS/T angle (a global measure of repolarization) were compared using ANOVA and adjusted for age, race and sex.

**Results:** One-thousand one-hundred and twenty-three participants (41%) in the DC and 1,078 (39%) in the VS arm had a baseline and at least one follow-up ECG. The DC arm had a higher incidence of Q wave abnormalities (signifying myocardial damage) compared with the VS arm: HR 1.48, 95%CI 1.06–2.07. There was also an increase in resting heart rate, and in the QRS/T spatial angle (each of which indicates increased risk of future CVD mortality) in the DC arm.

**Conclusions:** Intermittent, CD4-guided ART was associated with evidence of myocardial damage, increasing repolarization abnormality, and increase in heart rate — consistent with the outcome in the main trial results of excess CVD outcomes in the DC arm.

### ABSTRACT O-12

*Antiviral Therapy 2007; 12 Suppl 2:L11*

**Subclinical coronary atherosclerosis, HIV-infection and antiretroviral therapy: results from the multicentre AIDS cohort study**


1University of Pittsburgh, Pittsburgh PA, USA; 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; 3Northwestern University, Chicago IL, USA; 4Harbor-UCLA Medical Center, Torrance, CA, USA; 5Johns Hopkins School of Medicine, Baltimore, MD USA; 6University of California, David Geffen School of Medicine and the Los Angeles Biomedical Research Institute at Harbor-UCLA, Los Angeles, CA, USA

**Objectives:** Highly active antiretroviral therapy (HAART) use has raised clinical concern about atherogenic lipid and metabolic changes that could increase risk for coronary atherosclerosis in HIV-infected persons. We examined the effect of HIV itself and cumulative HAART exposure on the presence and extent of coronary artery calcification (CAC).

**Methods:** A cross-sectional study of 947 men (332 HIV-seronegative, 84 HAART-naive and HIV-infected, and 531 HAART-experienced and HIV-infected). Eligibility criteria included informed consent, age ≥20, no self-
Macrophage recruitment in adipose tissue from HIV-infected patients under ART: concomitant presence of classically activated pro-inflammatory M1 and alternatively activated M2 macrophages

V Arendt-Fenoel¹, M Kim², B Antuna³, A Borjabad¹, U Hazan¹, E Lanoy³, D Costagliola¹, P Leclercq¹, JP Bastard² and J Capeau²

¹Faculty of Medicine Cochin Université Paris-5, Paris, France; ²Inserm U680, Université Paris-6, AP-HP Hospital Tenon, Paris, France; ³Inserm U720, Université Paris-6, Paris, France; ⁴CHU Grenoble, Grenoble, France

Objectives: Invading macrophages are present in lipoatrophic patients' adipose tissue. Macrophage activation can lead to two separate states: M1, or classically activated macrophages, with enhanced pro-inflammatory cytokine production; and M2, or alternatively activated macrophages, generating high levels of anti-inflammatory cytokines. We evaluated 1) the phenotype of the macrophages present in lipoatrophic adipose tissue and 2) the evolution of this phenotype in fat tissue from patients stopping any ART for 6 months.

Methods: Affymetrix microarray assays were performed in subcutaneous fat samples from six non-obese controls and five HIV-infected patients under PI and stavudine. Expression of genes specific for adipocytes, M1 and M2 macrophages was compared. The results were validated by quantitative RT-PCR (QRT-PCR) in, respectively, 12 and 7 other controls and patients. The expression of some M1 and M2 macrophage-specific markers was also evaluated by QRT-PCR in 20 paired biopsies from HIV-infected patients obtained before stopping ART and 6 months after.

Results: Affymetrix microarray analysis indicates that expression of the reference gene TBP was equivalent in controls and patients while that of the adipocyte marker perilipin decreased twofold, in agreement with the strong decrease in the adipocyte proportion in patients' fat tissue. A strong increase in M1 marker expression was observed in patients' samples as compared with controls: CD68 (×4.9), CD14 (×9.4), CCL2 (×3.4). Similarly, a strong increase in the expression of M2 markers was present: CD163 (×2.9), chitinase (×98.3) and CH3L1 (×28.2). The microarray results were verified by QRT-PCR for CD14 and chitinase and confirmed the highly significant increase of M1 and M2 markers in patients' fat. We then evaluated whether a 6-month ART-interruption modified the expression of M1 and M2 markers. CD68 expression was decreased in patients stopping stavudine or zidovudine and expression of CD14 decreased in patients stopping PI; expression of the M2 markers CD163 and chitinase remained unmodified.

Conclusion: In HIV-infected patients under ART, pro-inflammatory M1 and anti-inflammatory M2 macrophages are concomitantly present in lipodystrophic adipose tissue. Stopping ART allows a specific reduction in pro-inflammatory macrophages.

ABSTRACT O-14

Antiviral Therapy 2007; 12 Suppl 2:i12

The effect of antiretroviral therapy on genes involved with glucose and lipid metabolism

M Boothby¹, JW Tomlinson², KC McGee³, S Das⁴, LL Gathercole², AL Harte², P Higgins³, CM Kusminski¹, PG McTernan³ and M Shahmanesh¹

¹University Hospital Birmingham, Birmingham, UK; ²University of Birmingham, Birmingham, UK; ³Warwick University, Warwick, UK; ⁴University Hospitals Coventry and Warwickshire, Coventry, UK

Objectives: To compare patterns of gene expression in the subcutaneous adipose tissue of HIV-positive subjects before and after 6 months of antiretroviral therapy with HIV-negative controls.

Methods: Subcutaneous fat biopsies from the iliac crest were performed on 18 HIV-positive patients and 10 HIV-negative controls. Following total RNA extraction, gene
expression was profiled using real-time PCR and quantified relative to an internal house-keeping gene (18S). Genes were involved in adipocyte differentiation, lipid metabolism, and glucocorticoid metabolism. HIV-positive patients were tested before, and 6 months after being randomized to either zidovudine/lamivudine or tenofovir/emtricitabine with efavirenz. Comparison between groups was by $t$-tests and Mann–Whitney test.

**Results:** Controls and patients were matched for sex and ethnicity. There were no differences in BMI, whole body DEXA and abdominal CT scans. $\beta$-Hydroxysteroid dehydrogenase type 1 ($\beta$-HSD1), which regenerates active glucocorticoid cortisol from inactive cortisone, is reduced in treatment-naive patients compared with controls but increases following treatment. ARV treatment increased mRNA expression of adipocyte differentiation markers and genes involved with glucose and lipid metabolism, including lipoprotein lipase (LPL) hormone-sensitive lipase (HSL), fatty acid binding protein 4 (FABP4), fatty acid synthase (FAS), glucocorticoid receptor-α (GR-α), and glucose transport protein (GLUT4). HOMA levels were similar between groups.

**Conclusion:** $\beta$-HSD1 mRNA expression is decreased in HIV patients, but increases after ARV treatment alongside markers of adipocyte differentiation, lipid and glucose metabolism. We speculate that enhanced local generation of cortisol through increased $\beta$-HSD1 expression may underpin these observations.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Naive HIV</th>
<th>6 months</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$ HSD1</td>
<td>0.38</td>
<td>1.06</td>
<td>0.006*, 0.001†</td>
</tr>
<tr>
<td>HiP3DH</td>
<td>0.64</td>
<td>1.41</td>
<td>NS</td>
</tr>
<tr>
<td>FAS</td>
<td>0.85</td>
<td>5.3</td>
<td>0.0004*</td>
</tr>
<tr>
<td>LPL</td>
<td>0.92</td>
<td>2.69</td>
<td>0.0002*</td>
</tr>
<tr>
<td>HSL</td>
<td>1.22</td>
<td>4.94</td>
<td>0.0005†</td>
</tr>
<tr>
<td>FABP4</td>
<td>1.1</td>
<td>3.56</td>
<td>0.0006†</td>
</tr>
<tr>
<td>GRα</td>
<td>1.05</td>
<td>2.81</td>
<td>0.00007†</td>
</tr>
<tr>
<td>GLUT-4</td>
<td>1.4</td>
<td>2.78</td>
<td>0.004†</td>
</tr>
</tbody>
</table>

*Naive versus control; †naive versus 6 months. NS, not significant. HiP3DH, hexose-6-phosphate dehydrogenase.

**ABSTRACT O-15**

*Antiviral Therapy* 2007; 12 Suppl 2:13

Zidovudine/lamivudine persistently contributes to peripheral insulin resistance by a body composition-independent mechanism demonstrated by repeated clamp studies during 2 years of first-line ART with zidovudine/lamivudine/lopinavir/ritonavir

*MG van Vanderen¹, RME Blümer², E Hassink³, J Sutinen⁴, MT Ackermans², MA van Agtmael¹, H Yki-Jarvinen⁵, SA Danner¹, HP Sauerwein⁶ and P Reiss²,³ and the MEDICLAS study group*

¹VU University Medical Center, Amsterdam, the Netherlands; ²Academic Medical Center, Amsterdam, The Netherlands; ³IATEC, Amsterdam, The Netherlands; ⁴Helsinki University Central Hospital, Helsinki, Finland

**Objectives:** NRTI are thought to contribute to insulin resistance by induction of lipoatrophy. Recently, however, stavudine was shown to reduce peripheral glucose disposal without changes in fat distribution within 4 weeks in healthy volunteers. We prospectively evaluated the role of zidovudine/lamivudine in glucose metabolism and body composition in HIV-infected patients initiating ART in a randomized trial.

**Methods:** ART-naive men were randomized to lopinavir/ritonavir (400/100 mg two times daily) + zidovudine/lamivudine or lopinavir/ritonavir (533/133 mg two times daily) + nevirapine. CT, DEXA and hyperinsulinaemic euglycaemic clamps (aimed at plasma insulin level 200 pmol/l) using stable isotopes were performed before and after 3, 12 and 24 months of ART. A mixed model repeated measures ITT analysis correcting for baseline differences was performed.

**Results:** Baseline age was 42 ± 9 years, BMI 23.3 ± 3.1 kg/m², CD4 count 201 ± 90 cells/ml, HIV-1 RNA 5 ± 0.5 log₁₀ c/ml (comparable between arms). Lopinavir plasma exposure was not significantly different between both arms.

**Conclusions:** The persistent decrease in insulin-mediated glucose uptake observed only on zidovudine/lamivudine/lopinavir/ritonavir, starting prior to measurable limb fat loss and visceral fat accumulation, suggests that zidovudine/lamivudine, independent of any GLUT-4 inhibition by lopinavir/ritonavir, contributes to peripheral insulin resistance by a mechanism which seems independent of changes in fat distribution. The observed adiponectin increases in both arms are remarkable given the reduced levels reported in patients with clinical lipoatrophy, and may suggest a compensatory response early on after initiating ART for the first time.
ABSTRACT O-16

**Antiviral Therapy** 2007; 12 Suppl 2:L14

Pioglitazone with or without exercise training reduces liver lipid content and improves insulin sensitivity in HIV with impaired glucose tolerance (IGT)

**DN Reeds, WT Cade, K Mondy, C Bopp, S Lassa-Claxton and KE Yarasheski**

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

**Aim:** In HIV, pioglitazone improves insulin sensitivity and modestly increases appendicular adipose mass. We hypothesized that pioglitazone and exercise training (PIO+E) would reduce liver lipid content and improve insulin sensitivity more than pioglitazone alone (PIO) in HIV and IGT (ADA criteria).

**Methods:** Fourteen HIV+ men and one woman (66% caucasian, 49 ± 5 years old, 14 ± 6 year HIV+, CD4 641 c/mm3, 100% undetectable HIV RNA, 23% body fat and 63% trunk fat) were randomly assigned to receive PIO (30 mg/day, 16 weeks), or PIO+E (resistance and aerobic exercise – 3 days/week, 1.5 h/day; 55–85% maximum capacity) for both drugs (ANOVA). Randomization to ATV (400 mg once daily for 24 weeks), or ATV+PIO+E (resistance and aerobic exercise – 3 days/week, 1.5 h/day; 55–85% maximum capacity).

**Results:** Liver lipid content (1H-MR spectroscopy) declined after PIO (-1.6 ±1.5%) and PIO+E (-7.9 ±3.6%; P=0.08). Trunk and appendicular fat (DEXA) increased with PIO (113 ±57 g and 475 ±207 g, respectively), but decreased with PIO+E (-1,844 ±987 g and -314 ±503 g, respectively). GDR during hyperinsulinaemia improved more (P=0.05) in PIO+E (92% increase over week 0) than PIO (62%). In both groups, baseline fasting EGP was increased (18 ±1 µmol/kg FFM/min), and insulin-induced suppression of EGP improved similarly after treatment (23% versus 31% P=NS). The improvement in EGP correlated with the reduction in liver lipid content (r²=0.62; P=0.002).

**Conclusion:** Pioglitazone with or without exercise training appears to improve hepatic insulin sensitivity, at least partially by reducing liver lipid content. PIO+E improved peripheral glucose disposal rate and insulin sensitivity more than PIO alone.

Supported by NIH

ABSTRACT O-17

**Antiviral Therapy** 2007; 12 Suppl 2:L14

Effects of 4 weeks of atazanavir, lopinavir/ritonavir or placebo on endothelial function and insulin sensitivity in healthy men

**MP Dubé, C Shen, ML Greenwald and K Mather**

Indiana University School of Medicine, Indianapolis, IN, USA

**Aim:** Vascular endothelial dysfunction plays a critical role in atherosclerosis and thrombosis. Dyslipidaemia alone does not fully explain the observed increase in cardiovascular events in patients receiving PI-based antiretroviral treatment. Some HIV-1 protease inhibitors (PIs), such as indinavir, directly induce endothelial dysfunction, an effect that may mediate the portion of the increase in cardiovascular events that is not attributable to dyslipidaemia.

**Methods:** Thirty healthy, non-obese, HIV seronegative men had invasive evaluation of vascular function and insulin sensitivity during the study. Subjects who smoked (67%) maintained their usual smoking habits during the study.

**Results:** Liver lipid content (1H-MR spectroscopy) declined after PIO (-1.6 ±1.5%) and PIO+E (-7.9 ±3.6%; P=0.08). Trunk and appendicular fat (DEXA) increased with PIO (113 ±57 g and 475 ±207 g, respectively), but decreased with PIO+E (-1,844 ±987 g and -314 ±503 g, respectively). GDR during hyperinsulinaemia improved more (P=0.05) in PIO+E (92% increase over week 0) than PIO (62%). In both groups, baseline fasting EGP was increased (18 ±1 µmol/kg FFM/min), and insulin-induced suppression of EGP improved similarly after treatment (23% versus 31% P=NS). The improvement in EGP correlated with the reduction in liver lipid content (r²=0.62; P=0.002).

**Conclusion:** Pioglitazone with or without exercise training appears to improve hepatic insulin sensitivity, at least partially by reducing liver lipid content. PIO+E improved peripheral glucose disposal rate and insulin sensitivity more than PIO alone.

Supported by NIH
Results: Median age (36 years) and mean body mass index (23.4 ±2.6 kg/m²) did not differ between groups. Endothelium-dependent vasodilation (EDV) did not change after 4 weeks of treatment in any group. EDV, assessed as the leg blood flow response to intrafemoral artery infusion of 15 μg/min of the endothelium-dependent vasodilator methacholine, was 154 ±102% above basal at baseline and 242 ±254% at week 4 with ATV (P=0.7), 82 ±63% and 76 ±79% at week 4 with LPV/rt (P=0.8), and 109 ±84% and 127 ±153% at week 4 with placebo (P=0.8; between groups P=0.9). The leg blood flow response to infusion of the endothelium-independent vasodilator nitroprusside was not different at week 4 in any group, nor was insulin-mediated vasodilation (the increase in leg blood flow during hyperinsulinaemia), whole-body insulin-mediated glucose uptake (M) or leg glucose uptake (all P-values >0.1).

Conclusions: Unlike the dramatic impairment seen with indinavir, the newer PIs atazanavir and lopinavir-ritonavir do not induce endothelial dysfunction in healthy subjects. Thus, endothelial dysfunction does not appear to be a PI class effect. The cause of the non-lipid-mediated increase in cardiovascular events reported with PIs remains unclear.

Acknowledgements: This work was supported by the NHLBI (grant RO1 HL72711), NCRR (grant RR-00750), and drug was provided by Abbott and Bristol-Myers-Squibb.

ABSTRACT O-18
Antiviral Therapy 2007; 12 Suppl 2: L15

Control of HIV viral replication is associated with rapid improvement in endothelial function sustained over 24 weeks: A5152s, a substudy of A5142

FJ Torriani1, L Komarow2, BR Cotter1, RL Murphy3, CJ Fichtenbaum4, JS Currie5, MP Dubé6, KE Squires2, M Gerschenson6, CK Mitchell6 and JH Stein8

1University of California San Diego, San Diego, CA, USA; 2Harvard School of Public Health, Boston, MA, USA; 3Northwestern University, Chicago, IL, USA; 4University of Cincinnati Medical Center, Cincinnati, OH, USA; 5University of California Los Angeles, Los Angeles, CA, USA; 6Indiana University School of Medicine, Indianapolis, IN, USA; 7University of Southern California, Los Angeles, CA, USA; 8University of Hawaii, Honolulu, HI, USA; 9University of Wisconsin Medical School, Madison, WI, USA

Background: In HIV-infected patients, endothelial dysfunction, an early marker of atherosclerosis, has been attributed to HIV and associated with use of protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI).

Methods: On ACTG A5142, a class-sparing ART trial, subjects were randomly assigned to: (1) NRTIs + elavirenz (EFV), (2) NRTIs + lopinavir/ritonavir (LPV) or (3) EFV + LPV. NRTIs were lamivudine plus stavudine or zidovudine or tenofovir. On substudy A5152s, brachial artery flow-mediated dilation (FMD) of subjects from five institutions was determined by high-resolution B-mode ultrasound before starting on ART, then after 4 and 24 weeks. Relationships between changes in FMD and changes in HIV RNA, CD4, metabolic, and inflammatory markers were analysed to identify predictors of changes in endothelial function on treatment.

Results: Eighty-two treatment-naive individuals (median age 35 years, 91% men, 54% white and 44% active smokers) entered. Baseline mean [SD] CD4 and HIV RNA values were 252 [168] cells/ml and 4.9 [0.6] log10 copies/ml, respectively. Pre-ART FMD was impaired (4.0 % [3.1] vs. normal >7%). After 4 and 24 weeks of ART, FMD increased by 1.1 % [2.8] (P<0.003) and 1.9 % [3.0] (P<0.001). FMD improvement was similar in each arm (P=0.50). Total and HDL cholesterol increased significantly in each arm (P<0.01); triglycerides in the LPV-containing arms only (P<0.01). Log HIV RNA decreased by 2.1 and 3.0 log10 copies/ml at 4 and 24 weeks of ART (P<0.001); CD4 counts increased by 152 after 24 weeks (P<0.01). Of all metabolic and inflammatory markers analysed, FMD improvement was significantly associated only with log HIV RNA reduction at week 24 (rs=-0.30, P<0.02).

Conclusions: During the first 24 weeks of ART, effective control of HIV replication improves endothelial function regardless of initial ART regimen or lipid effects. These data suggest that suppression of HIV replication may be more important in decreasing cardiovascular risk than the initial ART combination.

ABSTRACT O-19
Antiviral Therapy 2007; 12 Suppl 2: L15

Relationship of body composition, antiretroviral use, and HIV disease factors to endothelial dysfunction in HIV-infected subjects

MP Dubé, C Shen, JS Waltz, ML Greenwald, K Mather and SK Gupta

Indiana University School of Medicine, Indianapolis, IN, USA

Background: Vascular endothelial dysfunction may contribute to the increase in cardiovascular events during HIV-1 infection and its treatment. Antiretroviral therapy (ART) including protease inhibitor (PI) use, metabolic factors, lipodystrophy, and HIV infection itself may all contribute to this endothelial dysfunction.

Methods: Ninety-six HIV-infected subjects had evaluation of endothelial function by measurement of brachial artery flow-mediated dilation (FMD) by ultrasound, plus single-
slice CT of the abdomen and mid-thigh, whole-body dual X-ray absorptiometry (DXA) scans, and metabolic evaluations in a cross-sectional study.

Results: Median age was 40.4 years, 28% were female, 38% black, 3% Hispanic, 59% white. Forty-nine (51%) were receiving ART, which included PI in 28 (57%) and was non-PI-based in 21 (43%). FMD (±SD) in subjects not on ART was 5.5 ±4.3%, PI-ART 5.3 ±3.6%, and non-PI-ART 5.5 ±4.1% (P=0.9). Age, race, CD4 cell count, and HIV RNA did not correlate significantly with FMD. Females had significantly higher FMD than males (P=0.01, t-test). Among ART-treated subjects in the lowest tertile of DXA limb fat as percent of total body fat (range 18.6–36.5%), FMD was 3.7 ±2.8% and in the highest tertile (range 43.3–60.9%) FMD was 6.3 ±3.7% (P=0.03, t-test). Among ART-treated subjects in the lowest tertile of CT thigh subcutaneous (SC) fat area (range 3–31 cm²), FMD was 4.4 ±3.5% and in the highest tertile (range 67–237 cm²) FMD was 6.8 ±3.6% (P=0.07). Among ART-treated subjects in the lowest tertile of CT visceral to subcutaneous abdominal fat (VAT/SAT) ratio (range 0.12–0.33), FMD was 6.7 ±2.9% and in the highest tertile (range 0.65–4.42) FMD was 5.7 ±4.1% (P=0.5).

The body fat measure that correlated most closely with FMD in ART-treated subjects was thigh fat area (r=0.22, P=0.12).

Conclusions: ART use, PI use, CD4 cell count, and HIV RNA levels were not associated with endothelial dysfunction by brachial FMD. Among subjects receiving ART, those with lower limb fat percent and lower thigh SC fat area tended to have worse endothelial function. This suggests that lipoatrophy may be an important contributor to endothelial dysfunction in HIV-infected individuals on ART.

Acknowledgements: This work was supported by the NHLBI (grant R01 HL72711) and NCRR (grant RR-00750).

ABSTRACT O-20

Antiviral Therapy 2007; 12 Suppl 2:16

Relationship of fat distribution with adipokines in HIV infection: the FRAM study

L Kosmiski1, DP Kotler2, CE Lewis3, R Scherzer4, S Heymesfield5, P Bacchetti6, M Shlipak4,6 and C Grunfeld4,6

1University of Colorado at Denver and Health Sciences Center, Denver, CO, USA; 2St. Luke’s-Roosevelt Hospital Center, New York, NY, USA; 3University of Alabama, Birmingham, AL, USA; 4San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA; 5Merck Research Laboratories, Rahway, NJ, USA; 6University of California, San Francisco, CA, USA

Background: HIV-infected patients receiving potent antiretroviral therapy often develop changes in body fat distribution, with the dominant change being a reduction in subcutaneous adipose tissue (SAT). Because adipose tissue makes important hormones involved in whole-body energy metabolism, including leptin and adiponectin, we examined their plasma concentrations and their relationship to total and regional adiposity.

Methods: We studied 1,143 HIV-infected and 286 controls who had adipokine levels measured in the FRAM study, which includes controls from the CARDIA study and a representative sample of HIV-infected individuals. Total and regional adiposity were measured by MRI.

Results: Total and regional adiposity were positively correlated with leptin levels in both the HIV-infected and control populations (P<0.0001). In controls, total and regional adiposity were negatively correlated with adiponectin concentrations. In contrast, adiponectin had little correlation with percent body fat in the HIV-infected subjects, but maintained a negative correlation with visceral adipose tissue (VAT) and upper trunk SAT. However, leg SAT was positively associated with adiponectin in HIV-infected subjects; HIV-infected subjects in the lower decile of leg SAT for controls had paradoxically lower adiponectin concentrations (Men: HIV <10% =4.1 μg/ml versus control <10% 7.5 μg/ml, P=0.009; Women: HIV <10% 7.8 μg/ml versus control <10% 11.6 μg/ml, P=0.037). Even after controlling for leg SAT, exposure to stavudine in HIV was associated with 8% lower adiponectin (per year of exposure, 95% CI -10.3 to -5.7, P<0.0001), predominantly in those with lipoatrophy.

Conclusion: The normal relationships between adiponectin levels and total and regional adiposity are lost or weakened in subjects with HIV infection. This may be due to changes in adipocyte function associated with the HIV lipodystrophy syndrome. In contrast, the relationship between adiposity and leptin levels appears similar to controls in the HIV-infected population and unaffected by HIV lipodystrophy.
ABSTRACT O-21

*Antiviral Therapy 2007; 12 Suppl 2:1-17*

Proteinuria, creatinine clearance and immune activation in HIV-infected subjects: a secondary analysis of treatment-naive studies ACTG 384, A5095 and A5001

SK Gupta1, L Komarow2, RM Gulick1, RB Pollard1, GK Robbins1, N Franceschini6, LA Szczepanik2, SL Koletar8 and RC Kalayjian9

1Indiana University School of Medicine, Indianapolis, IN, USA; 2SDAC/Harvard School of Public Health, Boston, MA, USA; 3Weill Medical College of Cornell University, NY, NY, USA; 4University of California, Davis Medical Center, Sacramento, CA, USA; 5Harvard University, Boston, MA, USA; 6University of North Carolina, Chapel Hill, NC, USA; 7Duke University Medical Center, Durham, NC, USA; 8The Ohio State University, Columbus, OH, USA; 9MetroHealth Clinical Research, Cleveland, OH, USA

**Aim:** Proteinuria and increased serum creatinine, independently of viral load and CD4 count, predict progression to AIDS and overall mortality in HIV-infected women, although an explanation for these relationships remains unclear. Because activated T cells are more commonly found in the kidneys of HIV-infected patients with poorer renal function, we hypothesized that proteinuria and decreased creatinine clearance (CrCl) may be markers of higher peripheral immune activation, which itself is a strong predictor of outcomes.

**Methods:** Treatment-naive subjects enrolled in ACTG therapeutic studies 384 and A5095 with renal and advanced flow cytometry data at baseline (advanced flow data for the A5095 subjects were provided by the longitudinal follow-up study A5001) were included in the analysis. Levels of immune activation, defined as the percentage of peripheral blood activated CD8 lymphocytes (CD8+/CD38+/HLA-DR+ cells), were compared between those with and without dipstick proteinuria ≥1+ and between those with and without CrCl <90 ml/min (estimated using the Cockcroft–Gault equation). Comparisons between groups were performed using the Wilcoxon Rank Sum test stratified by study cohort.

**Results:** Dipstick proteinuria, CrCl <90 ml/min, and CrCl <60 ml/min were present, respectively, in 73/1,012 (7%), 195/1,071 (18%), and 91/1,071 (1%) of the subjects at baseline. Proteinuria was significantly associated with a higher median percentage of activated CD8 cells compared with those without proteinuria in the total cohort (55% versus 50%; P=0.01); significant associations were also found in the black non-Hispanic (n=346), Hispanic (n=176), and male subgroups (n=846), but not in the white non-Hispanic or female subgroups. Importantly, these differences were primarily driven by the ACTG 384 cohort (n=576/1,012). Percentages of activated CD8 cells were not significantly different between those with CrCl <90 ml/min compared with higher CrCl (53% versus 49%; P=0.08) in the total cohort, but the differences were significant (53% versus 48%; P=0.04) in the ACTG 384 cohort (n=615/1,071).

**Conclusions:** Dipstick proteinuria, but not CrCl, was associated with greater levels of activated peripheral CD8 cells in this study of ART-naive patients with relatively preserved glomerular function. The presence of dipstick proteinuria may be an inexpensive and easily obtained identifier of HIV-infected patients with higher immune activation and consequently greater risk for poor outcomes.

ABSTRACT O-22

*Antiviral Therapy 2007; 12 Suppl 2:1-17*

Important changes in bone metabolism soon after commencing HAART

E Bonnet1,2, L Mobile3, JB Ruidavets5, J Bernard1, F Marion-Latard1, L Cuzin1, F Busato1, F Lucas1, P Massip1, B Marchou1 and B Perret1,2

1University of Toulouse, Toulouse, France; 2Unité INSERM 563, Toulouse, France

**Aim:** To evaluate the early changes in bone metabolism in HIV-infected patients commencing HAART and to compare these changes in patients on non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI).

**Methods:** We conducted a prospective study in HIV-naive patients without dyslipidaemia at baseline. Biochemical

---

**Table 1. (Abstract O-22)**

<table>
<thead>
<tr>
<th></th>
<th>BAP, µg/l</th>
<th>OCN, ng/l</th>
<th>β-CTX, pg/l</th>
<th>BMC, g</th>
<th>T BMD, g/cm²</th>
<th>L2-L4 BMD, g/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0 (n=49)</td>
<td>9 (+3.5)</td>
<td>18.6 (+6.8)</td>
<td>339</td>
<td>3,010 (+525)</td>
<td>1.226 (+0.101)</td>
<td>1.218 (+0.183)</td>
</tr>
<tr>
<td>M6 (n=46)</td>
<td>14 (+6.3)</td>
<td>28.0 (+12.7)</td>
<td>529</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M9 (n=40)</td>
<td>16.6 (+10.0)</td>
<td>30.6 (+12.9)</td>
<td>540</td>
<td>3,030 (+553)</td>
<td>1.221 (+0.107)</td>
<td>1.210 (+0.207)</td>
</tr>
<tr>
<td>P-value (global changes over time)</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.009</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>P-value (group A versus group B)</td>
<td>0.72</td>
<td>0.14</td>
<td>0.61</td>
<td>0.12</td>
<td>0.65</td>
<td>0.03</td>
</tr>
</tbody>
</table>
parameters including bone alkaline phosphatase (BAP), osteocalcin (OCN) and \( \beta \)-cross-laps (\( \beta \)-CTx) were measured at baseline (M0) and 3, 6 and 9 months (M3, M6, M9) after starting treatment. For all patients, we also performed a dual energy X-ray absorptiometry (DXA). Bone mineral content (BMC), total bone mineral density (T BMD) and BMD of the lumbar spine (L2–L4 BMD) were measured at M0 and M9. A mixed regression model with random intercept and random slope was used to test the linear trend. Seventy-two patients were included. All patients received two NRTIs in combination with a PI (36 patients, group A) or a NNRTI (36 patients, group B).

**Results:** Mean results are presented in Table 1.

**Conclusion:** Initiating HAART in naive patients leads to a rapid increase in all markers of bone metabolism, including those of bone formation (BAP, osteocalcin) as well as those of bone resorption (\( \beta \)-cross-laps). Nine months after starting HAART, the result of these changes is a significant loss of bone mineral content and bone mineral density as measured by DXA. The loss of BMD in lumbar spine seems to be greater in those patients who received PI.

### ABSTRACT O-23

**Antiviral Therapy 2007; 12 Suppl 2:**

**Uridine supplementation with Mitocnol antagonizes zidovudine-induced mitochondrial myopathy and hyperlactataemia in vivo**

D Lebrecht, C Deveaud, B Beauvoit, J Bonner, J-B Kirschner and UA Walker

1Medizinische Universitätsklinik, Department of Rheumatology and Clinical Immunology, Freiburg, Germany; 2Institut de Biochimie et de Génétique Cellulaires, UMR 5095 CNRS-Université Victor Ségalen Bordeaux cedex, France; 3Medizinische Universitätsklinik, Department of Neuropediatrics and Muscle Disorders, Freiburg, Germany; 4Basel University, Department of Rheumatology, Basel, Switzerland

**Objective:** Zidovudine induces a mitochondrial myopathy in humans by interfering with the replication of mitochondrial DNA (mtDNA). We investigated if this form of myopathy is a class effect of antiretroviral nucleoside analogues and if muscle damage may be antagonized by uridine supplementation *in vivo*.

**Methods:** Balb/c mice were fed with Mitocnol (340 mg/kg/day) a dietary supplement with high uridine bioavailability with or without zidovudine or zalcitabine. Skeletal muscle histology and mitochondrial functions were assessed after 12 weeks.

**Results:** Zidovudine, unlike zalcitabine, induced a significant hyperlactataemia and mitochondrial myopathy with fiber thinning, depleted mtDNA, reduced levels of cytochrome c oxidase activity (COX) and mtDNA-encod-

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mitocnol</th>
<th>Zidovudine (100 mg/kg/day)</th>
<th>Zidovudine (100 mg/kg/day) + Mitocnol</th>
<th>Zalcitabine (13 mg/kg/day)</th>
<th>Zalcitabine (13 mg/kg/day) + Mitocnol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle fibre diameter, ( \mu )m</td>
<td>18.2 ±1.2</td>
<td>20.2 ±0.5*</td>
<td>13.3 ±1.3*</td>
<td>17.1 ±1.2*</td>
<td>18.2 ±1.5</td>
<td>18.5 ±1.8</td>
</tr>
<tr>
<td>Fibre per 0.09 mm(^2)</td>
<td>129 ±19</td>
<td>131 ±12</td>
<td>171 ±20*</td>
<td>151 ±19*</td>
<td>148 ±26</td>
<td>125 ±21</td>
</tr>
<tr>
<td>Oil-red O</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Muscle lipids, mg lipid/mg tissue</td>
<td>0.7 ±0.2</td>
<td>0.8 ±0.1</td>
<td>2.5 ±0.5*</td>
<td>1.5 ±0.2*</td>
<td>0.8 ±0.1</td>
<td>0.9 ±0.2</td>
</tr>
<tr>
<td>Fibre degeneration (PAS)</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>mtDNA copies, copies/mononucleus</td>
<td>587 ±58</td>
<td>632 ±129</td>
<td>472 ±88*</td>
<td>574 ±91*</td>
<td>577 ±77</td>
<td>579 ±81</td>
</tr>
<tr>
<td>COX activity, ( \mu )mol/min/g protein</td>
<td>29 ±4</td>
<td>26 ±14</td>
<td>15 ±8*</td>
<td>23 ±7*</td>
<td>27 ±5</td>
<td>24 ±4</td>
</tr>
<tr>
<td>COX/SDH-ratio %</td>
<td>100 ±25</td>
<td>102 ±11</td>
<td>51 ±34*</td>
<td>108 ±10</td>
<td>97 ±8</td>
<td>103 ±16</td>
</tr>
<tr>
<td>COX I/COX IV-ratio (% of control)</td>
<td>100 ±24</td>
<td>92 ±10</td>
<td>76 ±28*</td>
<td>103 ±19*</td>
<td>105 ±17</td>
<td>95 ±15</td>
</tr>
<tr>
<td>Malondialdehyde, ( \mu )mol/g tissue</td>
<td>45 ±26</td>
<td>44 ±16</td>
<td>91 ±55*</td>
<td>52 ±21*</td>
<td>48 ±24</td>
<td>38 ±31</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \) versus controls; †versus no Mitocnol; *\( P < 0.001 \) versus control; †versus no Mitocnol.
ed cytochrome c subunit I (COX I). Reactive oxygen species (malondialdehyde) were increased. Mitocnol had no side effects itself, but attenuated or fully normalized all muscle pathology (Table 1).

**Conclusion:** Zidovudine, but not zalcitabine, induces a mitochondrial myopathy with thin muscle fibres and hyperlactataemia, both of which are antagonized by Mitocnol.

### ABSTRACT O-24A

**Antiviral Therapy 2007; 12 Suppl 2:L19**

Racial differences in long-term changes in metabolic parameters in antiretroviral-naive persons initiating HAART

**CL Gibert**, **JC Shlay**, **S Sharma**, **G Bartsch**, **G Peng** and **C Grunfeld** for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)

1Wide-Reaching AIDS Program, Veterans Affairs Medical Center and George Washington University, Washington DC, USA; 2Denver Community Programs for Clinical Research on AIDS, University of Colorado Health Sciences Center, Denver, CO, USA; 3CPCRA Statistical and Data Management Center, University of Minnesota, Minneapolis, MN, USA; 4Veterans Affairs Medical Center and University of California, San Francisco, CA, USA

**Objectives:** To compare by race long-term changes in metabolic parameters in persons initiating HAART.

**Methods:** We studied 400 participants. Fasting metabolic parameters were measured at baseline, month 1, 4 and 4-month intervals. Mean changes and rates of change (slopes) were compared with a median follow-up of 60 months. Insulin resistance (IR) was determined using HOMA.

**Results:** Mean age was 38 years, 22% female, 11% Latino, 61% African-American (AA), 28% Caucasian (W). ART usage was similar except nelfinavir use was greater in Latinos. Mean changes from baseline and differences in mean change with P-values by race are provided in Table 1. AAs had the smallest increase in lipids. Latinos and Ws had significantly greater increases in triglycerides (TG) and LDL cholesterol than AAs. Glucose and IR increased significantly for Latinos and AAs. Glucose increase was greater in Latinos than AAs and Ws. Increase in IR was greater in Latinos than Ws. Rates of change given in Table 2. Slopes were positive for TG, glucose and IR, and negative for LDL due to early increases followed by decreases. Latinos had greater slopes for TG (versus AAs), glucose (versus AAs and Ws) and IR (versus AAs and Ws) (data not shown).

**Conclusions:** In this prospective non-randomized evaluation, changes in metabolic parameters differed by race with Latinos having more adverse changes. Changes in metabolic parameters following initiation of HAART differ by race in addition to recognized differences by specific ART.

### ABSTRACT O-24B

**Antiviral Therapy 2007; 12 Suppl 2:L19**

Racial differences in long-term changes in body composition in antiretroviral-naive persons initiating HAART

**CL Gibert**, **JC Shlay**, **S Sharma**, **G Bartsch**, **G Peng** and **C Grunfeld** for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)

1Wide-Reaching AIDS Program, Veterans Affairs Medical Center and George Washington University, Washington DC, USA; 2Denver Community Programs for Clinical Research on AIDS, University of Colorado Health Sciences Center, Denver, CO, USA; 3CPCRA Statistical and Data Management Center, University of Minnesota, Minneapolis, MN, USA; 4Veterans Affairs Medical Center and University of California, San Francisco, CA, USA

**Table 1. (Abstract O-24A)**

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Mean change from baseline (P-value)</th>
<th>Difference in mean change (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latino (n=43)</td>
<td>AA (n=239)</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>49.15 (&lt;0.01)</td>
<td>13.56 (&lt;0.01)</td>
</tr>
<tr>
<td>LDL Chol, mg/dl</td>
<td>16.06 (&lt;0.01)</td>
<td>5.91 (&lt;0.01)</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>11.34 (&lt;0.01)</td>
<td>5.29 (&lt;0.01)</td>
</tr>
<tr>
<td>IR</td>
<td>1.32 (&lt;0.01)</td>
<td>1.08 (&lt;0.01)</td>
</tr>
</tbody>
</table>

**Table 2. (Abstract O-24A)**

<table>
<thead>
<tr>
<th>Race</th>
<th>TG, mg/dl/month</th>
<th>LDL-cholesterol, mg/dl/month</th>
<th>Glucose, mg/dl/month</th>
<th>IR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>P-value</td>
<td>Slope</td>
<td>P-value</td>
</tr>
<tr>
<td>Latino</td>
<td>1.11</td>
<td>&lt;0.01</td>
<td>–0.43</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AA</td>
<td>0.15</td>
<td>0.30</td>
<td>–0.35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>W</td>
<td>0.42</td>
<td>0.05</td>
<td>–0.23</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Table 1. (Abstract O-24B)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>L (n=43)</th>
<th>AA (n=239)</th>
<th>W (n=112)</th>
<th>L- AA</th>
<th>L-W</th>
<th>W-AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBF, kg</td>
<td>0.64 (0.25)</td>
<td>1.97 (&lt;0.01)</td>
<td>1.71 (&lt;0.01)</td>
<td>-0.96 (0.18)</td>
<td>-1.72 (0.03)</td>
<td>0.76 (0.14)</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>1.52 (&lt;0.01)</td>
<td>1.67 (&lt;0.01)</td>
<td>2.62 (&lt;0.01)</td>
<td>-0.45 (0.43)</td>
<td>-1.37 (0.03)</td>
<td>0.92 (0.03)</td>
</tr>
<tr>
<td>Mid-arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STA*</td>
<td>-3.86 (&lt;0.01)</td>
<td>0.78 (0.14)</td>
<td>-0.50 (0.41)</td>
<td>-3.93 (&lt;0.01)</td>
<td>-3.12 (0.01)</td>
<td>-0.80 (0.31)</td>
</tr>
<tr>
<td>NSTA\†</td>
<td>5.78 (&lt;0.01)</td>
<td>2.87 (&lt;0.01)</td>
<td>4.63 (&lt;0.01)</td>
<td>2.46 (0.05)</td>
<td>0.62 (0.65)</td>
<td>1.84 (0.04)</td>
</tr>
<tr>
<td>Waist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STA*</td>
<td>-5.03 (0.29)</td>
<td>7.89 (&lt;0.01)</td>
<td>6.63 (0.03)</td>
<td>-4.36 (0.37)</td>
<td>-6.53 (0.21)</td>
<td>2.15 (0.53)</td>
</tr>
<tr>
<td>VTA\‡</td>
<td>33.49 (&lt;0.01)</td>
<td>30.55 (&lt;0.01)</td>
<td>43.81 (&lt;0.01)</td>
<td>3.02 (0.79)</td>
<td>-18.4 (0.13)</td>
<td>26.9 (&lt;0.01)</td>
</tr>
</tbody>
</table>

*Subcutaneous tissue area (cm²), †non-subcutaneous tissue area (cm²); ‡visceral tissue area (cm²).

Table 2. (Abstract O-24B)

<table>
<thead>
<tr>
<th>Race</th>
<th>STA*</th>
<th>VTA*</th>
<th>STA*</th>
<th>NSTA*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>P-value</td>
<td>Slope</td>
<td>P-value</td>
</tr>
<tr>
<td>L</td>
<td>-0.80</td>
<td>&lt;0.01</td>
<td>1.21</td>
<td>0.01</td>
</tr>
<tr>
<td>AA</td>
<td>-0.16</td>
<td>0.07</td>
<td>0.21</td>
<td>0.24</td>
</tr>
<tr>
<td>W</td>
<td>-0.31</td>
<td>0.02</td>
<td>1.32</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*(cm²/month).

Objectives: To compare by race long-term body composition changes in persons initiating HAART.

Methods: We studied 400 participants. Anthropometric measurements were performed at baseline and 4-month intervals. Fat-free mass (FFM) and total body fat (TBF) were estimated by BIA. Mean changes and rates of change (slopes) were compared.

Results: Mean age 38 years, 22% female, 11% Latino (L), 61% African-American (AA), 28% Caucasian (W). Median follow-up 60 months. Mean changes from baseline and differences in mean change by race are summarised in Table 1. Increases in FFM (all races) and TBF (AA and W) were significant. L had decreases in STA, whereas AA and W had mostly increases. The decrease in mid-arm STA in L was greater than AA and W. VTA increased in all. Rates of change are presented in Table 2. Waist and mid-arm STA slopes were negative (most negative in L), reflecting early increases followed by decreases. Positive slopes were observed for waist VTA and mid-arm NSTA (greatest in L).

Conclusions: In this prospective non-randomized evaluation, changes in body composition differed by race with Latinos having the most unfavourable changes and AAs the least. These changes are in addition to recognized differences by specific therapy.
POSTER PRESENTATIONS
ABSTRACT P-01

*Antiviral Therapy* 2007; 12 Suppl 2:L23

The effect of antiretroviral therapy on genes involved with mitochondrial function

*M Boothby*¹, JW Tomlinson², KC McGee³, S Das⁴, LL Gathercole⁵, AL Harte², P Higgins³, CM Kusminski³, PG McTernan¹ and M Shahmanesh¹

¹University Hospital Birmingham, Birmingham, UK; ²University of Birmingham, Birmingham, UK; ³Warwick University, Warwick, UK; ⁴University Hospitals Coventry and Warwickshire, Coventry, UK

**Objectives:** To compare patterns of gene expression in the subcutaneous adipose tissue of HIV-positive subjects before and after 6 months of antiretroviral therapy with HIV-negative controls.

**Methods:** Subcutaneous fat biopsies from the iliac crest were performed on 18 HIV-positive patients and 10 HIV-negative controls. Following total RNA extraction, gene expression was profiled using real-time PCR and quantified relative to an internal house-keeping gene (18S). Genes were involved in nuclear regulation of mitochondrial RNA or mitochondrial respiratory chain. HIV-positive patients were tested before, and 6 months after randomization to either zidovudine/lamivudine or tenofovir/emtricitabine with efavirenz. Comparison between groups was by *t*-tests and Mann–Whitney test.

**Results:** There were no differences in sex, ethnicity, BMI, whole body DEXA, and abdominal CT scans between groups. Mitochondrially encoded respiratory genes NADH dehydrogenase 4 (ND4), cytochrome b (CYT-B) and cytochrome c oxidase subunit III (COX3) were increased in HIV-naive patients versus controls. ND4 expression further increased after treatment alongside expression of human citrate synthase (HCS, a key enzyme in TCA cycle), genes controlling transcription of mitochondrial RNA (NRF-1 and TFAM) and uncoupling protein 2 (UCP2), but not UCP1 and UCP3. However, CYT-B and COX3 decreased after treatment. The reduction in expression of CYT-B (*P*<0.0001) and COX3 (*P*=0.003) was significant for zidovudine (0.6 and 1.0, respectively), but not tenofovir (1.5 and 1.6, respectively).

**Conclusion:** Expression of mitochondrial respiratory genes are increased with HIV infection compared to controls. These fall to control levels after 6 months use of zidovudine but not tenofovir. Increased mitochondrial respiratory chain activity in HIV infection may contribute to the abnormalities in adipocyte metabolism in HIV.

ABSTRACT P-02

*Antiviral Therapy* 2007; 12 Suppl 2:L23

Mitochondrial impairment in mononuclear cells of hyperlactatemic patients on HAART

G Garrabou¹, S Lopez¹, C Moren¹, V Rodriguez¹, A Milinkovic², E Martinez², J Riba¹, J Casademont¹, F Cardellach¹, JM Gatell² and O Miro¹

¹Mitochondrial Research Laboratory - IDIBAPS - Universitat de Barcelona - Internal Medicine Department, Hospital Clinic of Barcelona, Barcelona, Catalonia, Spain; ²Infectious Diseases Department, Hospital Clinic of Barcelona, Barcelona, Catalonia, Spain; ³Orthopedic Surgery and Traumatology Department, Hospital Clinic of Barcelona, Barcelona, Catalonia, Spain

**Objectives:** Hyperlactataemia is one of the most serious secondary effects developed by HIV patients on HAART. Mitochondrial toxicity of antiretroviral drugs, especially nucleoside analogues, has been suggested to underlay HAART-related hyperlactataemia. Hyperlactatemic mitochondrial impairment has been demonstrated on liver and muscle invasive studies. However, few approaches have been performed on peripheral blood mononuclear cells (PBMC), all containing reduced numbers of patients and exclusively based on mitochondrial DNA (mtDNA) quantification. We herein show mitochondrial genetic and biochemical analysis in PBMCs of HIV patients on HAART during an acute hyperlactatemic episode and after recovery.

**Methods:** We studied PBMCs of 20 HIV patients on HAART undergoing an hyperlactatemic crisis and after clinical recovery with respect to asymptomatic HIV subjects on HAART, naive individuals and non-infected controls. All subjects were matched by age, gender and those on treatment had similar HAART backgrounds. We measured mtDNA and mtRNA content by quantitative real-time PCR, enzymatic activities of mitochondrial respiratory chain (MRC) complexes II, III, IV and mitochondrial content by spectrophotometry and mitochondrial protein synthesis by western blot.

**Results:** MtDNA content and mitochondrial encoded enzymatic activities (III and IV) were decreased during the hyperlactatemic phase (1.49 ±0.22 versus 1.65 ±0.21, *P*<ns; 143.72 ±22.82 versus 214.12 ±27.63, *P*=0.002;
49.18 ±6.83 versus 84.44 ±9.84, P=0.001, respectively), as well as mitochondrial amount (72.82 ±7.97 versus 106.35 ±14.48, P=0.009) and mitochondrial protein expression (0.9 ±0.6 versus 1.03 ±0.05, P=0.039), all with respect to clinical recovery. Conversely, mtRNA content was increased (32.5 ±14.86 versus 20.61 ±14.48, P=ns) and the nuclear-encoded MRC complex II was conserved and similar to controls. After clinical recovery, studied parameters tend to achieve values found on asymptomatic individuals, which were lower than ranges of naive or non-infected controls.

Conclusions: HAART-related hyperlactataemia is associated with decreases in mtDNA content (although non-significant), mtDNA-encoded MRC enzymatic activities III and IV, mitochondrial amount and mitochondrial protein synthesis, despite the increase in mtRNA content (although non-significant). After the crisis all these parameters tend to normality.

Acknowledgements: This work has been supported by Fundació La Marató de TV3 (02/0210), Redes de Investigación en Mitocóndras (V-2003-RED06E-0) y SIDA (Redg 173) and Suports a Grups de Recerca (2001/SRG/00379).

ABSTRACT P-03

Antiviral Therapy 2007; 12 Suppl 2:L24

Risk factors for case fatality: do we need a new case definition for severe hyperlactataemia in HIV-infected patients exposed to NRTIs?

A Arenas-Pinto on behalf of the International Lactic Acidosis Study Group

University College London, London, UK

Background: Lactic acidosis (LA) and severe hyperlactataemia (HL) are rare but serious complications of antiretroviral therapy. Most case definitions of HL require symptoms and a raised blood lactate level. Methods: In a multinational study to identify risk factors for HL/LA, LA was defined as arterial blood pH <7.35, bicarbonate <20 mmol/l and lactate above normal; HL was defined as confirmed blood lactate >5 mmol/l. Logistic regression was used to identify factors associated with fatality among HL/LA cases.

Results: Among 110 cases most had gastro-intestinal (64.4%) or constitutional symptoms (57.0%) at the time of the event, but 10 (9%) cases were asymptomatic (median lactate 5.8 mmol/l, range 5.1–7.3). The case-fatality rate was 19/110 (17.3%). The median lactate for fatal, non-fatal and all cases was 8.3 mmol/l (IQR 7.2–13.1), 6.4 mmol/l (IQR 5.4–7.8) and 6.7 mmol/l (IQR 5.5–8.1), respectively. After adjusting for current CD4 cell count and didoxynucleoside exposure, lactate above 7 mmol/l (OR 7.8; 95%CI 1.6–37.8) was independently associated with case fatality. There was some evidence of an association between opportunistic infections and case fatality (OR 3.9; 95%CI 1.0–15.6). None of the asymptomatic cases died as a consequence of the event.

Conclusions: Our data suggest that a blood lactate higher than 7 mmol/l is associated with an increased risk of death and may be an appropriate threshold for the diagnosis of severe HL. Patients with confirmed blood lactate above 5 mmol/l may be asymptomatic. Therefore, a case definition based on blood lactate levels might be more appropriate than a definition combining symptoms and lactate values.

ABSTRACT P-04

Antiviral Therapy 2007; 12 Suppl 2:L24

The risk of developing NRTI-induced peripheral neuropathy decreases over time: evidence for special susceptibility from the Delta trial

A Arenas-Pinto1, K Bhaskaran2, D Dunn3 and I Weller2

1Centre for Sexual Health & HIV Research, University College London, UK; 2Clinical Trials Unit, Medical Research Council, London, UK

Objectives: Peripheral neuropathy (PN) is a common complication in HIV-infected individuals and is thought to be due to a toxic effect on mitochondria induced by nucleoside reverse transcriptase inhibitors (NRTI). This study was designed to assess the effect of cumulative NRTI exposure on the incidence of PN in patients included in Delta trial.

Methods: A time-to-event analysis was performed using data from the Delta trial where HIV-infected individuals...
were randomized to receive zidovudine (AZT) alone or in combination with either didanosine (ddI) or zalcitabine (ddC). A flexible parametric survival model based on Royston and Parmar method was used to estimate the effect of duration of NRTI. A likelihood ratio test was used to assess whether this model was a better fit than the nested Weibull model in which the hazard function is monotonic or constant.

**Results:** A total of 3,195 patients enrolled in Delta (1 and 2) trials were included in this sub-analysis. In a time-to-event analysis, the proportion of individuals that had experienced PN by 1 year from randomization was 3.0%, 2.9% and 8.2% in the AZT, AZT/ddI and AZT/ddC arms, respectively. The hazard of PN peaked over the first year following randomization. Compared with baseline, the estimated hazard of PN increased by 76% over the first 24 weeks, and then dropped. At 1 year, the risk was 32% higher than the baseline. There was strong evidence that this increase and decrease in the hazard of PN was a better fit to the data than a simpler model (P=0.0005 compared to a Weibull model).

**Conclusion:** Our results may support the hypothesis of a special susceptibility in a particular group of patients. Patients who are likely to develop PN when exposed to ddC tended to do so after a short exposure to the drug.

**ABSTRACT P-05**

*Antiviral Therapy 2007; 12 Suppl 2:L25*

Acute inhibition of mitochondrial respiration by Efavirenz in hepatic cells: a new mechanism of damage following bioenergetic stress.

A Blas-García, M Rocha, F Baixauli, A Alvarez, N Martínez-Martín, VM Victor and JV Esplugues

Department of Pharmacology, Faculty of Medicine, University of Valencia, Valencia, Spain

**Background:** Liver toxicity is the most relevant adverse effect of non-nucleoside reverse transcriptase inhibitors (NNRTIs) although there is no clear explanation of the mechanisms responsible. The present study evaluates in vitro the acute effects of efavirenz on mitochondrial function and its implication in the energetic metabolism of the hepatic cell.

**Methods:** Non-HIV-infected Hep3B cells, cultured in minimum essential medium, were placed in gas-tight chambers and O2 consumption was measured with a Clark-type O2 electrode. Following incubation with efavirenz, for 1 and 4 h respectively, intracellular ATP was measured by fluorescence (ATP Bioluminescence Assay Kit HSII, Roche), whereas mitochondrial cytochrome c release was measured in the cytosolic fraction and analysed by Western blotting. Ritonavir or lamivudine were used as comparison.

**Table 1. (Abstract P-05)**

<table>
<thead>
<tr>
<th>Treatment, µM</th>
<th>% of reduction in O2 consumption versus control (n=3)</th>
<th>ATP, nmol/mg protein (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-</td>
<td>16.97 ±2.38</td>
</tr>
<tr>
<td>Efavirenz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>26.57 ±5.73*</td>
<td>13.68 ±2.89</td>
</tr>
<tr>
<td>25</td>
<td>50.60 ±8.09†</td>
<td>9.42 ±2.04 *</td>
</tr>
<tr>
<td>50</td>
<td>54.67 ±3.35†</td>
<td>4.82 ±0.96†</td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>44.03 ±11.18†</td>
<td>6.77 ±2.13†</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>9.40 ±3.27†</td>
<td>-</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001

**Results:** The presence of efavirenz induces significant and dose-dependent (one-way ANOVA followed by Student’s t-test) inhibition of mitochondrial O2 consumption, which was noticeable immediately after the addition of the drug. This inhibition of mitochondrial function resulted in a similar dose-dependent and significant reduction of intracellular ATP following 1 h incubation with efavirenz. Both these effects were also present with lamivudine but not with ritonavir. Incubation with efavirenz (4 h) resulted in a dose-dependent increase in cytosolic cytochrome c.

**Discussion:** These preliminary results suggest that clinically used concentrations of efavirenz acutely reduce mitochondrial function in hepatic cells. This is followed by a significant diminution in intracellular ATP and probably leads to metabolic stress, which is accompanied by damage in the mitochondrial membranes as suggested by the release of mitochondrial cytochrome c. These mechanisms could be involved in the toxic effects of efavirenz in the liver.

**ABSTRACT P-06**

*Antiviral Therapy 2007; 12 Suppl 2:L25*

Single-dose and cumulative Pharmacokinetics of the food supplement Nucleomax® and mechanism for enhanced bioavailability of uridine

ME Weinberg1, MC Roman2, P Jacob1, M Wen1, L Yu1, UA Walker3, K Mulligan1 and M Schambelan1

1University of California San Francisco, San Francisco, CA, USA; 2Tampa Bay Analytical Research Inc., Largo, FL, USA; 3Medizinische Universitatsklinik, Freiburg, Germany

**Objectives:** Uridine supplementation is being investigated as a novel therapy for mitochondrial dysfunction. Administration of Nucleomax®, a food supplement derived from sugar cane, achieves higher peak uridine levels than those reported in studies using similar doses of
pure uridine. We performed single- and multiple-dose pharmacokinetic (PK) studies to determine whether repeated dosing with NucleomaxX® results in augmented plasma uridine levels, as well as product analysis to explore its enhanced bioavailability.

**Methods:** Eight healthy volunteers (four men and four women) were hospitalized on a metabolic ward for 7 days and fed a constant diet. One sachet (36 g) of NucleomaxX® mixed with 300 ml of liquid was administered as a single dose on Day 1. Subjects were then dosed every 8 h during days 2–6 and once on day 7. Twenty-four-hour PK parameters were compared between days 1 and 7 by paired t-tests. For the product analysis, nucleosides were extracted in aqueous solution containing ascorbic acid and quantified by reversed-phase HPLC with UV detection.

**Results:** In the men, plasma uridine levels at 0800 h were 4.8 ±0.5 μM and 33.4 ±4.2 μM (P=0.0008), rising to maximal concentrations of 128.1 ±25.4 μM and 162.7 ±21.2 μM (P=0.07) 1–2 h after dosing on days 1 and 7, respectively. Mean plasma uridine levels (95.4 ±60.3 versus 70.4 ±53.3 μM, P≤0.0001) and AUCs (1,429 ±427 versus 1,045 ±208 μM/h, P=0.013) were higher on day 7 than on day 1, indicating a cumulative effect after repeated dosing. Product analysis revealed that each sachet of NucleomaxX® contains 1.61% (0.6 g) uridine and 15.0% (5.4 g) 2′,3′,5′-tri-O-acetyluridine (TAU), which is converted to uridine by plasma esterases. Previous studies have shown that, compared with pure uridine, TAU exhibits enhanced gastrointestinal tract absorption and is resistant to catabolism by uridine phosphorylase.

**Conclusions:** Repeated dosing with NucleomaxX® resulted in a mean peak plasma uridine concentration >150 μM, a level far greater than that reported with equimolar amounts of pure uridine and in a range known to ameliorate mitochondrial toxicity in vitro. The increased bioavailability may be due to the high proportion (>90%) of TAU in the nucleoside component of NucleomaxX®.

<table>
<thead>
<tr>
<th>Table 1. (Abstract P-08)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>M61CC†</td>
</tr>
<tr>
<td>F38CC‡</td>
</tr>
<tr>
<td>M27AA¶</td>
</tr>
</tbody>
</table>

*Significantly different from the control (P<0.05). †RNA levels are expressed as fold change relative to the control (2 ΔΔCt). ‡For M27AA results were expressed as fold increase with the range of variation.

**ABSTRACT P-07**

*Antiviral Therapy 2007; 12 Suppl 2:S26*

Uridine supplementation with Mitocnol antagonizes zidovudine-induced mitochondrial myopathy and hyperlactataemia in vivo

D Lebrecht1, C Deveaud2, B Beauvoir2, J Bonner1, J-B Kirschner3 and UA Walker1,4

1Medizinische Universitätsklinik, Department of Rheumatology and Clinical Immunology, Freiburg, Germany; 2Institut de Biochimie et de Génétique Cellulaires, UMR 5095 CNRS-Université Victor Ségalen Bordeaux Cedex, France; 3Medizinische Universitätsklinik, Department of Neuropediatrics and Muscle Disorders, Freiburg, Germany; 4Basel University, Department of Rheumatology, Basel, Switzerland

This poster abstract will also be presented as an oral; see abstract O-23 for text.

**ABSTRACT P-08**

*Antiviral Therapy 2007; 12 Suppl 2:S26*

Effect of atazanavir and lopinavir on resistin expression in primary human macrophages

A Bellamine, C Elosua, C Cao and O Flint

Research and Development, Bristol-Myers Squibb, Princeton, NJ, USA

**Background:** Changes in adipokines have been associated with lipodystrophy and increased risk of type 2 diabetes. In particular, a SNP found in the resistin gene is associated with metabolic syndrome in HAART-induced lipodystrophy. We report the effect of atazanavir (ATV) or lopinavir (LPV) with or without ritonavir (ATVr or LPVr) on resistin expression by human primary macrophages.

**Methods:** Primary human monocytes from three different donors (M61CC, M27AA and F38CC) were differentiated in vitro into macrophages over 7 days. The cells were then treated with 3, 10 or 30 μM of each of the PIs with or without 2 μM of ritonavir for 24 h. Resistin mRNA expression was determined using RT-PCR and baseline
resistin concentrations by ELISA. **Results:** Resistin mRNA was reduced by both PIs, but only by LPV in a concentration-dependent fashion. LPV/r inhibited resistin expression more than ATV/r in M61CC and F38CC cells. Similar changes were observed in macrophages treated with ATV or LPV alone. M27AA cells were not affected, except by LPV at 30 μM. M27AA also differed from the other donors in the amount of resistin secreted (67 pg/ml) which was twofold less than F38CC and M61CC (135 and 150 pg/ml, respectively). **Conclusion:** Resistin expression was more affected by LPV than ATV, and there was interindividual variability in the response possibly reflecting variability in the underlying resistin genotypes of the donors and their response to the PIs. Further in vitro and clinical studies will be required to elucidate the mechanisms involved.

**ABSTRACT P-09**

*Antiviral Therapy 2007; 12 Suppl 2:L27*

The effect of antiretroviral therapy on genes involved with glucose and lipid metabolism

*M Boothby1, JW Tomlinson2, KC McGee3, S Das4, LL Gathercole2, AL Harte5, P Higgins6, CM Kusminski7, PG McTernan1 and M Shahmanesh1*

1University Hospital Birmingham, Birmingham, UK; 2University of Birmingham, Birmingham, UK; 3Warwick University, Warwick, UK; 4University Hospitals Coventry and Warwickshire, Coventry, UK

This poster abstract will also be presented as an oral; see abstract O-14 for text.

**ABSTRACT P-10**

*Antiviral Therapy 2007; 12 Suppl 2:L27*

Gender independent Th1/2 cytokine dysbalance associated with lipodystrophy in HIV-patients

*L Pontes-Cardoso1, LR Souza1, M Peraçoli1, M Stankov2, PC Pereira1 and GMN Behrens2*

1Sao Paulo State University, Botucatu, Brazil; 2Hannover Medical School, Hannover, Germany

**Objectives:** Abnormal fat redistribution and metabolic abnormalities, termed lipodystrophy syndrome, are frequently observed side effects of antiretroviral therapy. We analysed the relation between Th1/2 cytokines with lipodystrophy and various metabolic parameters including serum lipids, adiponectin, leptin, and insulin resistance in female and male HIV-patients on highly active antiretroviral therapy.

**Methods:** Cross-sectional study in 84 HIV-patients with and without lipodystrophy enrolled in a Brazilian ambulatory HIV clinic.

**Results:** Patients with lipodystrophy had a higher insulin resistance index (HOMA-IR 3.57 ±2.4 versus 2.36 ±1.6, \( P<0.05 \)), lower adiponectin (4.3 ±3.6 versus 6.2 ±3.8 pg/μl, \( P<0.05 \)) but comparable leptin levels. Lipodystrophic patients had significantly higher levels of TNF-α (63.5 ±131.9 versus 351.8 ±146.9 pg/μl, \( P<0.001 \)) and IL-10 (49.2 ±12.6 versus 39.2 ±16.5, \( P<0.01 \)), but lower circulating Th1-cytokines including IFN-γ (361.1 ±149.6 versus 568.5 ±174.3, \( P<0.001 \)) and IL-2 (101.8 ±23.5 versus 113.3 ±23.0, \( P<0.02 \)). The combination of ‘high’ circulating TNF-α receptor 2 and ‘low’ IFN-γ was highly predictive for the presence of lipodystrophy in both males and females. Differences of metabolic parameters associated with lipodystrophy were heavily influenced by gender. Differences in cytokine levels of TNF-α, IFN-γ, and IL-2 associated with lipodystrophy remained significant in both males and females.

**Conclusion:** Lipodystrophy is associated with a significant dysbalance of Th1/2 cytokines towards low circulating IFN-γ and IL-2 levels but higher proinflammatory TNF-α concentrations. These data implicate a relevant impact of the immune system in the pathogenesis of the HIV-therapy-associated lipodystrophy syndrome.

**ABSTRACT P-11**

*Antiviral Therapy 2007; 12 Suppl 2:L27*

Sex differences in the correlations between baseline anthropometric measurements and fat distribution in HIV-infection-associated adipose redistribution syndrome (HARS)

*K Mulligan1, M Glesby2 and E Freedland3*

1University of California, San Francisco, CA, USA; 2Weill Medical College of Cornell University, New York, NY, USA; 3EMD Serono, Rockland, MA, USA, on behalf of the Serostim in HARS Study Group

**Objectives:** HARS has been defined as a subset of HIV lipodystrophy with abnormal accumulation of central fat, including visceral fat. Combined baseline data from two clinical trials of patients with HARS were examined to determine whether there were sex-specific differences in the relationship between anthropometric measures and fat distribution.

**Methods:** Baseline data from two randomized, double-blind, placebo-controlled studies of recombinant human growth hormone in 561 patients with HARS are included in this analysis. Visceral and subcutaneous adipose tissue (VAT and SAT) were measured by single-slice computed tomography at L4–L5 and trunk fat (TF) by DXA. Data in men and women were compared using the Kruskal–Wallis test; Spearman correlation coefficients were generated for the whole cohort and for each sex.
Results: For the whole cohort, significant correlations (r>0.41) were found between baseline waist circumference (WC), and VAT, SAT and TF (all P<0.001). Correlations were also found between the waist/hip ratio (WHR) and VAT, and VAT/SAT ratio (VSR) (all P<0.001). Women had significantly less VAT, more SAT and TF, and lower VSR than men (all P<0.001). In men, WC correlated (P<0.001) with VAT (r=0.45), SAT (r=0.51), and TF (r=0.69). In contrast, in women, WC was highly correlated with SAT (r=0.78), VSR (r=0.63) and TF (r=0.89; all P<0.001), but not VAT (r=0.17, P=0.167).

Conclusions: These data demonstrate that, in HIV-infected patients with excess central fat, there are sex differences in the distribution of visceral and subcutaneous adipose tissue and their relationships to anthropometric measurements. It remains to be determined whether changes in WC and WHR during treatment correlate with changes in VAT or SAT, and if anthropometric measures could potentially serve as surrogate markers to estimate change in VAT.

ABSTRACT P-13

Antiviral Therapy 2007; 12 Suppl 2:S28

Hepatic lipid and adipose tissue distribution in HIV-infected men

Q He1, G Ionescu1, MJ Glesby2, DP Kotler1 and ES Engelson1

1Division of Gastroenterology, Department of Medicine, St. Luke's-Roosevelt Hospital Center, Columbia University, New York, NY, USA; 2Division of International Medicine & Infectious Disease, Department of Medicine, New York Presbyterian Hospital, Cornell University, New York, NY, USA

Background: Many studies have demonstrated associations between visceral adipose tissue (VAT) and hepatic lipid in non-HIV populations. However, a single study in HIV lipodystrophy patients, using proton magnetic resonance spectroscopy (MRS) for hepatic lipid and a single slice MRI for VAT, failed to find a correlation. This study further...
investigates the relationship between hepatic lipid and whole body adipose tissue content and distribution in HIV-infected men.

**Methods:** Data from 18 HIV-infected men were retrospectively analysed for this study. Eleven men with HIV-related fat redistribution and insulin resistance were studied prior to initiating a clinical study of growth hormone therapy and seven men taking zidovudine were studied prior to participating in a treatment-switch study. MRS was applied to quantify hepatic lipid volume, expressed as methylene/methylene+water×100%, using jMRUI spectrum analysis software, with water as an internal standard. Whole body adipose tissue volumes, that is, subcutaneous adipose tissue (SAT) and VAT, were measured by MRI. A simple correlation analysis was performed.

**Results:** Total VAT volume was 5.8±2.6 l (mean ±SD, range 1.5–10.6). Whole body SAT volume was 19.3±9.2 l (range 8.6–41.5). Hepatic lipid content was 3.7±2.5% (range 0.5%–9%) which is consistent with the previous report of hepatic fat in HIV-infected men (2.9–8.1%). Hepatic lipid correlated significantly with total VAT (r=0.52, P=0.028) but not with SAT (r=0.12, P>0.62).

**Conclusion:** Hepatic lipid content is associated with VAT volume in HIV-infected men.

**ABSTRACT P-14**

*Antiviral Therapy 2007; 12 Suppl 2:L29*

**Relationship of fat distribution with adipokines in HIV infection: the FRAM study**

*L Kosmiski1, DP Kotler2, CE Lewis3, R Scherzer4, S Heymesfield5, P Bacchetti6, M Shlipak4,6 and C Grunfeld1*

1University of Colorado at Denver and Health Sciences Center, Denver, CO, USA; 2St. Luke’s-Roosevelt Hospital Center, New York, NY, USA; 3University of Alabama, Birmingham, AL, USA; 4San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA; 5Merck Research Laboratories, Rahway, NJ, USA; 6University of California, San Francisco, CA, USA

This poster abstract will also be presented as an oral; see abstract O-20 for text.

**ABSTRACT P-15**

*Antiviral Therapy 2007; 12 Suppl 2:L29*

**Evolution of body composition in HIV-infected lipodystrophic men treated with antiretroviral therapy**

E Degris1, A Sommet1, F Bonnet2, P Massip2, M Obadia2, C Aquilina1, S Sire1, F Marion-Latard2, B Perret2, J Montastruc1 and J Bernard2

1Department of Pharmacology and Centre Midi-Pyrenees de Pharmacovigilance, de Pharmacopoeiologie et d’Informations sur le Medicament, Faculty of Medicine, University of Toulouse, Toulouse, France; 2Unit of Infectious and Tropical Disease, Purpan University Hospital, Toulouse, France; 3Unit of Dermatology, La Grave University Hospital, Toulouse, France; 4Unit of Interne Medicine, Cahors Hospital, Cahors, France

**Objective:** The aim of this study was to analyse evolution of body composition in HIV-infected lipodystrophic men treated with antiretroviral drugs.

**Methods:** We conducted a retrospective, longitudinal, observational study including HIV lipodystrophic men, (defined by a fat mass ratio (FMR) ≥1.6, which is the ratio of the percentage of trunk fat mass to the percentage of lower limbs fat mass), from Toulouse and Cahors hospitals (France). Records of body composition values (total, trunk, lower limb fat mass, total lean mass and Bone Mineral Density [BMD]) were determined by dual X-ray absorptiometry (DEXA) twice (that is DEXA 1 and DEXA 2 at least at one year intervals). For each DEXA, immuno-virological (CD4+ cell count, viral load) and epidemiological (age, body mass index [BMI], duration of HIV infection) data were collected. Cumulative duration of exposure to each drug was estimated before the first DEXA and during the period of the study.

**Results:** Eighty-four men were included: mean age 46, mean follow-up of 40 months, mean FMR1=2.08, mean FMR2=2.03. They were divided into three groups according to evolution of their lipodystrophy, based on the evolution of their lower limbs fat mass (LLFM) (≥10%): group 1 = ‘improvement’ (n=46; +39.3%), group 2 = ‘aggravation’ (n =20; -22.5%), and group three = ‘stable’ (n=18; +1.5%). At DEXA 1, the three groups were comparable for immuno-virological, epidemiological data, duration of follow-up, FMR and body composition. Drugs differed only on abacavir (P=0.02). Mean evolution of total body, trunk fat and total lean mass was, respectively, +25%+20.2%/-0.8% in group one, -16.9%/-14.4%/-0.8% in group two and +5.2%+5.7%+0.4% in group three. Decrease in BMD was observed in the three groups: -0.003 g/cm² (group one), -0.016 g/cm² (group two), -0.011 g/cm² (group three). Between the two DEXAs, a significant difference was observed in abacavir consumption (P=0.03).

**Conclusion:** These data show that lipodystrophy can
improve slowly after several years(94,82),(714,124), associated with a gain in total fat without modification in total lean mass. BMD seems to decrease irrespective of the evolution of lipodystrophy. We cannot conclude on a role of drugs in lipodystrophy.

**ABSTRACT P-16**

*Antiviral Therapy 2007; 12 Suppl 2:30*

Follow-up of lipodystrophy and metabolic alterations in the ANRS APROCO–COPILOTE cohort studying HIV-infected patients initiated with protease inhibitors in 1997 and 1998: relation to adiponectin, leptin and triglycerides levels and to TNF polymorphisms

JP Bastard1, E Pereira2, J Reynes3, M Kim1, C Tse1, S Herson4, M Maachi1, M Heller2, JL Ecobichon6, F Raffi6, G Chene2 and J Capeau1

1Inserm U680, Université-Paris6, Hopital Tenon AP-HP, Paris, France; 2Inserm U593, ISPED, Bordeaux, France; 3CHU Montpellier, Montpellier France; 4Hôpital Pitié-Salpétrière, AP-HP, Paris, France; 5Hôpital Bichat, AP-HP, Paris, France; 6CHU Nantes, Nantes, France

**Aim:** To evaluate the long-term contribution of adipokine, metabolic parameters and TNF polymorphisms to lipodystrophy and metabolic abnormalities in ART-treated patients

**Methods:** Patients were evaluated 12 or 20 months (phase 1, *n*=343), 24 or 36 months (phase 2, *n*=338) and 48 months (phase 3, *n*=239) after initiation of a treatment with PIs. Lipodystrophy was clinically recorded; metabolic parameters, insulin, adipokines and cytokines were determined at any phase. TNF polymorphisms -238 and -308 were investigated. In addition, clinical and metabolic parameters were assessed up to 72 months.

**Results:** Between phase 1 and 3, mean body mass index (BMI) was low and remained unmodified (22.5–22.8 kg/m²). The prevalence of lipodystrophy increased (66–73%) as did the prevalence of lipoatrophy (47–63%, isolated or associated with lipohypertrophy). Median leptin level increased from 1.8 to 2.5 ng/ml, and was related to sex, BMI, insulin resistance and adiponectin level. Median adiponectin level decreased from 4.4 to 3.0 μg/ml, and was inversely related to insulin resistance and adiponectin level. Median adiponectin level decreased from 4.4 to 3.0 μg/ml, and was inversely related to insulin resistance and adiponectin level.

**Conclusion:** The prevalence of lipoatrophy increased with time in patients initiated with PI in 1997–1998. Its presence was positively related to age, duration of infection and triglycerides, and negatively to BMI and adiponectin. TNF polymorphisms were not associated with lipodystrophy and metabolic alterations. The prevalence of a metabolic syndrome was unchanged during evolution while that of diabetes increased.

**ABSTRACT P-17**

*Antiviral Therapy 2007; 12 Suppl 2:30*

Long-term subcutaneous tissue changes among antiretroviral naive persons initiating three nucleoside regimens

JC Shlay1, S Sharma2, G Bartsch2, G Peng2, CL Gibert1 and E Granfeld2, for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)

1Denver Community Programs for Clinical Research on AIDS, University of Colorado Health Sciences Center, Denver, CO; 2CPCRA Statistical and Data Management Center, University of Minnesota, Minneapolis, MN; 3Wide-Reaching AIDS Program, Veterans Affairs Medical Center and George Washington University, Washington DC; 4Veterans Affairs Medical Center and University of California, San Francisco, CA, USA

**Aim:** Changes in adipose tissue assessed among ARV-naive patients initiating one of three NRTI-containing regimens.

**Methods:** We compared changes in 308 patients initiating stavudine+lamivudine (d4T; *n*=192) or abacavir+lamivudine (ZDV; *n*=192) or zidovudine+lamivudine (ZDV; *n*=192) with PIs, NNRTIs or both. Anthropometry performed at baseline and 4-month intervals. Rates of change (slopes) (mm/year) were compared over 36 months of follow-up.

Table 1. (*Abstract P-17*)

<table>
<thead>
<tr>
<th></th>
<th>d4T</th>
<th>ZDV</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Subscapular</td>
<td>0.22</td>
<td>-0.07</td>
<td>0.75</td>
</tr>
<tr>
<td>Suprascapular</td>
<td>0.37*</td>
<td>-0.44*</td>
<td>1.04*</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.23*</td>
<td>-2.75*</td>
<td>-0.29*</td>
</tr>
<tr>
<td>Thighs</td>
<td>0.03</td>
<td>-1.54</td>
<td>0.50*</td>
</tr>
<tr>
<td>Triceps</td>
<td>-0.54</td>
<td>-0.78</td>
<td>-0.36*</td>
</tr>
</tbody>
</table>

(*)comp. *P*-value <0.05

A metabolic syndrome, defined according to NCEP-ATPIII 2005, was present in 15–20% of patients at each phase up to 72 months, whereas the prevalence of diabetes increased from 6.7% to 11.2%. A metabolic syndrome was present in 47–69% of diabetic and 15–19% on non-diabetic patients.

**Conclusion:** The prevalence of lipoatrophy increased with time in patients initiated with PI in 1997–1998. Its presence was positively related to age, duration of infection and triglycerides, and negatively to BMI and adiponectin. TNF polymorphisms were not associated with lipodystrophy and metabolic alterations. The prevalence of a metabolic syndrome was unchanged during evolution while that of diabetes increased.
**Results:** Early slopes (month 4–12) were compared with late slopes (month 16–36) (Table 1). For d4T and ZDV, most early slopes showed gains, while late slopes showed loss. There was less late slope loss for ABC. Rates of change over all follow-up visits (Table 2). Losses seen for ZDV (abdomen, thigh, triceps) and d4T (abdomen, thigh) were significantly different compared with ABC. No differences seen between d4T versus ZDV.

**Conclusions:** In this prospective evaluation, subcutaneous tissue changes varied by regimen. Similar losses demonstrated for d4T and ZDV, while ABC had gains. Differences in early versus late slopes for d4T and ZDV suggest initial recovery followed by long-term treatment effect.

### Table 2. (Abstract P-17)

<table>
<thead>
<tr>
<th>Subscapular</th>
<th>ZDV slope (P)</th>
<th>ABC slope (P)</th>
<th>Comp. P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T slope (P)</td>
<td>0.16 (0.7)</td>
<td>0.01 (1.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Suprascapular</td>
<td>-0.04 (0.9)</td>
<td>0.71 (&lt;0.01)</td>
<td>-0.22 (0.6)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>-1.07 (0.03)</td>
<td>-1.11 (&lt;0.01)</td>
<td>1.01 (0.05)</td>
</tr>
<tr>
<td>Thigh</td>
<td>-1.31 (&lt;0.01)</td>
<td>-1.32 (&lt;0.01)</td>
<td>0.06 (0.9)</td>
</tr>
<tr>
<td>Triceps</td>
<td>-0.68 (0.09)</td>
<td>-1.54 (&lt;0.01)</td>
<td>-0.14 (0.7)</td>
</tr>
</tbody>
</table>

**Results:** Nine clinicians (five HIV physicians, four plastic surgeons) scored photographs from 101 adults. The global level of concordance was 0.68 ($P < 0.001$). Concordance levels for degrees ‘zero’, ‘one’, ‘two’ and ‘three’ were 0.89, 0.59, 0.54 and 0.73, respectively ($P < 0.0001$ each). Forty-four patients classified with degrees ‘one’ ($n = 7$), ‘two’ ($n = 25$), and ‘three’ ($n = 12$) underwent a CT scan of the face. The mean and 95% confidence interval 95% CI of cheek fat in patients with degrees ‘one’, ‘two’ and ‘three’ was 4.4 cm$^3$ (95% CI: 3.0 to 5.8), 3.0 cm$^3$ (95% CI: 2.3 to 3.7), and 1.7 cm$^3$ (95% CI: 0.9 to 2.6), respectively ($P < 0.005$ each).

**Conclusions:** This simple and easy-to-use clinical classification showed good reproducibility among different investigators and discriminated against the amount of cheek fat in HIV-infected adults with facial lipoatrophy. In the absence of simple and accurate methods to measure the degree of facial lipoatrophy, this classification may be useful for clinical and research purposes.
ABSTRACT P-19

*Antiviral Therapy* 2007; 12 Suppl 2:L32

Effects of tipranavir/r (500/200 or 500/100 mg BID) in comparison with lopinavir/r (400/100 mg BID) on changes in body composition and metabolic parameters in ARV-naive patients over 48 weeks

**A Carr** 1, **R Zajdenverg** 2, **C Workman** 3, **J Gatell** 4, **P Cahn** 5, **A Ritzhaupt** 6, **W Zhang** 7 and **R Chaves** 6

1St Vincent’s Hospital, Sydney, Australia; 2Projeto Praça Onze – UFRJ Hospital Escola São Francisco de Assis, Rio de Janeiro, Brazil; 3AIDS Research Initiative, Darlinghurst, Australia; 4Hospital Clinic de Barcelona, Barcelona, Spain; 5Fundación Huesped, Buenos Aires, Argentina; 6Boehringer Ingelheim GmbH, Biberach an der Riss, Germany; 7Boehringer Pharmaceuticals Inc, Ridgefield, CT, USA

This poster abstract will also be presented as an oral; see abstract O-07 for text.

ABSTRACT P-20

*Antiviral Therapy* 2007; 12 Suppl 2:L32

Lipoatrophy (LA) and lipohypertrophy (LH) are independently associated with depression and health-related quality-of-life (HRQOL); lipoatrophy is associated with adherence

**HM Crane** 1, **C Grunfeld** 2, **RD Harrington** 1 and **MM Kitahata** 1

1University of Washington, Seattle, WA, USA; 2University of California San Francisco, San Francisco, CA, USA

**Background:** Studies of depression, adherence, and lipodystrophy have provided contradictory findings and not examined LA and LH separately. We examined the independent effect of LA/LH on depression, HRQOL, and adherence using two scoring methods for self-reported LA/LH.

**Methods:** Cross-sectional study of 311 University of Washington HIV Cohort patients. Patients completed depression (PHQ-9), HRQOL (EQ-5D), adherence, drug/alcohol use and body morphology (FRAM) assessments. We scored FRAM using categories (none, mild LA, mild LH, moderate-to-severe LA or moderate-to-severe LH), and also continuous LA/LH scores. We used linear and ordinal logistic regression to examine the association between depression, HRQOL and adherence with LA/LH controlling for covariates.

**Results:** In adjusted analyses, mean depression scores were highest among patients with moderate LA (15.8), intermediate among those with moderate LH (13.3), mild LA (10.3) and mild LH (11.2), and lowest among those without abnormalities (8.1) (P-values <0.003–0.05). In adjusted analyses using continuous LA/LH scores, each point worsening in LA was associated with a 0.4 point worsening in depression, and each point worsening in LH was associated with a 0.3 point worsening in depression (P-values <0.001). A change of ≥0.074 in HRQOL score is considered clinically important. Mean HRQOL scores were lower for patients with moderate LA (0.62, P=0.03), moderate LH (0.64, P=0.002), mild LA (0.70, P=0.005) and mild LH (0.69, P=0.001) than patients without LA/LH (0.8). When depression was also included, worse depression was significantly associated with poorer HRQOL and the association between LA/LH and HRQOL was no longer present. LA but not LH scores were associated with poorer adherence while controlling for demographic/clinical factors, depression, and HRQOL (P=0.02). Each point worsening in LA was associated with a 10% increase in risk for decreased adherence (OR 1.1, P=0.01). There was no association between adherence and LA/LH categories.

**Conclusions:** LA/LH are independently associated with poorer HRQOL, an effect that appears to be mediated through depression severity. LA but not LH is associated with poorer adherence independent of depression. Using combined or categorized LA/LH results in a loss of information that may have practical implications. In addition to potential long-term cardiovascular implications, LA/LH may impact clinical outcomes via depression and adherence.

ABSTRACT P-21

*Antiviral Therapy* 2007; 12 Suppl 2:L32

Impact of lipoatrophy on quality of life in HIV-infected individuals receiving antiretroviral therapy (ART)

**R Rajagopalan** 1, **D Laitinen** 2 and **B Dietz** 2

1Abbott Laboratories, Abbott Park, IL, USA; 2Abbott Laboratories, Ludwigshafen, Germany

**Objective:** Metabolic and morphological side effects occur in HIV-infected individuals receiving antiretroviral treatment (ART). Peripheral fat loss, particularly in the face, limbs and/or buttocks, is referred to as lipoatrophy and has been found to be highly stigmatizing and to adversely impact quality of life. Consumer Health Sciences Survey data collected in 2006 were analysed to evaluate the impact of lipoatrophy on quality of life in HIV-infected individuals receiving ART.

**Methods:** The impact of lipoatrophy was evaluated using multiple regression with item scores and mental component summary (MCS) and physical component summary (PCS) scores from the Medical Outcomes Trust questionnaire, SF-8 as dependent variables and lipoatrophy as independent variable controlling for baseline age, sex and...
HIV lipodystrophy is characterized by excess visceral adipose tissue (VAT), and/or loss of subcutaneous fat (SAT) in association with dyslipidaemia and insulin resistance, resulting in significant body dysmorphia with impaired body image and health-related quality of life (HRQOL). Treatment with tesamorelin for 26 weeks has been previously shown to significantly reduce VAT while preserving SAT. Data on body image and HRQOL are reported here.

Methods: Patients on ART with abdominal fat accumulation were randomized to tesamorelin 2 mg daily (n=273) or placebo (n=137) for 26 weeks. Standardized patient-reported outcomes were measured at baseline and week 26. Body image included belly appearance distress, belly size and belly profile silhouette assessments; HRQOL included global HRQOL, mental health, general perceived health, and symptom impact.

Results: Patients (86% male, 48 ±7 years) treated with tesamorelin reported significantly less body image distress for face, belly and composite body assessment (P<0.05 for all comparisons versus placebo). No significant changes were noted in body size parameters, but more tesamorelin-treated patients than placebo patients improved their current belly profile (P<0.05) and weight evaluation (P=0.05). Changes in belly appearance distress, composite body distress and belly profile were significantly correlated with changes in VAT (P<0.01) for tesamorelin-treated patients. Summary analogue HRQOL also improved (P=0.05), with no significant changes in symptom incidence or distress.

Conclusion: ART-related changes in body conformation are potential barriers to treatment adherence. Tesamorelin 2 mg daily treatment significantly improved body dysmorphia through improvement in body appearance distress and belly profile, resulting in improved overall HRQOL with no significant increase in symptom incidence or distress. Successful reduction of body image distress and improved HRQOL may have important implications for HIV treatment outcomes.

Objective: HARS is characterized by excess truncal fat, including visceral adipose tissue (VAT), and r-hGH reduces trunk fat and VAT. Reported here is the impact of 12 weeks (wks) of therapy with r-hGH on lean body mass (LBM) and anthropometric parameters in patients with HARS.

Methods: In a randomized, placebo-controlled, double-blind study, 322 pts with documented HIV infection and excess abdominal adipose deposition were randomized to receive either 4 mg once daily r-hGH (n=243; 207M, 36F) or placebo (n=79) for 12 weeks. This modified ITT population included all subjects who had a baseline and >1 post-baseline efficacy measurement.

Results: There were small but significant increases in total body weight (Wt) in both groups at 12 wks (P<0.05; Table 1). However, only r-hGH resulted in a significant increase in LBM (+5.9% versus -0.3%; P<0.001), whereas these parameters differed significantly in VAT (+5.6% versus +1.5%; P<0.001). Patients in the r-hGH group had a significant increase in hip circumference and decrease in waist circumference (WC, all P<0.001), whereas these parameters did not change significantly in patients on placebo. Waist to hip ratio (WHR) decreased significantly in r-hGH recipients (P<0.001).

Conclusions: A modest gain in Wt with r-hGH is associated...
with an increase in LBM, decreased total body fat and favourable anthropometric changes, including reductions in WC and WHR.

ABSTRACT P-24

_Antiviral Therapy_ 2007; 12 Suppl 2: L34

A randomized comparison of the safety of continued zidovudine plus lamivudine (Combivir, CBV) versus switching to tenofovir DF plus emtricitabine (Truvada, TVD) each plus efavirenz (EFV) in stable HIV-infected persons: results of a planned 24-week analysis

**G Moyle**¹, **M Fisher**² and SWEET Study Group

¹Chelsea and Westminster Hospital, London, United Kingdom; ²Elton John Centre, Brighton, United Kingdom

**Background:** Long-term success with antiretroviral therapy requires maintenance of adherence and avoidance of long-term toxicities. We sought to investigate if these benefits were observed when TVD was used to replace CBV.

**Methods:** A 48-week study of 220 subjects with HIV RNA <50 copies/ml stable on twice daily CBV + once daily EFV for ≥6 months randomized 1:1 to continue this regimen or switch to once daily TVD + EFV. The primary endpoint was change in haemoglobin (g/dl) at 24 weeks. Secondary endpoints included changes in fasting lipids, quality of life, CD4 and viral load. Study follow up through 48 weeks is planned.

**Results:** Two-hundred and fifty subjects were randomized, 234 received at least one dose of study medication. One-hundred and seventeen continued CBV (CBV arm), 117 switched to TVD (TVD arm). Subjects had received a median 36 months prior CBV, with 86% having received no other prior thymidine analogues. Subjects were well matched for baseline characteristics. At 24 weeks, switch to TVD maintained VL <50 copies/ml. By ITT Missing = Failure or Switch = Failure analyses, rates of viral suppression at week 24 were 89.7% (CBV) versus 94.0% (TVD).

**Conclusion:** Switching from CBV to TVD in persons receiving EFV provides a simplified once daily regimen that maintains virological control and leads to improvements in both haemoglobin levels and key lipid parameters.

ABSTRACT P-25

_Antiviral Therapy_ 2007; 12 Suppl 2: L34

Autologous fat grafts are safe and durable in HIV-infected adults with facial lipoatrophy

**J Fontdevila**¹, **J Berenguer**², **E Prades**³, **T Pujol**², **E Guisantes**¹, **JM Serra-Renom**¹, **J Gatell**⁴ and **E Martinez**⁴

¹Plastic Surgery Department, Hospital Clínic, University of Barcelona, Barcelona, Spain; ²Center for the Diagnosis by the Image, Hospital Clinic, University of Barcelona, Spain; ³Statistic evaluator, Hospital Clinic, University of Barcelona, Spain; ⁴Infectious Diseases Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain

**Objectives:** Autologous fat grafts have been less appealing than other fillers for the treatment of facial lipoatrophy in HIV-infected adults owing to potential post-operative complications and possible progressive resorption. So far, studies with autologous fat grafts have included few patients with a limited follow-up and without objective assessment of results. We designed an observational study to evaluate the safety and durability of this technique.

**Methods:** HIV patients with facial lipoatrophy and enough subcutaneous fat in any area of the body were treated infiltrating the cheeks with fat obtained by liposuction and purified by centrifugation. The volume of fat of the studied area (in height 9 mm down from nasal anterior spine, in depth from skin to bone, and in width from masseteric
Anterior rim to the nasolabial fold, was assessed using computed tomography (CT) with the software VOLUME® (Siemens AG). Measurements were performed before the surgery and 2 and 12 months after. Statistical comparisons between them were done with the paired t test or Wilcoxon t test for abnormal data distribution. Multivariate regression models were constructed to assess the variables associated with a higher fat increase from baseline. The study was approved by the Ethics Committee and each participant gave written informed consent.

**Results:** Forty-four patients (28 males, 16 females) with a median age of 46 years completed the study. Donor areas were abdomen (n=21), hump (n=15), male breast (n=7), and lateral upper trunk (n=1). Hypocorrection (14.3%) and hypercorrection and skin irregularities (6.1% each) were the only remarkable complications. Mean volumes increased from 2.9 cm³ (95% CI: 2.4–3.4) at baseline to 5.7 cm³ (95% CI: 5.2–6.2) at 2 months and 6.3 cm³ (95% CI: 5.8–6.8) at 12 months (P<0.0001 each). Factors independently associated with a higher increase from baseline until 12 months included the amount of fat infiltrated (P<0.001), regular exercise (P=0.001), treatment with statins (P=0.001), and absence of hypertension (P=0.002).

**Conclusions:** Autologous fat grafts are a safe and long-lasting option for facial lipoatrophy treatment, achieving durable results (longer than 12 months) with only one procedure without fat reabsorption, demonstrated by objective measurements (CT).

**ABSTRACT P-26**

_**Antiviral Therapy 2007; 12 Suppl 2:**_ L35

**Effectiveness and long-term durability of autologous fat transplant for HIV-related face lipoatrophy**

_G Orlando1, G Guaraldi1, N Squillace1, D De Fazio2, A Rottino2, P Bonucci2, E Padalino2, A Grisotti2, G Nardini1, B Beghetto1 and R Esposito1_

1Infectious Disease Clinic, University of Modena and Reggio Emilia, Italy; 2Plastic Surgery Division, Villa Salus Hospital Reggio Emilia, Italy

Objective: Autologous fat transplant (AFT) according to Coleman technique is an effective option for surgical treatment of HIV-related face lipoatrophy; nevertheless, both patients and surgeons are often concerned about durability of this procedure in the fear of early fat reabsorption in the recipient area. The purpose of this study was to evaluate effectiveness and long-term durability of AFT with a 104-week follow up in patients who were treated with a single surgical procedure and in those who needed lipofilling reintervention or aesthetic correction with subcutaneous filler.

**Methods:** Forty-five patients undergoing AFT were analysed. Patients were evaluated every 24 weeks after surgery and offered to have aesthetic correction with either AFT reintervention or with polyactic infiltrations. Aesthetic satisfaction was evaluated with a 0 to 100 Visual Analogue Scale (VAS) and with Assessment of Body Change and Distress questionnaire question 7 (ABCD7). Objective outcome was assessed with a single operator cheeks ultrasound to measure cheek thickness increase. All surgical procedures were provided out of charge for the patients.

**Results:** Baseline characteristics of the 45 patients: 21 (46.7%) female, mean age 47.6 ±7.2 years, mean CD4 counts 602 ±305/μl, mean HIV-RNA log viral load 2.5 ±0.9, CDC group C 35.6% and HIV since 156 ±3 months. Twenty-three (51.1%) had a single surgical treatment (cases) and 22 (48.9%) needed reintervention (controls) or with polylactic infiltrations. No statistically significant differences emerged between cases and controls in baseline clinical, viro-immunological and anthropometric variables in univariate analysis. Two years after the first AFT cheek thickness increased significantly (right cheek +6.2 ±4.4 mm, left cheek +6.5 ±4.3 mm, P=0.0001), while VAS and ABCD7 scores expressed an important improvement of face and body image satisfaction (respectively +3.3 ±2.8 and -0.8 ±0.7, P=0.0001) in all patients without difference among cases and controls.

**Conclusions:** AFT is a safe and effective procedure for face lipoatrophy treatment. In our study its major limitation was...
the need of reintervention in a long follow-up for almost half of patients. Nevertheless, patients reached an important augmentation of cheek thickness and expressed a significant improvement of face and body image satisfaction.

**ABSTRACT P-27**

_Antiviral Therapy_ 2007; 12 Suppl 2:L36

_Efavirenz and atazanavir induce leukocyte-endothelial cell interactions in the microvasculature_

*A Alvarez, F Baixauli, M Andrade, A Blas-García, I Boscá and JV Esplugues_

Department of Pharmacology, Faculty of Medicine, University of Valencia, Spain

**Background:** Combined antiretroviral therapy is associated with atherosclerosis and cardiovascular complications. Since patients receive various drugs simultaneously it has been difficult to determine the role of each particular antiretroviral group or specific agent in these side effects. The present study was designed to analyse the acute effects of three widely used antiretroviral agents, each from a different pharmacological group, on one of the first steps in the pathogenesis of atherosclerosis – leukocyte recruitment.

**Methods:** Leukocyte rolling, adhesion and emigration were monitored in the mesenteric postcapillary venules of anaesthetized rats by intravital video microscopy. We compared the effects of the nucleoside reverse transcriptase inhibitor lamivudine, the non-nucleoside reverse transcriptase inhibitor efavirenz and the protease inhibitor atazanavir. All drugs were administered orally 4 h before measurements and doses were chosen according to the literature in order to mimic plasma levels clinically present (3–30 μM).

**Results:** As shown in the table (Table 1), the acute administration of lamivudine did not cause any effect on leukocyte parameters. Atazanavir promotes a significant increase in leukocyte rolling flux, adhesion and emigration. Efavirenz induces a significant increase on leukocyte rolling and adhesion; however, it had no effect on leukocyte emigration.

**Discussion:** Our results indicate that acute exposure to atazanavir or efavirenz, but not lamivudine, induces leukocyte recruitment. This suggest that both drugs can be implicated in the preliminary events that lead to the cardiovascular complications observed in HIV-infected patients on combined antiretroviral therapy.

**ABSTRACT P-28**

_Antiviral Therapy_ 2007; 12 Suppl 2:L36

_Coronary artery disease in HIV-infected patients_

*RG Micheletti, GA Fishbein, MC Fishbein, EJ Singer and JS Currier_

University of California Los Angeles, Los Angeles, CA, USA

**Objectives:** Studies suggest HIV+ patients have an increased risk of coronary artery disease, yet little is known about the histopathology, severity or distribution of lesions.

**Methods:** The coronary arteries of 66 patients with advanced AIDS (age < 55) were dissected at 3 mm intervals and graded histologically for percent luminal stenosis by intimal lesions, percent of intima involved with lipid, and the extent of intimal calcification on a scale of 0 to 3. Chart reviews were conducted for medical histories, antiretroviral therapies, and coronary artery disease (CAD) risk factors.

**Results:** The average patient age was 43 ± 6.86%, were men, and 40% were smokers. Results of the histological examination are shown in Table 1.

**Conclusions:** Young to middle-aged patients dying from advanced AIDS have a burden of coronary artery disease that at times results in clinically significant narrowing and heavy calcification that could be detected by imaging studies. Based on clinical experience and published reports of the natural history of atherosclerosis, the pattern of disease and plaque composition are typical of atherosclerosis that occurs in HIV patients. Comparison of these data to a large age and sex-matched control population is necessary before further conclusions can be drawn.

---

**Table 1. (Abstract P-27)**

<table>
<thead>
<tr>
<th>Treatment, mg/kg</th>
<th>Rolling, cells/min</th>
<th>Adhesion, cells/100 μm</th>
<th>Emigration, cells/field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>31.9 ±1.1</td>
<td>2.4 ±0.2</td>
<td>4.2 ±0.6</td>
</tr>
<tr>
<td>Lamivudine 100</td>
<td>34.2 ±6.4</td>
<td>4.4 ±0.7</td>
<td>3.4 ±1.0</td>
</tr>
<tr>
<td>Atazanavir 100</td>
<td>59.8 ±16.6*</td>
<td>16.1 ±4.3†</td>
<td>7.5 ±1.7*</td>
</tr>
<tr>
<td>Efavirenz 50</td>
<td>16.8 ±2.1</td>
<td>5.0 ±1.4</td>
<td>4.8 ±0.4</td>
</tr>
<tr>
<td>Efavirenz 85</td>
<td>24.5 ±2.9</td>
<td>7.2 ±1.2†</td>
<td>6.0 ±1.7</td>
</tr>
<tr>
<td>Efavirenz 160</td>
<td>60.2 ±15.6†</td>
<td>5.8 ±1.5*</td>
<td>5.2 ±1.6</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01 relative to control values. All values are mean ±SEM of at least five experiments.
Table 1. (Abstract P-28)

<table>
<thead>
<tr>
<th></th>
<th>LM</th>
<th>LAD</th>
<th>LCX</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average narrowing per artery, percent (±SD)</td>
<td>26.8 (±21.5)</td>
<td>50.5 (±26.0)</td>
<td>37.4 (±25.3)</td>
<td>43.3 (±24.9)</td>
</tr>
<tr>
<td>Number of arteries with ≥75% stenosis (%)</td>
<td>2/65 (3.1%)</td>
<td>17/66 (25.8%)</td>
<td>7/66 (10.6%)</td>
<td>10/66 (15.2%)</td>
</tr>
<tr>
<td>Vessel sections with grade 2 or 3 calcification (%)</td>
<td>20/66 (30.3)</td>
<td>40/66 (60.6)</td>
<td>20/66 (30.3)</td>
<td>23/66 (34.8)</td>
</tr>
<tr>
<td>Average intimal lipid content, percent (±SD)</td>
<td>25.6 (±24.9)</td>
<td>37.0 (±27.0)</td>
<td>29.0 (±27.7)</td>
<td>34.5 (±28.9)</td>
</tr>
</tbody>
</table>

LAD, left anterior descending; LCX, left circumflex; LM, left main; RCA, right coronary artery.

ABSTRACT P-29

*Antiviral Therapy* 2007; 12 Suppl 2:l37

Rosiglitazone inhibits CIMT progression but may reverse plaque area in low-moderate risk HIV patients

KW Johns1, M Harris2, JS Montaner1,3, H Zhang3, J Singer2,4, SY Chan1,4, GB Mancini1,5 and GP Bondy1,4

1University of British Columbia, Vancouver, BC, Canada; 2Canadian HIV Trial Network, Vancouver, BC, Canada; 3Centre for Excellence in HIV/AIDS, Vancouver BC, Canada; 4Healthy Heart Lipid Clinic, St. Paul’s Hospital, Vancouver, BC, Canada; 5Cardiovascular Image Core Laboratory, Vancouver BC, Canada

Background: Rosiglitazone is an oral anti-diabetic medication that decreases insulin resistance leading to improvements in glucose and lipid metabolism that has shown a favourable effect on the vascular system as measured by carotid intima media thickness (CIMT), a widely used surrogate marker of atherosclerosis.

Objectives: This study sought to determine if rosiglitazone, would alter vascular progression as measured by CIMT in non-diabetic patients with HIV-lipodystrophy and metabolic abnormalities.

Methods: Fifty patients with HIV and at least one CVD risk factor were randomly assigned to receive either rosiglitazone (8 mg once daily) or placebo (n=25) for 48 weeks. The primary endpoint was change in CIMT. Secondary endpoints covered changes in plaque area.

Patients: Respective demographics for rosiglitazone versus placebo groups were as follows: age (years) = 50.4 versus 47; years with HIV = 15.8 versus 10.4; systolic blood pressure (mmHg) = 122 versus 120; smokers = 25.0% versus 41.2%; fasting blood glucose (mmol/l) = 5.3 versus 5.2; metabolic syndrome = 45.0% versus 59.1%; and Framingham risk score = 65% versus 68.2% low risk, and 35% versus 31.8% moderate risk.

Results: Treatment analysis with CIMT as the outcome was performed using ANCOVA and revealed an adjusted mean difference of -0.0043 mm (95% CI -0.0412–0.0326, P=0.8193). ANCOVA was again used to assess treatment effect on total plaque area (TPA) using logTPA as the outcome. The resulting adjusted mean difference was -0.0359mm² (95% CI -0.2673–0.1955, P=0.7635).

Conclusions: In spite of the analyses not reaching statistical significance, encouraging trends did emerge from the treatment effect analysis. CIMT thickening was slowed in the rosiglitazone group relative to placebo and secondary analysis examining TPA was promising as the rosiglitazone group did show a decrease in TPA relative to the placebo group. The latter finding is relevant since this is the first study to demonstrate a decrease in TPA with thiazolidinedione therapy in this population.

This study was underpowered due to the small sample size and short duration. Future directions would include conducting further trials examining the effect of rosiglitazone on CIMT and TPA wherein the group size and the study duration are each increased, which will increase the likelihood of more significant and conclusive results.

ABSTRACT P-30

*Antiviral Therapy* 2007; 12 Suppl 2:l37

The anti-inflammatory agent salsalate improves HIV-related endothelial dysfunction: a pilot study

SK Gupta, RM Johnson, C Saha, KJ Mather, J Rehman and MP Dubé

Indiana University School of Medicine, Indianapolis, IN, USA

Aim: HIV-infected patients may be at higher risk of cardiovascular events when not receiving antiretrovirals. HIV may directly activate the key inflammatory regulator NF-κβ, thereby increasing systemic inflammation. Therefore, we hypothesized that reduction of systemic inflammation with salsalate, an NF-κβ inhibitor, would improve endothelial dysfunction, a precursor to atherosclerosis, in those not receiving CART.

Methods: An open-label, single-arm study of salsalate, 1,500 mg twice daily, was performed in 11 HIV-infected adults who had not received CART for at least 6 months and had CD4 counts above 350/μl. Exclusion criteria included known vascular or pro-inflammatory conditions, diabetes, hypertension or receipt of lipid-lowering, anti-inflammatory or antiretroviral drugs during the study.
The Wilcoxon signed-rank test was used to evaluate changes in flow-mediated dilation (FMD) of the brachial artery at 4 and 8 weeks (primary objectives) and changes in metabolic, inflammatory and endothelial activation markers at 8 weeks (secondary objectives).

**Results:** Median age, CD4 count, and viral load of the subjects were 38 years, 449/μl and 21,400/ml, respectively; 55% were black and 73% were men. Median baseline FMD was low at 2.7% (n=11; range 0.2–7.1%). FMD did not significantly improve after 4 weeks (n=9; median absolute increase 1.2% [range, -2.3–10.6%]; P=0.4), but did significantly increase after 8 weeks (n=8; median absolute increase 4.2% [range, -2.1–12.9%]; P=0.02). Two subjects stopped study drug before week 4 due to symptomatic elevations in hepatic transaminases; two other subjects experienced minor elevations at week 4 that resolved with dose reduction. In exploratory analyses at week 8, median HOMA-IR (P=0.04), IP-10 (P=0.02), and TIMP-1 (P=0.01) significantly increased, while median spot urine albumin/creatinine (P=0.02), adiponectin (P=0.04) and vWF (P=0.02) significantly decreased. No significant changes occurred in hsCRP, IL-6, MCP-1, VCAM or ICAM. Additional data from multiplex ELISA quantitation of serum inflammatory markers are being analysed.

**Conclusions:** Salsalate improved endothelial function in HIV-infected patients not receiving CART. These results suggest that systemic inflammation might play a role in the development of endothelial dysfunction and cardiovascular events in HIV-infected patients. More research is needed to gain insight into the mechanism(s) of reversible endothelial dysfunction associated with HIV infection.

**ABSTRACT P-31**

*Antiviral Therapy* 2007; 12 Suppl 2:L38

Association of antiretroviral therapy with fibrinogen levels in HIV infection

E Madden1, GA Lee1,2, R Scherer1, C Wanke2, D Kotler3, S Heymsfield5, P Bacchetti1, M Shlipak1,2 and C Granfeldt1,2

1San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA; 2University of California, San Francisco, CA, USA; 3Tufts University, Boston, MA, USA; 4St. Luke’s-Roosevelt Hospital, New York, NY, USA; 5Merck Research Laboratory, Rahway, NJ, USA

**Background:** HIV infection is thought to be associated with an increased risk of coronary artery disease, but the contributing factors are not well understood. Fibrinogen is an inflammatory factor that is associated with atherosclerosis. Adiposity is associated with increased fibrinogen and previous studies of the association of antiretroviral therapy with fibrinogen did not adjust for differences in adipose tissue. We therefore assessed the relationship of fibrinogen to HIV-associated factors, including antiviral therapy, adjusting for total and regional adiposity.

**Methods:** Cross-sectional analysis of fibrinogen levels and associated factors in 1,131 HIV-infected participants in the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM).

**Participants:** A random sample of geographical and ethnically diverse HIV-infected participants and population-based sample of healthy Caucasian and African-American men and women.

**Results:** Median fibrinogen levels were 11% higher in HIV-infected subjects currently using any protease inhibitor compared with those not using a protease inhibitor (P<0.0001). The strongest univariate associations were with the individual protease inhibitors, ritonavir and indinavir. Subjects taking indinavir boosted with ritonavir had fibrinogen levels 8% higher than those on indinavir alone (P=0.049). Lower levels of fibrinogen were seen in those HIV-infected subjects currently using any of the non-nucleoside reverse transcriptase inhibitors (NNRTI) compared with those not using an NNRTI (nevirapine -14.4%, P<0.0001; efavirenz -7%, P=0.0002). The positive associations of ritonavir and indinavir and the negative associations of efavirenz and nevirapine with fibrinogen levels persisted after multivariable analysis and were independent of other antiretroviral use, as well as adiposity and fat distribution.

**Conclusions:** Specific antiviral therapies have different associations with fibrinogen levels. Protease inhibitors are associated with increased fibrinogen levels, which may contribute to increased risk of atherosclerosis in HIV-infected subjects. Conversely, NNRTIs are associated with lower fibrinogen levels, which may decrease the risk of atherosclerosis.

**ABSTRACT P-32**

*Antiviral Therapy* 2007; 12 Suppl 2:L38

Lack of association between antiretroviral therapy and predictors of endothelial function and cardiovascular disease (CVD) risk among HIV-infected persons on long-term HAART

K Mondy, L de las Fuentes, N Önen, A Waggoner, C Bopp, S Lasso-Claxton, V Davilá-Román and K Yarasheski

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

**Aim:** Controversy exists with regard to CVD risk factors in HIV+ persons. We assessed multiple metabolic and clinical predictors of endothelial function in HIV+ subjects and compared results with HIV-negative controls. Correlation with carotid intima media thickness (cIMT) and Framingham Risk Score (FRS), other well-known surrogates for CVD risk, were also performed.
Methods: Cross-sectional study of healthy, HIV+ subjects (n=45) on stable HAART. Flow-mediated vasodilation (FMD) of the brachial artery, cIMT, oral glucose tolerance test, DEXA, C-reactive protein, and fasting lipids were obtained on all subjects. Multiple linear regression modeling was used to determine significant predictors of FMD and cIMT based on data from univariate models. HIV-negative controls were matched by age, sex and race (n=45).

Results: Among HIV+, mean age was 42, 49% African-American, 33% women, 33% hypertensive, 31% smokers, mean body mass index (BMI) 28.7 kg/m², median CD4 count 536 cells/μl, mean time on HAART 74 months. Eighty-seven percent had HIV RNA <50 copies/ml. No subjects were diabetic or using illegal drugs. In multivariate analyses, predictors of endothelial dysfunction (lower FMD) in HIV+ were lower brachial artery diameter, worsening insulin resistance, and abstinence from alcohol (r²=0.411, P<0.05); predictors of higher cIMT were hypertension (HTN) and increasing trunk/limb fat ratio (r²=0.449, P<0.01). There was no association between type or duration of HAART and either FMD or cIMT. Compared with controls, HIV+ subjects had similar mean FMD, cIMT and FRS (11.87 versus 12.86% for FMD, 0.69 versus 0.68 mm for cIMT, 0.5 versus -0.4 for FRS, P=NS for all). Groups did not differ significantly by HTN, BMI, insulin or smoking but HIV+ had lower LDL- and HDL-cholesterol, and higher triglycerides compared with controls (P<0.05). Among HIV+ there was good correlation between FMD and cIMT (r=0.37, P=0.01 by Spearman’s rank), cIMT and FRS (r=0.54, P<0.001), but not FMD and FRS.

Conclusions: Persons with well-controlled HIV had a CVD risk comparable to matched controls based on FMD, cIMT and FRS. Despite good correlation between FMD and cIMT, insulin resistance was a stronger predictor of endothelial dysfunction (FMD), whereas traditional CVD risk factors were more predictive of cIMT.

Acknowledgement: Supported by the NIH.

ABSTRACT P-33

Antiviral Therapy 2007; 12 Suppl 2:139

All-cause death and markers of early atherosclerosis in a cohort of HIV-infected subjects from nutrition for healthy living (NFHL)

A Mangili1,2, J Gerrior1, S Abraham1, J Polak2 and C Wanke1,2

1Tufts University School of Medicine, Boston, MA, USA; 2Tufts-New England Medical Center, Boston, MA, USA

Objectives: HIV-infected individuals are at increased risk of cardiovascular (CV) disease. Antiretroviral regimens have been inconsistently linked to adverse CV events. There is increasing evidence that uncontrolled viral replication could contribute to CV risk. We examined the association of all-cause death with surrogate markers of atherosclerosis, carotid intima-media thickness (c-IMT) and coronary calcium score (CCS).

Methods: We measured common and internal c-IMT by B-mode ultrasonography and CCS by high-resolution computed tomography in 327 NFHL participants. We compared c-IMT and CCS in those who died and those who are alive using Chi-square test for binary and ANOVA for continuous outcomes.

Results: Thirty-one (9.4%) participants have died since study enrollment. There was no significant difference between those who died and the rest of the cohort with regards to age, sex, race, smoking status, blood pressure, BMI, triglycerides, total cholesterol, LDL-C or glucose. Those who died had lower HDL-C and higher CRP than those alive (36 versus 42, P=0.046; 4.8 versus 2.7, P=0.028). CD4 count was lower and log10 viral load was higher in those who died compared to those alive (343 versus 470, P=0.027; 3.8 versus 3.0, P<0.0001). HAART, PI and NNRTI use were similar in both groups. Common c-IMT and CCS was significantly higher in those who died compared to those alive (0.69 mm versus 0.59 mm, P=0.002; 161 versus 34, P=0.004), but internal c-IMT did not significantly differ (0.79 mm versus 0.73 mm, P=0.54). Participants who died were more likely to have common c-IMT >0.8 mm than those who are alive (23% versus 7%, P=0.005). Internal c-IMT >1.0 mm and CCS>100 was present more frequently in those who died (23% versus 14%, P=0.19, 17% versus 7%, P=0.118). In a multivariate model adjusted for sex, race and smoking, participants who died had significantly higher common c-IMT and CCS compared with those alive, but not higher internal c-IMT.

Conclusions: Our study demonstrates that all-cause death in HIV-infected individuals is associated with more abnormal surrogate markers of atherosclerosis when compared with those who are alive, despite being similar with respect to traditional CV risk factors. Abnormal HIV-specific parameters, as well as low HDL-C and high hs-CRP are more common in those who died. Assessment of subclinical atherosclerosis in HIV infection could help identify those at greater risk of death. Therapy should include a stronger focus on HDL-raising and CRP-lowering strategies to prevent future adverse CV events and death in this population.
ABSTRACT P-34

Antiviral Therapy 2007; 12 Suppl 2: L40

Framingham risk score (FRS) analysis in treated HIV patients: modelling differential effects on risk reduction of lipid-lowering therapy versus stopping cigarette smoking

J Falutz and L Rosenthall
Montreal General Hospital, McGill University Health Centre, Montreal, Canada

Objectives: FRS assessment reliably predicts the increased CVD risk occurring in treated HIV patients (pts). We modelled the effects of FRS of lipid-lowering therapy (LLRx) versus smoking cessation.

Methods: FRS was determined by chart review in a male HIV cohort, and results assigned to low (<9% 10-year risk), moderate (10–19% 10-year risk) and high (>20% 10-year risk) risk categories. The FRS was recalculated assuming that: (1) cigarette smokers were reclassified as non-smokers; and (2) pts with increased total cholesterol (TC) for age achieved a 25% decrease in TC to LLRx, the average published response in HIV pts. Results are reported as medians (±95% CI). Comparison of the altered proportion of pts in each FRS category in both models was by Fisher’s exact test. One-way ANOVA determined the overall effect of risk reduction on the cohort’s FRS score.

Results: The median age in 279 stable, treated pts (median CD4=420, [384–462], 64% with VL<50) was 46 years (45–48), and FRS was 6.0 (5.0–6.0). There were 179 pts (65%) in the low-risk group, 71 (25%) in the moderate-risk group and 29 (10%) in the high-risk group. Overall 50% of pts smoked cigarettes. Recalculating the FRS with all smokers as non-smokers changed the distribution so that: 209 (75%) were low-risk (17% decrease, \( P=0.008 \)), 59 (21%) were moderate-risk (17% decrease, \( P=NS \)), and 11 (4%) were high-risk (62% decrease, \( P=0.005 \)). Recalculating the FRS after 25% TC reduction showed that: 209 (75%) were low-risk (17% increase, \( P=0.008 \)); 59 (21%) were moderate-risk (17% decrease, \( P=NS \)), and 11 (4%) were high-risk (62% decrease, \( P=0.005 \)).

Conclusion: Significantly more pts were in the low-risk group after smoking cessation than after reducing TC. In the initially moderate risk group, lowering TC had no effect on risk reduction, whereas smoking cessation significantly reduced this risk. Overall, smoking cessation may lead to a greater benefit on 10-year CVD risk reduction than TC reduction.

ABSTRACT P-35

Antiviral Therapy 2007; 12 Suppl 2: L40

Effect of alternate treatment protocols on the incidence of electrocardiographic abnormalities among HIV-infected adults in the SMART trial

R Prineas1, M Roediger2, A Carr3, W El-Sadr4, S Esser5, G Grandits6, B Knysz7 and A Palfreeman8 for the SMART Study Group and INSIGHT

1University of Wake Forest School of Medicine, Division of Public Health Sciences, Winston-Salem, USA; 2University of Minnesota School of Public Health, Biostatistics, Minneapolis, USA; 3St Vincents Hospital, Sydney, Australia; 4Columbia University, New York, USA; 5Universittklinikum Essen, Essen, Germany; 6University of Minnesota, Biostatistics, Minneapolis, USA; 7Wroclaw University, Infectious Diseases, Wroclaw, Poland; 8Edith Cavell Hospital, Sexual Health, Peterborough, UK

This poster abstract will also be presented as an oral; see abstract O-11 for text.

ABSTRACT P-36

Antiviral Therapy 2007; 12 Suppl 2: L40

Clinically evident facial lipoatrophy is associated with a higher cardiovascular risk

E Martinez on behalf of RICVih Study group
Hospital Clinic, Barcelona, Spain; and other 125 Spanish hospitals, Spain

Objectives: A direct role of lipoatrophy in the risk for cardiovascular disease was not confirmed in the DAD Study. We hypothesized that the accuracy of lipoatrophy assessment in the DAD Study could have been suboptimal. We assessed the impact of clinically evident facial lipoatrophy defined by a validated classification on the estimation of cardiovascular risk in a large cohort of HIV-infected patients in Spain.

Methods: During two consecutive weeks, every clinically stable HIV-infected adult with a regular visit to any of 126 hospitals distributed throughout Spain was offered to participate. We collected data on demographics, HIV infection, antiretroviral therapy, family history of premature cardiovascular disease, tobacco smoking, prior diagnosis of hypertension, dyslipidaemia, and diabetes mellitus. Weight, height, blood pressure, waist circumference, fasting glucose, triglycerides, total-, LDL-, and HDL-cholesterol were also measured. Facial lipoatrophy was assessed according a validated clasification. This classification includes four categories according to the skin shape from lower orbital cavity to nasogenian wrinkle: 0 (slight protrusion, normal) 1 (flattening), 2 (slight shrinking) and 3 (deep shrinking with evidence of zygomatic major muscle).
For the purpose of study, facial lipoatrophy was defined as categories 2 or 3. Cardiovascular risk was estimated through Framingham score (ATP III).

Results: There were 1,181 (37%) of 3,174 patients with facial lipoatrophy. Patients with facial lipoatrophy were older (42 versus 39 years, \( p<0.001 \)) and had higher prevalence of hypertension (26% versus 21%, \( p<0.001 \)), diabetes (11% versus 6%, \( p<0.001 \)), obesity (7% versus 5%, \( p<0.001 \)), metabolic syndrome (14% versus 7%, \( p<0.001 \)) and prior ischaemic disease (4% versus 3%, \( p<0.028 \)), although lower prevalence of tobacco smoking (60% versus 67%, \( p<0.001 \)) than those without. The proportion of patients with triglycerides <200 mg/dl (63% versus 77%, \( p<0.001 \)), total cholesterol <200 mg/dl (61% versus 67%, \( p<0.001 \)), and non-HDL-cholesterol <130 mg/dl (34% versus 43%, \( p<0.001 \)) was lower in patients with facial lipoatrophy than in those without. The estimated 10-year cardiovascular risk in patients with and without facial lipoatrophy was low (<5%) in 37% versus 48%, moderate (5–10%) in 34% versus 31%, moderate-high (10–20%) in 12% versus 9%, and high (>20%) in 18% versus 11%, respectively (\( p<0.001 \)).

Conclusion: Clinically evident facial lipoatrophy was associated with a higher cardiovascular risk in HIV-infected patients in Spain.

**ABSTRACT P-37**

*Antiviral Therapy 2007; 12 Suppl 2*L41

The rate at which therapy-naive patients develop metabolic syndrome when treated and its association with different components of antiretroviral therapy: the Swiss HIV Cohort Study

J Young1, T Glass1, R Weber2, E Bernasconi2, M Rickenbach4, HJ Furrer5, M Cavassini4, P Vernazza6, B Hirschel7, M Battegay1 and HC Bucher1

1University Hospital Basel, Switzerland; 2University Hospital Zurich, Switzerland; 3Regional Hospital Lugano, Switzerland; 4University Hospital Lausanne, Switzerland; 5University Hospital Bern, Switzerland; 6Canton Hospital St Gallen, Switzerland; 7University Hospital Geneva, Switzerland

This poster abstract will also be presented as an oral; see abstract O-10 for text.

**ABSTRACT P-38**

*Antiviral Therapy 2007; 12 Suppl 2*L41

The role of virological and immunological parameters on the diagnosis of metabolic syndrome in HIV-associated lipodystrophy

N Squillace1, G Guaraldi1, G Orlando1, A Roverato2, G Nardini1, B Beghetto1 and R Esposito1

1Department of Medicine and Medical Specialties, Infectious Diseases Clinic, University of Modena and Reggio Emilia, Modena, Italy; 2Department of Statistics Sciences, University of Bologna, Bologna, Italy

Objectives: The aim of our study is to analyse metabolic syndrome (MS) prevalence in a cohort of HIV patients and to apply a statistical model to HIV viro-immunological and MS parameters to explore relations among variables.

Methods: A cross-sectional study of consecutive HIV patients attending the Metabolic Clinic (MC) of Modena University (Italy) using NCEP-ATP III MS criteria. The interaction model was analysed with the statistical software MIM (http://www.hypergraph.dk/).

Results: Three-hundred and sixty-one patients were evaluated for anthropology, DEXA, triglycerides (TG), HDL-cholesterol (HDL), glucose (Glu), insulin, waist circumference (WC), and blood pressure (BP). Patients with MS (25.4% of our sample) differed significantly from patients without MS for the following anthropometric and metabolic variables: BMI (mean 24.9 [SD 3.7] versus 22.6 [3]; \( p<0.0001 \)), WHR (0.99 [0.07] versus 0.94 [0.07]; \( p<0.0001 \)), WC (91.34 [10.3] versus 83.86 [8.8]; \( p<0.0001 \)), trunk fat (7,021.05 [3,765.06] versus 5,736.00 [2,845.23]; \( p<0.0001 \)), HOMA-IR (6.9 [8.86] versus 4.01 [6.4]; \( p<0.0001 \)), HDL (34.55 [10.14] versus 23.25 [14.15]; \( p<0.0001 \)) and TG (283.3 [217.48] versus 202.38 [196.85]; \( p<0.0001 \)). We elaborated a statistical interaction model between the following variables: CD4 absolute count, HIV viral load, antiretroviral therapy, HDL and TG. This model showed that HIV appears to be a cause of metabolic syndrome because of its primary effect on HDL and TG mean, antiretroviral therapy seems to be directly related only to TG.

Conclusions: These results might help to explain the dual role of antiretroviral therapy on cardiovascular risk. We could argue that the therapy reduces cardiovascular risk, because it suppresses HIV replication which is a risk factor for the development of metabolic syndrome; on the other hand, therapy produces metabolic alterations such as insulin resistance that increase cardiovascular risk.
ABSTRACT P-39
Antiviral Therapy 2007; 12 Suppl 2:L42

Cardiovascular disease risk analysis in treated HIV males: does use of combined Framingham risk score (FRS) and metabolic syndrome (MetS) diagnosis improve the identification of patients at increased CVD risk?

J Falutz and L Rosenthall
Montreal General Hospital, McGill University Health Centre, Montreal, Canada.

Objectives: Treated HIV patients (pts) have an increased CVD risk, which is accurately identified using the FRS. MetS is also associated with increased CVD risk. We evaluated whether combining FRS and MetS diagnoses identifies a subgroup of pts at higher risk than using the FRS alone.

Methods: The FRS and MetS diagnoses were determined by chart review in a male HIV cohort. MetS was diagnosed by NCEP, WHO, and IDF criteria. Within each FRS group (low ≤9% 10-year risk, moderate =10–19% 10-year risk, and high ≥20% 10-year risk), pts meeting at least one MetS criteria were identified. Results are expressed as median (±95% CI). Differences in the proportions of MetS-associated diagnostic criteria in the MetS positive versus MetS negative pts in each FRS group was determined by Chi-square analysis. Comparison of available DXA-derived trunk fat indices between MetS positive and MetS negative pts was similarly determined.

Results: FRS assessments and MetS diagnoses were available in 256 stable, treated HIV males (median CD4 = 420 [391–462], 56% with VL<50). DXA scans were available in 57 pts with similar HIV virological and metabolic parameters to the 199 pts without DXA scans. There were 144 pts (56%) in the low-risk group, 38 (23%) in the moderate-risk group and 26 (10%) in the high-risk group. In the low-risk group, 45 (31%) also had MetS; in the moderate-risk group, 17 (29%) had MetS; and in the high-risk group, 14 (54%) had MetS. In the low-risk group, MetS-positive pts had significantly increased waist circumference (P=0.000), increased BMI (P=0.000), low HDL (P=0.01), increased triglycerides (TG) (P=0.000), increased BP (P=0.000) and DXA-derived trunk fat to total body mass ratio (P=0.002), compared with low-risk MetS negative pts. Similar results were found comparing MetS-positive pts with MetS-negative pts in the moderate FRS group. No differences in these parameters occurred between high-risk MetS-positive pts and -negative pts.

Conclusion: A diagnosis of MetS in pts with FRS low or moderate CVD risk identifies a subgroup of pts with potentially greater 10-year CVD risk than predicted by the FRS alone.

ABSTRACT P-40
Antiviral Therapy 2007; 12 Suppl 2:L42

Heart for HAART. A novel screening programme for cardiovascular risk in HIV-infected populations

V Carter, I Woolley, N Dervan, E Ridley, K Watson and A Mijch
1Nutrition Department, The Alfred Hospital, Melbourne, Australia; 2Infectious Diseases, The Alfred Hospital, Melbourne, Australia

Aim: There has been an increasing appreciation of the role HIV and its treatment can play in cardiovascular events in HIV-infected persons. However, optimal approaches to screening and indicators for intervention remain unclear. Despite increasing physician awareness, fasting lipids are not routinely performed and cardiovascular disease (CVD) risk is not routinely assessed in our general HIV clinic. We aimed to develop an awareness, raising health promotion programme to address this.

Method: Since 2003 we have had an annual CVD risk screening programme coinciding with World AIDS Day known as ‘Heart for HAART’. The programme is promoted externally and internally and invites HIV-infected patients and/or their primary carers to self refer. The screening is completed by the dedicated lipodystrophy clinic Dietitian for a 2-week period. Data collected included BMI, glucose, lipids and blood pressure (BP). Ten year CVD risk was determined using the Framingham equation and referral for specialised consultation in our dedicated lipodystrophy clinic could then be made.

Results: Up to 38 patients have been screened annually. In 2005, 22 individuals were screened for hypertension, increased lipids and diabetes. Indications for further intervention were common. Four participants had diabetes, one was diagnosed through this screening process. Two participants were on antihypertensives; the other 25 had a diastolic BP >90 (range 90–106). Ten participants had a known history of hyperlipidaemia; nine had cholesterol >5.5 mmol/l (range 5.5–8.7 mmol/l), ten had triglycerides >2.0 mmol/l (range 2.03–6.87 mmol/l). Nine participants were current smokers. Six participants had a ‘high’ (>20%) 10 year calculated CVD risk with one patient having a 10 year CVD risk of 30%.

Conclusion: Primary health promotion activities such as the ‘Heart for HAART’ programme can unveil previously unappreciated opportunities for intervention and potential reduction of CVD risk in an HIV-infected population.
ABSTRACT P-41

Antiviral Therapy 2007; 12 Suppl 2:L43

Myeloperoxidase level does not predict future cardiovascular events in HIV-infected subjects

D El-Bejjani1, S Hazen2, W Mackay3, T Hulgan4, NE Glass4, M Tungsiripat2 and GA McComsey5

1MetroHealth Medical Center and Case Western Reserve University, Cleveland, OH, USA; 2Cleveland Clinic Foundation, Cleveland, OH, USA; 3Center for AIDS Research of Case Western Reserve University, Cleveland, OH, USA; 4Vanderbilt University School of Medicine, Nashville, TN, USA; 5Rainbow Babies and Children's Hospital and Case Western Reserve University, Cleveland, OH, USA

Objectives: Studies have linked increased myeloperoxidase (MPO) levels to high cardiovascular (CV) risk. The value of MPO as a CV marker in the HIV population has not been investigated.

Methods: Medical records from the John T Carey Special Immunology Unit of Case Medical Center, Cleveland, OH and the Comprehensive Care Center, Nashville, TN were reviewed to identify HIV+ patients with a documented CV event (myocardial ischaemia/infarction or stroke) and stored plasma samples within 12 months prior to the event. HIV+ adults with no CV history and with available stored plasma samples were age- and gender-matched 1:1 to cases. MPO levels were measured in the stored plasma drawn prior to the CV event. We collected CV risk factors, HIV disease and antiretroviral (ARV) history. Data were analysed using Wilcoxon signed rank and McNemar’s tests.

Results: We identified 128 subjects (64 case-control pairs); 94% male and median age 46 (26–70) years. Both groups were similar for demographics, HIV and ARV history. Median [interquartile ranges] MPO levels (pmol/l) were lower in cases versus controls: 290 [236–330] versus 314 [250–461]; P=0.003. Cases were more likely to have other CV risk factors, including smoking (84% versus 63%; P=0.048), hypertension (34% versus 17%; P=0.04) and higher levels of cholesterol (201 [174–237] versus 175 [145–214] mg/dl; P=0.003) and triglycerides (212 [155–347] versus 159 [96–247] mg/dl; P=0.048). The observed MPO directional difference persisted despite controlling for CV risk factors (P=0.03). CD4 was negatively correlated with MPO in cases (r=-0.38; P=0.004), but not in controls (r=-0.08; P>0.9); this was the only factor with significant correlation within groups.

Conclusion: In contrast to the general population, higher MPO levels were not predictive of CV events in this study, underscoring the fact that pathways operative in HIV arteriopathy may be distinct from traditional CVD pathogenesis.

ABSTRACT P-42

Antiviral Therapy 2007; 12 Suppl 2:L43

Hypertriglyceridaemia and small dense LDL-cholesterol in HIV-infected patients with myocardial infarction

S Mauss1, F Berger1, G Schmutz2 and W Richter2

1Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; 2Institute for Lipid Metabolism, Windach/Munich, Germany

Objectives: HIV infection and HAART are thought to be associated with an increased cardiovascular risk. Hypertriglyceridaemia is a frequent finding in HIV patients. However, in the general population isolated hypertriglyceridaemia is not regarded as a cardiovascular risk factor per se. We investigated the prevalence of triglycerides >150 mg/dl in 53 patients with myocardial infarction (MI). In addition we assessed the role of small, dense LDL (sd-LDL) as a risk factor. These particles are suggested to mediate the cardiovascular risk in some hypertriglyceridaemias in HIV-negative subjects.

Methods: Fasting lipids and lipoproteins were determined enzymatically in 53 HIV-infected subjects with an MI (47 men, 6 women, age 50.1 ±8.9 years), apolipoproteins were measured by turbimetry and sd-LDL as sd-LDL-apolipoprotein-B-100 after ultracentrifugation of plasma at a density of 1.044 g/ml in the resulting infranatant.

Results: Twenty-one of 53 HIV-infected subjects (40%, 18 men, 3 women, 51.9 ±9.6 years) with MI were found to have triglycerides >150 mg/dl, total cholesterol 203 ±35 mg/dl, triglycerides 377 ±227 mg/dl, HDL-cholesterol 35 ±12 mg/dl, LDL-cholesterol 101 ±32 mg/dl, VLDL-cholesterol 66 ±33 mg/dl, VLDL-triglycerides 241 ±189 mg/dl, VLDL-apolipoprotein B 26.7 ±0.0 mg/dl, LDL-apolipoprotein B 63 ±15 mg/dl, lipoprotein (a) 14 mg/dl (IQR 6.75–34.75); sd-LDL-apolipoprotein B was 16.2 (IQR 12.8–18.6) mg/dl, which was significantly higher (P<0.001) than in 135 age and sex matched HIV-positive subjects without coronary heart disease (8.3 [IQR 6.1–11.8] mg/dl). Only 4/21 patients (19%) had sd-LDL-apolipoprotein B <13.5 mg/dl, which is regarded to be normal in HIV-negative individuals.

Conclusions: Hypertriglyceridaemia is common in patients on antiretroviral therapy. But the incidence of MI is still low in HIV patients. In this study, about 80% of HIV-infected patients with MI and hypertriglyceridaemia showed high sd-LDL (which is typical for familial combined hyperlipidaemia and the metabolic syndrome with high cardiovascular risk). Determination of sd-LDL seems to be useful to identify those HIV-infected patients with increased triglycerides at very high risk of cardiovascular disease. sd-LDL may be the mediator of cardiovascular disease in these patients.
ABSTRACT P-43

Antiviral Therapy 2007; 12 Suppl 2:l44

Factors affecting the short term nutritional response to HAART in Rwandan women

Z Lin1, ES Engelton1, J Rusine2, A Binaquwaho3, MH Cohen4, M Fabri5, F Ndamage6, J Mugabo6, JMV Ndawimana7, DP Kotler1 and K Anastos8

1St. Luke’s-Roosevelt Hospital Center, Columbia University; 2National Reference Laboratory, Kigali, Rwanda; 3Rwandan National Commission to Combat AIDS; 4Core Center/Cook County Hospital, Chicago, IL, USA; 5 Kovler Center, Chicago, IL, USA; 6Treatment and Research in AIDS Center, Rwanda; 7 WE-ACTx Rwanda (JMV); 8Montefiore Medical Center, Bronx, NY, USA.

Objective: HAART is associated with weight gain, and increased lean and fat mass in the developed world. We analysed short term nutritional responses to HAART and analysed factors affecting outcome in a cohort of Rwandan women (RWISA).

Methods: Studies were performed in 808 women, 599 HIV+ and 209 controls. HAART was given for 160 ±88 days prior to repeat studies in 328 subjects, while 271 remained untreated. Body weight, waist:hip ratio and body composition by BIA were obtained. Post traumatic stress (PTSD - modified Harvard trauma questionnaire [HTQ]) and depression (CES-D) were assessed at baseline, improvement of a magnitude similar to that seen in the developed world. We increased lean and fat mass in the developed world. We analysed short term nutritional responses to HAART and analysed factors affecting outcome in a cohort of Rwandan women (RWISA).

Results: At baseline, the ‘treated’ group had lower mean values for CD4, weight, FFM and fat compared with untreated and uninfected groups, though a substantial proportion (approximately 20%) of all groups were underweight (BMI<18.5). All three groups gained weight and body fat significantly, while losing fat-free mass. Increases in weight, but not body fat, were significantly greater in treated patients than in the other groups, while FFM losses were significantly lower. Waist:hip ratio did not change, with or without treatment. After treatment, weight and body composition did not differ significantly from the other groups. The nutritional response to HAART for fat and FFM were inversely related to baseline CD4 lymphocyte counts. The response also was greater in subjects with lower baseline body cell mass. There were no relationships between the nutritional response and age, days of therapy, baseline HTQ or CES-D scores.

Conclusions: Malnutrition is common in HIV+ and HIV-Rwandan women. HAART is associated with nutritional improvement of a magnitude similar to that seen in the US, which is related to pre-treatment CD4 and body cell mass depletion, but not to PTSD or depression.

ABSTRACT P-44

Antiviral Therapy 2007; 12 Suppl 2:l44

Adverse effects of standard first-line antiretroviral therapy on black South African patients

JA George, N Lutchman and NJ Crowther

National Health Laboratory Service and University of the Witwatersrand, Johannesburg, South Africa

Aim: The aim of this study was to describe adverse effects of antiretroviral therapy on black South African HIV-positive patients.

Methods: Sixty treatment-naive patients were recruited and followed up for 24 months. Before initiating therapy the following investigations were carried out: CD4, viral load, fasting lipogram, fasting blood glucose, insulin and C peptide. Anthropometric data collected included body mass index, waist to hip ratios (WHR) and skin fold thicknesses measured at the triceps, scapula and iliac crest. Patients were then started on stavudine 40 mg twice daily, lamivudine 150 mg twice daily and Stocrin 600 mg once daily. Repeat measurements were made at four monthly intervals. Body shape changes were assessed based on patient perception and physician assessment.

Results: Forty-three patients completed the study. At the start of the study subjects who developed lipodystrophy (LD) were fatter (BMI: 24.8 ±4.8 versus 22.2 ±3.2; P=0.01) and had significantly higher skin fold thicknesses at all sites (P<0.001) than subjects who never developed lipodystrophy (NLD). At the end of the study BMI was similar in both groups. WHR increased to a greater extent in the LD group compared with the NLD group (12.4 ±7.1% versus 4.3 ±3.2%; P=0.004). This was attributable to a fall in hip circumference in those with lipodystrophy (–3.9 ±5.5% versus +2.7 ±7.0%; P=0.003). Triceps skin thicknesses fell significantly in the LD group (17.2 ±5.5 mm to 13.3 ±5.1 mm; P=0.03) compared with the NLD group (12.0 ±6.3 mm to 11.5 ±6.3; P<0.05). Triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol increased significantly in both groups but to very similar extents.

Conclusions: In the South African black population lipodystrophy is characterized by lipoatrophy of the hips and arms, increased lactate production and deterioration in glucose tolerance.

Acknowledgements: Thank you to Sisters Holden and Ramela for anthropometric data collected, to all the patients who participated in this study and to the Carnegie foundation for funding this study.
ABSTRACT P-45
Antiretroviral treatment related adverse events (AEs) in the TREAT Asia HIV Observation Database (TAHOD)

J Zhou1, PL Lim2 and S Pujari 3 on behalf of The TREAT Asia HIV Observational Database

1National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, Australia; 2Tan Tock Seng Hospital, Singapore; 3Institute of Infectious diseases, Pune, India

Background: In this paper we assess the feasibility of collecting extended AE data in TAHOD, a multicentre prospective cohort of patients with HIV in the Asia-Pacific region.

Methods: AEs were collected previously as reasons for antiretroviral treatment change/stop during prospective follow-up. Since September 2005, specific clinical AEs (grade 3 and 4) according to ACTG criteria, and additional laboratory tests, have been incorporated into the data specification.

Results: A total of 2,150 patients have been on antiretroviral treatment since March 2003, when reasons for treatment change/stop were recorded. The majority of treated patients (60%) started with three or more drugs containing at least one NNRTI (nevirapine or efavirenz), at least one NRTI (lamivudine [55%], stavudine [35%] or zidovudine [19%]). Up to September 2006, there were 1,367 patients with 2,121 episodes of treatment change/stop, of which 36% were reported to be due to AEs, with lipodystrophy (25% of all AEs), rash (15%), anaemia (10%), peripheral neuropathy (7%), and abnormal laboratory tests (6%) the most common. Since September 2005, grade 3 or 4 clinical AEs were reported in 9% of patients (284 AEs among 219 patients). The most common were lipoatrophy (39%), rash (17%), fat accumulation (11%) and peripheral neuropathy (7%). Grade 4 AEs (11 cases) or death (3 cases) were relatively rare. Laboratory testing varied considerably across the sites. Anaemia (26% of abnormal tests) was the most common AE identified from laboratory tests, followed by low HDL (16%), hypertriglycerideamia (14%), increased SGPT (11%), hypercholesterolaemia (10%), and hyperbilirubinaemia (8%).

Conclusions: The pattern of clinical and laboratory AE collected prospectively appeared to be relatively stable and follow a similar pattern to that reported in western countries. Our approach to collecting limited numbers of grade 3 or 4 AEs seems to be a feasible method in Asian HIV patients with diverse ethnic, social and economic backgrounds.

ABSTRACT P-46
Differential willingness to accept adverse event (AE) risks among ART-naive HIV-positive African Americans (AA)

AB Hauber1, ME Watson2, AF Mohamed1, F Reed Johnson1 and JE Hernandez2

1RTI Health Solutions, RTP NC; 2GlaxoSmithKline, RTP, NC

Objective: To estimate the willingness of treatment-naive HIV-positive AAs to accept AE risks in exchange for improvements in treatment efficacy.

Methods: Self-identified, ART-naive, HIV-positive AAs were recruited through clinics. Respondents completed a series of choice-format conjoint tradeoff tasks that required them to select between hypothetical treatment alternatives with varying levels of efficacy and adverse events (AEs). Treatment attributes included virological failure (VF), hypersensitivity reaction (HSR), bone damage, kidney damage, and outcomes of bone damage or kidney damage (degree to which the problem could be treated successfully). All attributes were expressed as probabilities of occurrence. For each AE, we calculated the level of risk patients would accept to achieve a reduction in the risk of VF.

Results: A total of 153 patients completed the survey. Without considering the different outcomes associated with the long-term AEs, the maximum acceptable risk (MAR) associated with short-term HSR was higher than the MAR for either kidney or bone damage. When the outcome of long-term AEs was considered the MAR for HSR was higher than that for bone damage if the damage could not be treated successfully or if the outcome was uncertain. The MAR for HSR, however, was lower than that for bone damage when the damage could be treated successfully. Similarly, the MAR for HSR was also higher than the MAR for kidney damage that could not be treated successfully. When kidney damage could be successfully treated, the MAR was higher than that for HSR.

Conclusions: HIV-positive, ART-naive, AA patients in this study were willing to accept an increased risk of AEs in exchange for a lower risk of VF. The level of risk they were willing to accept to reduce their risk of VF was higher for HSR than for bone or kidney damage overall, but varied depending on the outcome of either of these AEs. The results indicate that these patients are willing to accept some level of risk in order to achieve the benefits of antiretroviral treatment. Physicians should consider such risk tolerance when talking with their patients about alternative treatment options.
ABSTRACT P-47
Antiviral Therapy 2007; 12 Suppl 2:L46

The acute effects of HIV protease inhibitors on glucose production in healthy HIV-negative men

GA Lee1, JM Schwartz1,2, S Patzek1, A Dyachenko2, M Wen1, K Mulligan1, M Schambelan1 and C Grunfeld1

1University of California San Francisco, San Francisco, CA, USA; 2Touro University, Vallejo, CA, USA

Objectives: Protease inhibitors (PIs) have been shown to induce peripheral insulin resistance. We previously reported that 4 weeks of indinavir in healthy men induced hepatic insulin resistance by blunting the ability of insulin to suppress endogenous glucose production (EGP). It is not known whether other PIs also alter EGP in the hyperinsulinaemic state. Here, we measure the acute effects of indinavir, full-dose ritonavir, and amprenavir on EGP during the hyperinsulinaemic state in three separate, randomized, placebo-controlled, crossover trials of identical study design in healthy volunteers.

Methods: In three separate studies, EGP was quantified using stable isotope tracer dilution techniques in 20 healthy HIV-negative men (six in the indinavir study, eight in the ritonavir study and six in the amprenavir study). Subjects received a single dose of placebo or drug (indinavir 1,200 mg, ritonavir 800 mg, amprenavir 1,200 mg) prior to a 3-h euglycaemic hyperinsulinaemic clamp with infusion of labelled glucose. Studies were repeated with subjects receiving the alternate treatment 1–4 weeks later.

Results: Comparable insulin levels were achieved during the paired clamp studies. Indinavir significantly blunted the ability of insulin to suppress EGP (placebo 2.2 ±0.8 μmol/kg·min; indinavir 4.1 ±1.3 μmol/kg·min, P=0.04). With ritonavir administration, there was a trend towards a blunting of insulin-induced suppression of EGP (placebo 3.0 ±0.5 μmol/kg·min, ritonavir 3.6 ±0.3 μmol/kg·min, P=0.08), whereas there was no significant difference with amprenavir administration (placebo 3.2 ±0.7 μmol/kg·min; amprenavir 2.9 ±0.04 μmol/kg·min, P=0.63).

Conclusions: Indinavir and full-dose ritonavir blunted the suppression of EGP by insulin, whereas amprenavir had no effect on EGP in the hyperinsulinaemic state. Both indinavir and ritonavir altered EGP within several hours after administration suggesting an acute process. These results paralleled the acute effects of these PIs on insulin-mediated glucose disposal in the same studies. Indinavir and ritonavir decreased insulin-mediated glucose disposal by 34% and 16%, respectively, whereas amprenavir had no significant effect on insulin sensitivity. These findings emphasize the specificity of individual PI effects on glucose metabolism.

ABSTRACT P-48
Antiviral Therapy 2007; 12 Suppl 2:L46

Zidovudine/lamivudine persistently contributes to peripheral insulin resistance by a body composition-independent mechanism demonstrated by repeated clamp studies during 2 years of first-line ART with zidovudine/lamivudine/lopinavir/ritonavir

MGA van Vonderen1, RME Blümer2, E Hassink3, J Sutinen4, MT Ackermans2, MA van Agtmael5, H Yki-Jarvinen6, SA Danner1, HP Sauerwein2 and P Reiss2,3 and the MEDICLAS study group

1VU University Medical Center, Amsterdam, the Netherlands; 2Academic Medical Center, Amsterdam, The Netherlands; 3IATEC, Amsterdam, The Netherlands; 4Helsinki University Central Hospital, Helsinki, Finland

This poster abstract will also be presented as an oral; see abstract O-15 for text.

ABSTRACT P-49
Antiviral Therapy 2007; 12 Suppl 2:L46

A randomized double-blind control study of benfluorex versus placebo in HIV-infected patients with insulinresistance or impaired glucose tolerance

L Poizot-Martin1, MP Droguet Vey1, D Di Stefano2, E Jouve1, G Fabre1, A Saout1 and JA Gastaut1

1APHM Sainte-Marguerite, Marseille, France; 2Département d’Imagerie Médicale-Institut Paoli Calmettes, Marseille, France; 3APHM-CIC-UPCET Timone, Marseille, France

Objective: We previously reported a beneficial effect of benfluorex (BFL) on oral glucose tolerance test (OGTT) and visceral fat mass (VAT) in an open-label study conducted in 60 HIV-infected patients. The objective of this study was to assess whether administration of BFL compared with placebo (PBO) improves insulin resistance (IR) and decreases VAT in HIV+ with HAART-induced lipodystrophy.

Methods: We conducted a pilot randomized, placebo-controlled, double-blinded study in 22 HIV-infected patients (16M/6F; mean age 45 years ±7.7) with IR (fasting insulinaemia >12 UI/l) or impaired glucose tolerance (IGT) diagnosed with 75 g OGT-T. Patients were randomly assigned to receive BFL 3 tablets/day (n=12) or PBO (n=10) for 24 weeks. The main efficacy criterion was insulin level analysed as the change from baseline to the end of treatment (Delta-Ins). Secondary criteria were anthropometric measurements (VAT and subcutaneous [SAT] abdominal fat mass measured with computed tomography, waist circumference, body weight), fasting plasma glucose (FPG), plasma lipid and lactate level.
Results: Delta-Ins was –8.78 UI/l ±20.10 in BFL group versus –0.66 UI/l ±8.29 (P=0.34) with a delta FPG of –0.22 ±0.77 in BFL group versus +0.06 ±0.33 in PBO group (P=0.40). Mean body weight decrease in BFL group (D0: 74.69 ±12.15; W24: 70.83 ±11.16) and increase in PBO group (D0: 74.94 ±17.42; W24: 79.63 ±16.69) (P=0.01). Mean VAT was at D0 in BFL and PBO group respectively 168.78 cm² ±86.35 and 170.8 cm² ±91 and at W24, 132.8 cm² ±76 and 177.3 ±84 (P=0.10). No change was observed on SAT, plasma lipid and lactate levels.

Conclusions: The body weight loss, Delta-Ins and VAT measurement observed in the BFL arm might be mediated by the effect of BFL on sensitivity to insulin. However, the sample size of this pilot controlled study were too low to show a statistically significant difference in Delta-Ins and VAT measurement.

ABSTRACT P-50

Antiviral Therapy 2007; 12 Suppl 2: L47

Correlation of HDL-cholesterol and insulin resistance in HIV-patients with lipodystrophy

M Wiese, M Kaspari, U Moebius, RE Schmidt and GMN Behrens

Hannover Mectal School, Hannover, Germany

Background: The prevalence of lipodystrophy remains at 9th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV� subjects with central adiposity.

K Mondy1, WT Cade1, DN Reeds1, S Lassa-Claxton1, C Bopp1, S Tucker2 and KE Yarasheski3

1Washington University School of Medicine; 2Living-By-Design, St. Louis, MO, USA

ABSTRACT P-51

Antiviral Therapy 2007; 12 Suppl 2: L47

Hatha/Ashtanga yoga intervention modestly improves cardiovascular disease (CVD) risk parameters in dyslipidaemic HIV� subjects with central adiposity.

Aim: Anecdotal evidence suggests that the practice of yoga can enhance immune function and reduce risk for the cardiometabolic syndrome. We hypothesized that training in the practice of yoga (2 days/week, 20 weeks) that included breathing, relaxation, stretching and posture would improve oral glucose tolerance, fasting lipid/lipoprotein levels, resting blood pressure, and body composition in HIV� men and women with at least one cardiometabolic risk factor.

Methods: Forty-one HIV� men and women (44% minority, 25% women, CD4 507 ±34 c/ml, 89% undetectable HIV RNA, 11 ±1 years HIV+, 24 ±2% body fat and 58 ±2% trunk fat) were randomly assigned to receive 20 weeks of individual and group instruction in the practice of Hatha/Ashtanga (‘physical’) yoga from a certified yoga instructor, or 20 weeks of continued standard-of-care treatment (SToC). Both groups received monthly nutrition counseling/advice (AHA guidelines) from a research dietician.

Results: Intent-to-treat analyses indicated that yoga practice reduced fasting triglycerides (-58 ±24 mg/dl versus 6 ±12 mg/dl; ANOVA P=0.019), total-cholesterol (-28 ±10 mg/dl versus -5 ±4 mg/dl; P=0.037), and non-HDL-cholesterol levels (-27 ±9 mg/dl versus -6 ±5 mg/dl; P=0.014) more than SToC. Yoga reduced resting systolic (-8 ±4 mmHg versus -2 ±4 mmHg) and diastolic blood pressures (-9 ±3 mmHg versus 0 ±2 mmHg; P=0.008), whereas these were unchanged in SToC. Both groups lost similar (P=NS) amounts of weight (-1.9 ±0.8 kg versus -1.2 ±1.1 kg), trunk (-0.8 ±0.5 kg versus -0.6 ±0.5 kg), and appendicular (-0.3 ±0.2 kg versus -0.2 ±0.3 kg) adipose mass. Framingham 10-yr risk scores tended to decline more in the yoga group (-1.9 ±0.8% versus -0.3 ±0.5%; P=0.10).
On average, baseline oral glucose tolerance and insulin area under the curve were normal in both groups, and unchanged after 20 weeks. CD4 and plasma HIV RNA were unchanged in both groups.

**Conclusion:** The practice of yoga modestly improved CVD risk profiles in HIV+ men and women with baseline dyslipidaemia and central adiposity.

Supported by NIH

**ABSTRACT P-52**

*Antiviral Therapy 2007; 12 Suppl 2:L48*

**Resistance to highly potent statin therapy in patients with HIV metabolic syndrome**

*KW Johns¹ and GP Bondy¹,²*

¹University of British Columbia, Vancouver, BC, Canada; ²HIV Metabolic Clinic/Healthy Heart Lipid Clinic, St. Paul’s Hospital, Vancouver, BC, Canada

**Background:** Patients with HIV are subject to development of HIV metabolic syndrome characterized by dyslipidaemia, lipodystrophy and insulin resistance secondary to highly active antiretroviral therapy (HAART). Rosuvastatin, a new, highly potent HMG-CoA reductase inhibitor (statin) offers a promising outlook in the treatment of HIV metabolic syndrome. Rosuvastatin is effective at lowering LDL and poses a low risk for drug–drug interaction, as it does not share the same metabolic pathway as HAART drugs. This pilot study sought to determine the efficacy of rosuvastatin on lipid parameters in HIV-positive patients with HIV metabolic syndrome.

**Methods:** This study was a retrospective analysis of 130 HIV-positive patients attending a tertiary referral center in Vancouver, BC. Patients prescribed rosuvastatin and who remained on therapy for longer than 4 weeks were included in the study. Lipid parameters, including total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglycerides (TG) and apolipoprotein B (ApoB), were recorded at baseline and following initiation of therapy. Results: Mean TC decreased from 6.54 to 4.89 mmol/l (25.0% reduction, *P*<0.001). Mean LDL-C decreased from 3.39 to 2.24 mmol/l (30.8% reduction, *P*<0.001). Mean HDL rose from 1.04 to 1.06 mmol/l (2.0% increase, *P*=ns). Mean triglycerides decreased from 5.26 to 3.68 mmol/l (30.1% reduction, *P*<0.001). Secondary analysis examining the effectiveness of rosuvastatin monotherapy (*n*=70) versus rosuvastatin plus fenofibrate (*n*=43) showed an improvement of 21.3% in TG and a decrease of 4.1% in HDL-C in the monotherapy group. The rosuvastatin plus fenofibrate showed a greater drop in triglycerides (45.3%, *P*<0.001) and an increase in HDL of 7.6% (*P*=0.08).

**Conclusions:** Although this study found that rosuvastatin is effective at improving potentially atherogenic lipid parameters in HIV-positive patients, an emerging theme from our results is an apparent resistance to statin therapy in our study population. A study investigating rosuvastatin effectiveness in non-HIV positive patients with metabolic syndrome (*n*=240) noted improvements of -33.6% for TC, -46.7% for LDL-C and +9.3% for HDL-C. Our results are further supported by a small, pilot trial examining rosuvastatin effectiveness in HIV which reported similar median changes from baseline of -21.7% (TC), -22.4% (LDL-C), -30.1% (TG) with the exception of a 28.5% median increase in HDL. In light of the results revealed by this pilot study, clinicians might want to consider a possible resistance to statin therapy when treating patients with HIV metabolic syndrome.

**ABSTRACT P-53**

*Antiviral Therapy 2007; 12 Suppl 2:L48*

**Adherence to dyslipidaemia guidelines in patients taking protease inhibitors at an inner-city academic medical centre**

*J Joseph¹, R Jain¹, M Diaz-Linares¹ and M Kulkarni²*

¹University of Illinois at Chicago, Chicago, IL, USA; ²Advocate Illinois Masonic Hospital, Chicago, IL, USA

**Background:** Dyslipidaemia is a prevalent condition affecting HIV-infected adults receiving antiretroviral therapy, particularly in those taking protease inhibitors (PI). Expert panel guidelines have been established to aid clinicians in lipid monitoring and management for patients receiving antiretroviral therapy.

**Objective:** To evaluate our adherence over time to the Infectious Disease Society of America (IDSA) dyslipidaemia guidelines for patients on PI-based regimens.

**Methods:** A retrospective chart review of patients taking PI at a HIV specialty clinic was conducted between January 2000 and December 2005.

**Results:** We identified 225 patients taking PIs, of which 44% were females and 68% were African American. The most common risk factor for cardiovascular disease was smoking (*n*=88). Twenty-four percent of patients never had a lipid panel checked during study period. Fifty-three percent of patients did not have lipids checked 6 months after PI initiation and only 36% routinely had lipids monitored annually. The frequency of lipid monitoring, however, increased over time from 9% in 2000 to 34% in 2005. The average number of follow-up visits for patients who had lipids monitored yearly was 24 over a 5-year period versus 20 for those patients who did not have lipids checked regularly. Lipid-lowering therapy was indicated in 38 (17%) patients, but only initiated in 28. Overall, lipid lowering therapy was not addressed by the clinician in 52% of patients.
Conclusion: Low adherence rates to the national dyslipidaemia guidelines were found at our institution. After publication of the 2000 and 2003 IDSA dyslipidaemia guidelines, there was a trend toward more frequent lipid monitoring over time, however, it still remains low. Potential barriers to guidelines implementation include patient non-compliance with clinic follow-up and fasting requirements, and lack of clinician recognition of dyslipidaemias. Efforts are in order to educate patients and clinicians to monitor lipids.

ABSTRACT P-54

Antiviral Therapy 2007; 12 Suppl 2: L49

Changes in lipid parameters during treatment with lopinavir/ritonavir (LPV/r) plus zidovudine/lamivudine (ZDV/3TC) induction followed by maintenance on LPV/r monotherapy compared with efavirenz (EFV) + ZDV/3TC through 96 weeks

BA da Silva¹, P Domingo³, V Joly³, A Rachlis⁴, R Rubio², MP Dellaan¹, KJ Wikstrom¹, B Bernstein¹, MS King¹ and GJ Hanna¹

¹Abbott, Abbott Park, Illinois, USA; ²Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ³Bichat Claude Bernard Hospital, Paris, France; ⁴Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; ⁵Hospital 12 Octubre, Madrid, Spain

Objective: Lipids form a part of cardiovascular risk assessment. The LDL:HDL ratio is important in determining cardiovascular risk. We compared lipid parameters for subjects treated with LPV/r-based induction-maintenance versus an EFV-based combination regimen.

Methods: One-hundred and fifty-five antiretroviral-naive HIV-infected subjects randomized 2:1 to LPV/r+ZDV/3TC induction for 24–48 weeks followed by LPV/r monotherapy (LPV/r arm, n=104) or EFV+ZDV/3TC (EFV arm, n=51). Total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, apolipoprotein (Apo) A1, Apo B, Apo C3, hs-CRP levels obtained at baseline and through 96 weeks. Changes in TC and TG tested for association with 37 chemistry- and metabolic-test baseline values.

Results: Ninety-two (88%) of 104 LPV/r subjects started monotherapy after a median of 24 weeks induction. In subjects completing 96 weeks, baseline and changes from baseline were comparable between treatment groups except for larger increases in Apo-C3 in the LPV/r arm and trends toward differences in triglycerides and hsCRP changes (Table 1). Changes from baseline generally occurred within the first 24 weeks and remained stable thereafter. Results were similar if subjects using lipid-lowering agents were excluded from the analysis.

Conclusions: Consistent with a trend towards higher TG in the LPV/r group, larger increases in Apo C3 were observed in LPV/r-treated subjects. Dynamics of TC, HDL-C, LDL-C, TG, Apo A1, Apo B were comparable with LPV/r-based induction-maintenance strategy compared to EFV+ZDV+3TC. Discontinuation of ZDV/3TC did not impact lipid changes in LPV/r-treated subjects. Despite increases in TC and LDL, the LDL:HDL ratio was unchanged through 96 weeks for both regimens. Hs-CRP remained low throughout the study.

<table>
<thead>
<tr>
<th>Variable, mg/dl (except LDL:HDL ratio)</th>
<th>LPV/r (n=104)</th>
<th>EFV (n=51)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change to week 96</td>
<td>Baseline</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>160</td>
<td>+57†</td>
<td>159</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>128</td>
<td>+91†</td>
<td>119</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40</td>
<td>+14†</td>
<td>42</td>
</tr>
<tr>
<td>LDL-C</td>
<td>100</td>
<td>+32†</td>
<td>100</td>
</tr>
<tr>
<td>LDL:HDL ratio</td>
<td>2.74</td>
<td>-0.15</td>
<td>2.57</td>
</tr>
<tr>
<td>Apo A1</td>
<td>102</td>
<td>+29†</td>
<td>107</td>
</tr>
<tr>
<td>Apo B</td>
<td>76</td>
<td>+17†</td>
<td>74</td>
</tr>
<tr>
<td>Apo C3</td>
<td>8.0</td>
<td>+7.7†</td>
<td>8.0</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.37</td>
<td>-0.10</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Between-group difference; †P-values >0.10 not displayed; ‡Within-group change from baseline P<0.05. No baseline variable was significantly correlated with either TC or TG changes from baseline to week 96.
ABSTRACT P-55

Evolution of the lipid profile in patients treated with tenofovir DF and protease inhibitors. Data from the PROTECTION cohort study

JM Llibre, MJ Galindo, M Marquez, J Berenguer, S Echevarria, LE Morano, O Ferrero, R Sánchez-de la Rosa and E Pedrol

1Hospital Germans Trias i Pujol, Lluita contra la SIDA Foundation, Barcelona, Spain; 2Hospital Clínico Universitario de Valencia, Spain; 3Hospital Virgen de la Victoria, Málaga, Spain; 4Hospital Gregorio Marañon, Madrid, Spain; 5Hospital Universitario Marquez de Valdecilla, Santander, Spain; 6Hospital Meixoeiro, Vigo, Spain; 7Hospital de Basurto, Bilbao, Spain; 8Gilead Sciences, Madrid, Spain; 9Hospital de Granollers, Spain

Objectives: To describe changes in triglycerides (TG) and cholesterol (C) (total-c, LDL-c and HDL-c) in HIV-1-infected patients treated with TDF and boosted or unboosted protease inhibitors (PI).

Methods: PROTECTION was a retrospective, multicentre cohort study conducted at 80 HIV units across Spain, designed to identify the effectiveness and safety of combinations including TDF and PIs in common clinical practice. The present analysis is focused on TG and C evolution during the first year of follow-up. Student’s t-test (paired t-test) was used to detect within-group differences.

Results: One-thousand and forty-two patients were included: 74% male, 89% Caucasian, 56% former-IVDU, mean age 41 years, 52% in salvage therapy and median time of previous ARV treatment 64 months (IQR 28–98). Used PIs included LPV/r (55%), boosted (18%) and unboosted ATV (6%) and FPV/APV (7%). During a 48-week follow-up, 202 patients (14%) presented TG >200 mg/dl, 23 patients (1.6%) TG >500 mg/dl and only two of them (0.04%) withdrew the treatment (both LPV/r). Sixty-seven (4.7%) patients suffered hypercholesterolaemia (total-c >240 mg/dl) by 48-week and none withdrew treatment. The evolution of TG and total-c was analysed by the NRTI backbone and the only significance obtained linked higher total-c levels with d4T (P<0.05). Extended analyses failed to identify any significant differences in LDL-c or HDL-c among the different NRTI groups. Boosted PI combinations presented higher TG levels than the unboosted ones (226 mg/dl versus 175 mg/dl). Differences concerning the different boosted PIs showed significance with LPV/r use and the total-c increase (P<0.05).

Conclusions: The proportion of dyslipidaemia in this cohort treated with TDF and PIs is low. Total-c and TG increase are significantly higher in patients receiving boosted PI. d4T and LPV/r use is associated with a statistically significant increase in total-c.

ABSTRACT P-56

Evaluation of the impact of highly active antiretroviral therapy (HAART) on lipid profiles – data from the 24-week interim analysis of the Gemini Study: saquinavir/r (SQV/r) twice daily versus lopinavir/r (LPV/r) twice daily plus emtricitabine/tenofovir (FTC/TDF) once daily in ARV-naive HIV-1-infected patients

S Walmsley, U Bredeek, A Avihingsanon, J Slim and C Guittari

1University of Toronto, Toronto, Canada; 2El Rio, Special Immunology Associates, Tucson, USA; 3HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; 4St Michael’s Medical Center, Newark, USA; 5Roche, Nutley, USA

Objectives: HAART is associated with varying lipid abnormalities, potentially increasing the long-term risk of cerebrovascular and cardiovascular disease. Comparisons

Table 1. (Abstract P-56)

<table>
<thead>
<tr>
<th></th>
<th>SQV/r mean values in mg/dl</th>
<th></th>
<th>LPV/r mean values in mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
<td>LDL</td>
<td>TG</td>
</tr>
<tr>
<td>Baseline</td>
<td>158</td>
<td>94</td>
<td>134</td>
</tr>
<tr>
<td>Change by week 24</td>
<td>+20</td>
<td>+12</td>
<td>+14</td>
</tr>
</tbody>
</table>

Table 2. (Abstract P-56)

<table>
<thead>
<tr>
<th></th>
<th>SQV/r</th>
<th></th>
<th>LPV/r</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC ≥ grade 1</td>
<td>LDL ≥ grade 1</td>
<td>TG ≥ grade 2</td>
<td>TC ≥ grade 1</td>
</tr>
<tr>
<td>Baseline</td>
<td>13.9%</td>
<td>15.8%</td>
<td>1.9%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Week 24</td>
<td>25.6%</td>
<td>22.7%</td>
<td>1.5%</td>
<td>30.8%</td>
</tr>
<tr>
<td>(Change)</td>
<td>(+11.7)</td>
<td>(+6.9)</td>
<td>(+0.4)</td>
<td>(+21.1)</td>
</tr>
</tbody>
</table>
of the lipid changes of different agents are best understood in randomized trials. Gemini is an ongoing, 48 week (wk) prospective, multinational, open-label study that assessed the efficacy and tolerability of SQV/r versus LPV/r plus FTC/TDF in 337 ARV-naive patients.

**Methods:** Subjects with HIV RNA >10,000 copies/ml and CD4 ≥350 cells/mm³ were randomized to SQV/r 1,000/100 mg BID (n=166) or LPV/r 400/100 mg BID (n=171) plus FTC/TDF 200/300 mg QD for 48 wks. This sub-analysis evaluates the lipid changes of the two regimens from 331 patients completing 24 wks of therapy.

**Results:** Table 1 gives changes in lipid parameters over 24 wks; Table 2 gives changes in lipid grades of clinical relevance (total cholesterol >200 mg/dl, LDL >130 mg/dl, TG >400 mg/dl). Both regimens improved HDL levels and changes in higher grade total cholesterol were similar.

**Conclusions:** At 24 weeks, the mean increase of triglycerides is lower and fewer patients in the SQV/r arm experienced an increase in their lipid grades, as evaluated by the NCEP (National Cholesterol Education Program) guidelines. The differences between arms need to be confirmed in the final 48 wk analysis and should be considered in the context of other cardiac risk factors when choosing a treatment regimen.

**ABSTRACT P-57**

*Antiviral Therapy 2007; 12 Suppl 2:L51*

**Comparison of the effects of darunavir/ritonavir and atazanavir/ritonavir on lipid and glucose-related laboratory parameters in healthy volunteers**

*E Tomaka¹, E Lefebvre¹, V Sekar¹, B Van Baelen², R DeMasi¹, A Vandevooorde² and D Miralles²*

¹Tibotec Inc., Yardley, USA; ²Tibotec BVBA, Mechelen, Belgium

**Background:** This study compared the effects of darunavir (TMC114) plus low-dose ritonavir with atazanavir/ritonavir on lipid and glucose metabolism. Darunavir/ritonavir 800/100 mg qd is being evaluated in treatment-naive and early treatment-experienced HIV patients and is expected to become the most widely used dosage.

**Methods:** Forty-nine HIV-negative healthy males with normal screening lipids received ritonavir 100 mg once daily (qd) for 7 days, followed by either darunavir/ritonavir 800/100 mg qd or atazanavir/ritonavir 300/100 mg qd for 21 days. Lipid and glucose measurements were made under fasting conditions. Mean differences between treatment groups at day (d) 28 were calculated using d7 (post-ritonavir only) as a reference. Short-term safety and tolerability were evaluated.

**Results:** Observed incidences of treatment-emergent lipid and glucose-related laboratory abnormalities, mean values at d7 and 28 and mean differences between groups at d28 from d7 in high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (Chol), triglycerides (TGs), glucose and insulin are shown for treatment with darunavir/ritonavir (DRV/r) or atazanavir/ritonavir (ATV/r) (Table 1). No lipid or glucose-related adverse events were reported. All 24 volunteers experienced hyperbilirubinaemia with atazanavir/ritonavir (grade 3: 10 and grade 4: 5). No grade 3 or 4 laboratory abnormalities were observed with darunavir/ritonavir.

**Conclusions:** Administration of once-daily ritonavir followed by co-administration of darunavir or atazanavir in HIV-negative healthy volunteers over a 28-day period resulted in similar mean values in lipid and glucose parameters.

**Table 1. (Abstract P-57)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRV/r (n=25)</th>
<th>ATV/r (n=24)</th>
<th>Mean difference (95% CI) in changes at d28 versus d7 between DRV/r and ATV/r</th>
<th>Treatment-emergent laboratory abnormalities, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL, mg/dl</td>
<td>55.7</td>
<td>47.4</td>
<td>-3.0 [-6.2–0.1]</td>
<td>Cut-off, mg/dl (insulin: mU/ml)</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>107.6</td>
<td>119.7</td>
<td>-0.3 [-9.7–9.1]</td>
<td>DRV/r (n=25)</td>
</tr>
<tr>
<td>Chol, mg/dl</td>
<td>165.5</td>
<td>170.7</td>
<td>3.7 [-6.2–13.6]</td>
<td>ATV/r (n=24)</td>
</tr>
<tr>
<td>TGs, mg/dl</td>
<td>105.8</td>
<td>102.9</td>
<td>-7.6 [-28.9–13.7]</td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>83.2</td>
<td>83.4</td>
<td>0.7 [-2.6–4.1]</td>
<td></td>
</tr>
<tr>
<td>Insulin, mU/ml</td>
<td>6.7</td>
<td>6.4</td>
<td>-1.7 [-3.0–0.4]</td>
<td></td>
</tr>
</tbody>
</table>

9th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV
ABSTRACT P-58
Antiviral Therapy 2007; 12 Suppl 2:i52
Heart Positive 4: fuel selection for oxidation in the fasted state is markedly abnormal in HIV patients – implications for a uniquely dysregulated form of energy metabolism
RV Sekhar, P Clark, E Cuevas, J Villanueva, I Coraza, C Mendez and A Balasubramanyam
Translational Metabolism Unit, Division of Diabetes, Endocrinology and Metabolism, Baylor College of Medicine, Houston, TX, USA

Introduction: HIV-associated dyslipaemic lipodystrophy (HADL) is a syndrome characterized by severe hypertriglyceridaemia, centripetal fat redistribution and abnormal lipid turnover. We measured fuel selection for oxidation in the fasted state in HIV patients recruited to the Heart Positive Study, a randomized study to determine optimal treatment of dyslipidaemia in patients with HIV/HAART.

Methods: Using indirect calorimetry after an overnight 10-h fast, gas exchange was measured to obtain VO₂, VCO₂ and the respiratory quotient (RQ) in the following four categories of subjects: a) HIV/HAART patients enrolled in Heart Positive (n=69), b) patients with type 2 diabetes (T2DM; n=9), c) non-diabetic elderly persons (E; n=9) and non-diabetic young adults (Y; n=7). Fuel selection for oxidation (fat versus carbohydrate) was calculated.

Results: Subjects with HIV/HAART had the highest fasting RQ among all four groups (0.86 ±0.00 compared with 0.79 ±0.01 [T2DM], 0.82 ±0.01 [E] and 0.76 ±0.00 [Y] [mean ±SE]; P<0.0001). The high RQ in the HIV group was associated with a striking preponderance of carbohydrate oxidation (723.0 ±26.6 compared with 281.9 ±39.1 [T2DM], 241.4 ±86.4 [E] and 115.7 ±15.7 [Y] μmol/kg/h; P<0.000001) over fat oxidation (114.6 ±4.8 compared with 151.0 ±38.2 [T2DM], 86.4 ±22.7 [E] and 153.5 ±58.9 [Y] μmol/kg/h; P<0.001). The contribution of fat oxidation to resting energy expenditure was markedly attenuated in the HIV group compared with the diabetic group (29.8 ±1.4 compared with 51.9 ±3.9%; P<0.01), and the contribution of carbohydrate oxidation to REE was significantly increased (70.2 ±1.4 compared with 48.2 ±3.9%; P<0.01).

Conclusions: These results point to severely dysregulated substrate selection for oxidation in HIV patients on HAART, characterized by marked attenuation of fat oxidation (despite high fatty acid flux) and an exaggerated reliance on carbohydrate oxidation for energy needs in the fasted state. These results offer novel insights into the nature of metabolic dysregulation in HIV patients that is often attributed to ‘insulin resistance’. Compared to other insulin resistant states such as diabetes and aging, the pattern of fuel selection for oxidation in the fasted state is practically reversed, suggesting that HIV patients have a primary defect in fatty acid disposal (‘insulin resistance with respect to fat metabolism’) rather than a dependence on fat oxidation due to impairment of carbohydrate oxidation (‘insulin resistance with respect to glucose metabolism’). Since the high prevalence of whole body insulin resistance in HIV patients is not paralleled by a marked increase in the frequency of diabetes, it is possible that increased carbohydrate oxidation in this population could protect against the development of diabetes.

ABSTRACT P-59
Antiviral Therapy 2007; 12 Suppl 2:i52
Heart Positive 2: increased resting energy expenditure in HIV patients on HAART is related to fat redistribution and insulin resistance
P Clark¹, P Ehsanzadeh², E Chang¹, I Coraza¹, E Cuevas¹, C Mendez¹, J Essien², RV Sekhar¹ and A Balasubramanyam¹
¹Translational Metabolism Unit, Division of Diabetes, Endocrinology and Metabolism, Baylor College of Medicine, Houston, TX, USA; ²University of Houston, Houston, TX, USA

Background: Resting energy expenditure (REE) is increased in HIV patients, both HAART-naive and HAART-treated. It is unclear whether increased REE is related to HIV-associated features such as body fat redistribution, dyslipidaemia and insulin resistance. Heart Positive is a randomized study to determine optimal treatment of dyslipidaemia in patients with HIV/HAART. We analysed the relationship of REE to an array of metabolic parameters obtained at baseline in Heart Positive subjects.

Methods: We correlated REE measured by indirect calorimetry and REE corrected for fat free mass (FFM) in the first 85 patients recruited to Heart Positive with measurements of fasting lipids, insulin sensitivity (by fasting and GTT glucose/insulin levels and HOMA) and body composition (by BIA and anthropometry). In a subset of 23 patients, we also correlated REE with regional fat mass by CT.

Results: See Table 1.

Conclusions: These data suggest that increased REE in HIV patients on HAART is related to characteristic features of HIV-associated lipodystrophy. Specifically, REE appears to increase with measures of fat redistribution (increased waist circumference, decreased hip circumference and increased waist:hip ratio), and is inversely related to insulin sensitivity (HOMA %S). It is possible that pathophysiological factors that lead to these features of HIV lipodystrophy also induce or aggravate the tendency to abnormal energy expenditure manifested by increased REE. There was no significant correlation between REE and fasting lipid levels.
Long-term trends in plasma lipids and glucose in antiretroviral-naive HIV-infected patients starting highly active antiretroviral therapy

**E Martinez, M Gnarini, E de Lazzari, M Larrousse, A León, JL Blanco, J Mallolas and J Gatell**
Infectious Diseases Unit, Hospital Clínic, University of Barcelona, Barcelona, Spain

**Objectives:** We assessed the long-term trends and the impact of CD4 cells, HIV-1 RNA, and antiretroviral therapy (ART) on plasma lipids and glucose in a large cohort of antiretroviral-naive, HIV-infected patients starting therapy.

**Methods:** Patients starting two NRTI plus a PI or a NNRTI from 1997 until 2004 were followed for at least 1 year until lost to follow-up or death. Random clinical and fasting laboratory data were collected. Random effects regression models were constructed to assess the trends of triglycerides (TG), total (TC) and HDL cholesterol (HDL-C), and glucose (G) over time; the effects of baseline CD4 cells and plasma HIV-1 RNA, and first-line thymidine NRTI (tNRTI), NNRTI, or PI by intent-to-treat were also assessed.

**Results:** There were 1,580 (75% men, 30% AIDS) patients with median values of age 36 years, baseline CD4 211/mm³ and HIV-1 RNA 120,500 copies/ml. First-line ART consisted of PI with tNRTI (61%; from 97% in 1997 to 22% in 2004), NNRTI with tNRTI (28%; from 3% in 1997 to 39% in 2004), PI without tNRTI (5%; from 1% in 1997 to 8% in 2004), and NNRTI without tNRTI (6%; from 0% in 1997 to 31% in 2004). Median years on ART were 4 and median number of regimens was two. Eighty-three (5%) patients died. One-hundred and thirty-nine (9%) patients used lipid-lowering therapies (from 14% in 1997 to 1% in 2004). Adjusted TG increased by 1.014 (95% CI 1.010–1.018, P<0.001 per year, by 1.169 (95% CI 1.036–1.318) in patients starting PI with tNRTI, by 1.187 (95% CI 1.002–1.405) in patients starting PI without tNRTI compared with patients starting NNRTI without tNRTI (reference), (P=0.022); by 1.006 (95% CI 1.002–1.009, P=0.001) per %CD4 unit decrease, and by 1.058 (95% CI 1.021–1.097, P=0.002) per log HIV-1 RNA unit increase (n=875). Unadjusted TC decreased by 0.996 (95% CI 1.002–1.009, P=0.002) per %CD4 unit decrease, and by 1.058 (95% CI 1.002–1.097, P=0.002) per log HIV-1 RNA unit increase (n=875). Unadjusted TC decreased by 0.996 (95% CI 1.002–1.009, P=0.002) per %CD4 unit decrease, and by 1.058 (95% CI 1.002–1.097, P=0.002) per log HIV-1 RNA unit increase (n=875).
Conclusions: TG increased over time and were associated with PI-containing ART and worse baseline HIV status. By contrast, TC, HDLc, and G decreased over time and were not associated with ART or HIV-1 RNA.

ABSTRACT P-61

Antiviral Therapy 2007; 12 Suppl 2: l54

Dyslipidaemia in an urban HIV-infected population

DJ Cennimo, S Kim, J LI, and SL Hodder

University of Medicine and Dentistry of New Jersey - New Jersey Medical School, Newark, NJ, USA

Background: Antiretroviral (ARV) side effects and increasing patient longevity have increased concerns for amplified occurrence of multiple metabolic abnormalities associated with HIV infection and treatment. We describe the prevalence of dyslipidaemia in an urban population ofcolour.

Methods: Retrospective chart reviews were performed on all patients seen three or more times between 2001 and December 2006 in the Infectious Disease Practice of University Hospital in Newark, New Jersey. Dyslipidaemia was defined as total cholesterol (TC) ≥240 mg/dl or LDL ≥160 mg/dl or Triglycerides (TG) ≥300 mg/dl or HDL <40 mg/dl, or prescription for lipid modifying medication. Descriptive statistics on the population were generated and comparisons were made using Fisher’s exact test.

Results: Of the 1,369 patients seen, 42% were female, 76% African American, 16% Hispanic, and 4% were Caucasian. Mean follow-up time was 3.6 years, and cumulative follow-up totaled 4,874 patient-years. A total of 782 patients (60.5%) met the definition of dyslipidaemia of whom 14.5% met criteria for increased TC, 9.2% for increased LDL, 19.6% for increased TG and 47.2% for HDL<40 mg/dl. One-hundred and seventy-five patients (23.8% of those with dyslipidaemia) received lipid-modifying agents. 52.9% of women versus 66.0% of men met the definition for dyslipidaemia and men were significantly more likely to have HDL<40 mg/dl (P<0.001). African-Americans were less likely to meet the definition of dyslipidaemia than whites or Hispanics (P<0.001). Significantly more patients with dyslipidaemia (77.9%) had received a PI during the course of the study than patients without dyslipidaemia (69.8%; P=0.003). Atherosclerosis, Baylor College of Medicine, Houston, TX, USA

Conclusions: Dyslipidaemia is a significant concern in this urban HIV population. However, low HDL was the most commonly observed lipid abnormality as opposed to high LDL, often seen in non-HIV populations. These data suggest that the degree of HIV progression in this population may be an important factor driving presence of dyslipidaemia. African-American HIV-infected patients were less likely to have dyslipidaemia compared to Hispanic and Caucasian patients.

ABSTRACT P-62

Antiviral Therapy 2007; 12 Suppl 2: l54

Heart Positive 3: Low cholesterol ester transfer protein (CETP) concentrations are associated with the lack of an inverse relationship between plasma triglyceride and HDL-C concentrations in HIV patients on HAART

RV Sekhar1, E Chang1, R Hoogeveen2, S Kamble1, CM Ballantyne1, H Pownall2 and A Balasubramanyam1

1Translational Metabolism Unit, Division of Diabetes, Endocrinology and Metabolism, TX, USA; 2Section of Atherosclerosis, Baylor College of Medicine, Houston, TX, USA

Introduction: HIV-associated dyslipemic lipodystrophy (HADL) is a syndrome characterized by severe hypertriglyceridaemia, centripetal fat redistribution and abnormal lipid turnover. We previously reported the absence of an inverse correlation between fasting plasma triglycerides and HDL-cholesterol, a characteristic feature of many insulin resistant states that is generally attributed to increased activity of cholesterol ester transfer protein (CETP). We hypothesized that the absence of an inverse TG:HDL-C relationship in HIV patients is due to lack of increased plasma CETP activity. We therefore compared plasma CETP mass (which correlates strongly with CETP activity) in non-HIV subjects with a wide range of triglyceride levels and patients enrolled in the Heart Positive Study, a randomized study to determine optimal treatment of dyslipidaemia in patients with HIV/HAART.

Methods: We first compared the relationship of fasting plasma levels of triglycerides to HDL-C in non-HIV, healthy, normolipidaemic adults (n=32, mean TG 93 mg/dl, range 46-137 mg/dl) and those with Type IV hypertriglyceridaemia (n=42, mean TG 853 mg/dl, range 456-2,909 mg/dl) and patients with HIV/HAART (n=80, mean TG 313.7 mg/dl, range 51-1,580 mg/dl). We then measured plasma CETP concentrations (by ELISA) in the same HIV/HAART patients and non-HIV healthy normolipidaemic adults, as well as in non-HIV obese subjects with metabolic syndrome (n=40, mean TG 255 mg/dl). We correlated CETP concentrations with HDL-C and TG concentrations in the HIV and non-HIV groups.

Results: The HIV patients showed no correlation between fasting plasma TG and HDL-C concentrations (R=0.04; P=NS), while collectively the non-HIV subjects with a range of TG levels from normal to severely increased showed an inverse correlation (R=-0.2; P<0.05). CETP concentrations were not increased in the HIV group compared with the non-HIV group (1.6 ±0.2 μg/dl compared with 0.96 ±0.2 μg/dl; P=NS). However, while the non-HIV group showed a significant inverse correlation between CETP mass and fasting triglyceride concentra-
tions (R = 0.249; P < 0.05), there was no such relationship in the HIV/HAART patients across the entire range of TG levels from normal to severely increased (R = 0.04; P = NS).

Conclusions: These results suggest several striking features of the characteristic hypertriglyceridaemia and low HDL-C state in patients with HIV/HAART that differ from those of non-HIV persons: 1) patients with HIV/HAART do not manifest an inverse relationship between HDL-C and triglyceride concentrations; and 2) this is associated with, and could be due to lack of, increased plasma CETP concentrations in these patients. Unique mechanisms are likely to account for the co-occurrence of high TG and low HDL in this population.

ABSTRACT P-63
Antiviral Therapy 2007; 12 Suppl 2 l55

Correlation between in vitro and in vivo effects of HIV protease inhibitors on the hepatocyte and adipocyte metabolome

A Bellamine1, C Elosua1, C Cao1, MA Noor1, A Berger2, D Alexander2 and O Flint1

1Research and Development, Bristol-Myers Squibb, Princeton, NJ, USA; 2Metabolon Inc., Research Triangle Park, NC, USA

Background: The use of protease inhibitors (PIs) in HAART has been associated with metabolic side effects including disturbance of glucose homeostasis and dyslipidaemia. To better understand the mechanisms underlying these changes, we compared the endogenous metabolite profiles (metabolome) of hepatocytes and adipocytes treated with atazanavir (ATV) or lopinavir (LPV), and compared them with the plasma metabolome of HIV patients treated with these PIs.

Methods: Human hepatoma cells (HepG2) and human primary adipocytes were exposed to LPV or ATV at 30 μM (threefold higher than the reported Cmax) for 24 h. Cellular metabolites were analysed by GC-MS or LC-MS. We also profiled 25 plasma samples of HIV-infected patients treated with these PIs and ritonavir (r): ATV/r (300 mg/100 mg) or LPV/r (400 mg/100 mg). The expression of each endogenous metabolite was analysed using Spotfire and treatment comparisons were done by ANOVA (reported P < 0.05).

Results: The number of metabolites changed with either PI was similar in adipocytes (See Table 1). In hepatocytes, treatment with LPV led to more changes than ATV. Similarly, more metabolites were affected by LPV/r than by ATV/r in the plasma samples. These included amino acid, carbohydrate and lipid intermediary metabolite alterations. LPV uniquely induced arachidonate, octadecanoate, monopalmitin and cholesterol.

Conclusions: In general LPV induced greater changes than ATV in the metabolome. Further, LPV/r induced significantly more changes in lipid metabolites in clinical plasma samples than ATV/r. These data provide further insights into the known contrast in lipid profiles of patients treated with LPV/r or ATV/r.

ABSTRACT P-64
Antiviral Therapy 2007; 12 Suppl 2 l55

Nevirapine increases high density lipoprotein-cholesterol by stimulation of apolipoprotein AI synthesis

RR Sankatsing1, R Franssen1, E Hassink2, HP Sauerwein1, K Brinkman3, R Oesterholt1, A Arenas-Pinto4, I Williams4, S Storfer5, JJ Kastelein1, P Reiss1 and ES Stroes1

1Academic Medical Center, Amsterdam, the Netherlands; 2IATEC bv, Amsterdam, the Netherlands; 3Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; 4Royal Free & University College Medical School, London, UK; 5Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, USA

This poster abstract will also be presented as an oral; see abstract O-02 for text.

Table 1. (Abstract P-63)

<table>
<thead>
<tr>
<th>Metabolites altered, %*</th>
<th>ATV</th>
<th>LPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolites altered, %*</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Upregulated, %</td>
<td>5.36</td>
<td>25.5</td>
</tr>
<tr>
<td>Downregulated, %</td>
<td>18</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Table 2. (Abstract P-63)

<table>
<thead>
<tr>
<th>Metabolites altered, %*</th>
<th>ATV</th>
<th>LPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolites altered, %*</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Upregulated, %</td>
<td>5.36</td>
<td>25.5</td>
</tr>
<tr>
<td>Downregulated, %</td>
<td>18</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Results are expressed as percent control (eight samples treated with 0.1 % DMSO). *Significant changes compared to the control (all numbers) or between drugs are report for P<0.05. Numbers of metabolites detected were 503 in hepatocytes, 391 in adipocytes and 404 in the plasma. †In the plasma samples, results are expressed as percent baseline.
ABSTRACT P-65

_Antiviral Therapy_ 2007; 12 Suppl 2:L56

Molecular mechanism for efavirenz effects on lipid metabolism

_O Flint, A Bellamine, M Noor and R Parker_

Research and Development, Bristol-Myers Squibb Co, Princeton, NJ, USA

This poster abstract will also be presented as an oral; see abstract O-03B for text.

ABSTRACT P-66

_Antiviral Therapy_ 2007; 12 Suppl 2:L56

Effects of efavirenz on lipid metabolism in APOE*3*Leiden hCETP double-transgenic mice: evidence for antagonism of LXR pathway

_OP Flint1, A Bellamine1, MA Noor1, JWA van der Hoorn1, HMG Princen2 and RA Parker2_

1Pharmaceutical Research and Development, Bristol-Myers Squibb Co, Princeton, NJ, USA; 2TN Biosciences, Leiden, The Netherlands

This poster abstract will also be presented as an oral; see abstract O-03A for text.

ABSTRACT P-67

_Antiviral Therapy_ 2007; 12 Suppl 2:L56

Impact of patient-selected self-injection devices on the development of injection site reactions associated with Enfuvirtide use

_M Gottlieb1, C Farthing2, CJ Guittari3 and E DeJesus4_

1Synergy Hematology Oncology Med. Assoc., Los Angeles, CA, USA; 2AIDS Healthcare Foundation, Los Angeles, CA, USA; 3Roche Laboratories, Nutley, NJ, USA; 4Orlando Immunology Center, Orlando, FL, USA

Objectives: In registration studies of enfuvirtide (ENF), 98% of patients developed ≥1 injection site reaction (ISR) over 48 wks – mostly mild to moderate in severity (Grade ≤2). This analysis explores the prevalence and severity of ISRs when self-injecting ENF using a 31G/8mm needle/syringe (N/S) versus Biojector needle-free device (B2000).

Methods: Protocol-defined interim analysis of the first half of total patients (pts) enrolled (n=142) completing a prospective, 24-week, open-label, efficacy/safety study of twice-daily ENF 90 mg + DRV/r 600/100 mg with optimized background treatment (OBT) in triple-class-experienced, DRV/ENF-naive pts participating in a DRV EAP. Patients received self-injection training according to their preferred device selection. All ongoing ISR signs/symptoms were recorded/graded only if present at weeks 1, 4, 12, 16 and 24 visits. Also, maximum pain/discomfort severity grade since last visit was recorded and characterized by patient recall as being mostly immediate and/or reactive, developed/persisted <1 h or ≥1 h post-injection, respectively.

Results: Sixty-two pts who received at least one ENF dose are included in this safety analysis. No pts discontinued due to ISRs. Among pts who reported ISRs through wk 24 using 31G/8mm N/S or/and B2000 devices, the worst sign/symptom by grade and device are summarized in Table 1. Patients who used >1 device (n=7) were included in >1 device category. No ongoing ISR signs/symptoms were observed in 7 pts. No haematomas or nerve-bundle

<table>
<thead>
<tr>
<th>Device (n)</th>
<th>31G/8 mm (14)</th>
<th>B2000 (40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>Erythema</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Induration</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Pruritus</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Nodules/cysts</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Immediate pain</td>
<td>67*</td>
<td>27*</td>
</tr>
<tr>
<td>Reactive pain</td>
<td>33*</td>
<td>33*</td>
</tr>
</tbody>
</table>

*n=15; n=52. *: grade 3 is maximum severity for these signs/symptoms.
pain were reported in this analysis. Serious AEs (11) occurred in 7 pts – none considered drug-related.

Conclusions: Although this study was not designed to compare ISR risk, both injection devices were generally safe and well tolerated. There was a trend toward fewer pts with nodules/cysts, but more grade 3 ecchymosis and grade 3/4 erythema with B2000. These results require cautious interpretation until data are available from all pts through wk 24.

ABSTRACT P-68
Antiviral Therapy 2007; 12 Suppl 2:A57

A randomized study to evaluate injection site reactions (ISRs) using three different mechanisms for delivery of enfuvirtide (ENF): a 27-gauge needle, a 31-gauge needle and a needle-free device

MA Boyd1, M Truman2, G Hales2, J Anderson3, DE Dwyer4 and A Carr5

1National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia; 2Roche Pty Ltd; 3The Carlton Clinic, Melbourne, Australia; 4Westmead Hospital, Sydney, Australia; 5St. Vincent’s Hospital, Sydney, Australia

Objectives: Enfuvirtide (ENF) is injected subcutaneously using a 27-gauge needle. Most patients experience injection site reactions (ISRs) that can affect long-term ENF tolerability. Alternative ENF delivery methods may ameliorate ISRs.

Methods: A multicentre, open-label trial of patients receiving stable antiretroviral therapy including ENF for ≥12 weeks who were randomized to receive ENF by either a 27-gauge (27G) needle, a 31-gauge (31G) needle or a needle-free device (NF). The primary study endpoint was the proportion of participants with ≥grade 2 ISR induration at week 12. Pre-defined secondary endpoints included ISR pain, erythema, pruritus, nodules, bruising, and a composite ISR severity score, as well as HIV RNA, CD4 counts, ENF injection complications and serious adverse events (SAEs). Analysis was by intention to treat.

Results: Sixty-one patients were randomized: mean age 49.2 years, 57 (95%) male, mean ENF duration 847 (range 86–1,987) days. Two subjects withdrew before week 12 (1 27G, 1 31G). Response rates for ISR induration at week 12 were 38%, 25% and 42% for the 27G, 31G and NF groups, respectively, with no significant difference between group comparisons (all P-values >0.2). There was no between-group difference for any other ISR endpoint, except for changes in the composite ISR score, which significantly favoured the 27G and NF groups over the 31G group (P<0.012 and 0.047, respectively). Viral load outcomes were comparable across groups. There were seven delivery system-related adverse events; five of which were attributed to the NF device. None of 12 SAEs was related to the ENF delivery system. At week 12, 51/60 (85%) patients elected to use the ENF NF delivery system.

Conclusion: Needle-free injection of ENF offers a reasonable, reliable alternative to needle-based injecting.

ABSTRACT P-69
Antiviral Therapy 2007; 12 Suppl 2:A57

Lack of evidence of metabolic abnormalities and mitochondrial toxicity with enfuvirtide: a double-blind, placebo-controlled, cross-over study with random sequence assignment in healthy adult volunteers

MC Villarroel1, E Martinez2, N Riba1, M Manriquez1, G Santana1, S Lopez2, G Garrabou3, M Larrousse3, JL Blanco4, A Scalise1, J Mallolas2, O Miró3, X Carne4 and JM Gatell2

1Phase I Unit, Hospital Clinic Barcelona, Barcelona, Spain; 2Infection Disease Department, Hospital Clinic Barcelona, Barcelona, Spain; 3Hospital Clinic from Barcelona, Barcelona, Spain; 4Hospital Clinic from Barcelona, Barcelona, Spain

Objective: We assessed the effects of the fusion inhibitor enfuvirtide on lipid and carbohydrate metabolism and metabolism parameters in healthy adult volunteers.

Methods: Healthy normal-weight males aged 18–45 years without history of dyslipidaemia or drug use had extensive blood cell and chemistry, urine chemistry, serologies for HIV and hepatitis B and C, ECG, and screening for abuse drugs done at baseline and at the end of each period. Participants were randomized to Enfuvirtide 90 mg or placebo administered at hospital every 12 h in two 7-day periods separated by a 4-week washout period. Major endpoint was total cholesterol (TC) change. Secondary endpoints were changes in HDL-C, LDL-C, triglycerides (TG), oral glucose tolerance test (OGTT), lactate, mtDNA and overall safety. The effects of period, treatment, and sequence (carry-over) were evaluated for each endpoint. Based on an expected interindividual variability <10 mg/dl of TC in healthy adults, a sample size of 12 persons would be needed to detect an increase ≥25 mg/dl in TC with 80% power and 0.025 one-sided α.

Results: Of 17 persons recruited, 12 (six enfuvirtide + placebo, 6 placebo + enfuvirtide) completed the study. Baseline characteristics were similar in both groups. Laboratory variables were normally distributed. Mean ±SD final/baseline TC and mean ±SD TC (mg/dl) were: period 1, 0.93 ±0.07 and 171 ±45 (enfuvirtide + placebo) and 0.91 ±0.05 and 167 ±38 (placebo + enfuvirtide); period 2, 0.98 ±0.05 and 180 ±44 (enfuvirtide + placebo) and 0.96 ±0.10 and 174 ±27 (placebo + enfuvirtide); and considering the sequence enfuvirtide + placebo, 0.96 ±0.03 and 175 ±44 and placebo + enfuvirtide, 0.94 ±0.04 and 170 ±32 (P>0.4, each comparison). No patient showed an increase of ≥25 mg/dl in TC from baseline. Similarly, non-significant changes were also
detected on considering HDL-C, LDL-C, TG, OGTT, and lactate. There were no effects of period, treatment or sequence in laboratory endpoints other than mtDNA. A higher increase in final minus baseline mtDNA was associated with enfuvirtide treatment; higher mtDNA values were also associated with the second period. There were no remarkable clinical and laboratory adverse effects.

Conclusions: We were unable to detect any metabolic abnormalities or mitochondrial toxicity of enfuvirtide in healthy adult volunteers.

ABSTRACT P-70
Antiviral Therapy 2007; 12 Suppl 2 L58

HAART-induced viral suppression compensates potential negative effects of TDF on renal function

G Guaraldi1, A Roverato2, C Giovanardi1, F Ravera1, N Squilace1, G Orlando1, G Cappelli1, R Esposito1 and F Palella3

1Dipartimento di medicina e specialità mediche, University of Modena and Reggio Emilia, Italy; 2Dipartimento di Scienze Statistiche, University of Bologna, Italy; 3Division of Infectious Diseases, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Objectives: The aim of our study was to assess the impact of HIV-1 viral load variation and TDF exposure on kidney function evaluated by means of delta glomerular filtration rate over a 48-week period in patients with mild renal impairment.

Methods: This was a prospective observational study that included all consecutive HIV-infected patients attending the metabolic clinic at the University of Modena and Reggio Emilia, Italy, between January 2004 and December 2005. Inclusion criteria were HIV-infected adult patients on antiretroviral therapy for at least 6 months, naive to tenofovir (TDF), being evaluated for kidney function by means of the simplified Modification of Diet in Renal Disease Study equation (MDRD) with a glomerular filtration rate between 0 and 90 ml/min. Cases (Arm A) were patients starting TDF therapy at baseline and controls (Arm B) were patients not modifying therapy. The study population was stratified into three subgroups according to delta HIV-1-RNA viral load (VL) change observed in the follow up period: group 1 VL <50 copies/ml, group 2 VL increase >0.5 log, and group 3 VL decrease >0.5 log.

Results: Ninety-nine patients were enrolled and included in the analysis. Within arm B mean delta MDRD were not different (ANOVA, P=0.94) in the follow-up period. Within arm A mean delta MDRD were highly significantly different (ANOVA, P<0.01). In particular comparison of delta MDRD in group 3 (+8.4 ±12.4 ml/min) was significantly different both to group 1 (-1.0 ±8.8 ml/min) (P<0.05) and to group 2 (-4.6 ±8.8 ml/min) (P<0.01).

Group A3 only experienced a delta MDRD significantly different from zero (P<0.01).

Conclusion: Observed improvements in MDRD as a consequence of HAART-induced viral suppression seems to offset any potential negative effect of TDF on renal function.

ABSTRACT P-71
Antiviral Therapy 2007; 12 Suppl 2 L58

Renal safety profile of TDF in combination with protease inhibitors (PI) in a clinical setting. Results from the PROTECTION cohort

P Viciana1, E Deig2, V Asensi3, J Pasquau4, T Martin5, J Goikoetxea6, J Flores7, S Perez8 and E Pedrol2

1Hospital General Virgen del Rocio, Sevilla, Spain; 2Hospital General Granollers, Granollers, Spain; 3Hospital Nuestra Señora de Covadonga, Asturias, Spain; 4Hospital Virgen de las Nieves, Granada, Spain; 5Clinica Puerta de Hierro, Madrid, Spain; 6Hospital de Cruces, Vizcaya, Spain; 7Hospital Arnau de Vilanova, Valencia, Spain; 8Gilead Sciences, Madrid, Spain

Objective: To describe the renal safety profile of TDF + PIs outside the clinical trial environment.

Methods: PROTECTION study cohort included retrospective data from 80 different HIV units in Spain, including patients treated with TDF + PI combinations. We have analysed the data for renal safety outcomes.

Results: One-thousand four-hundred and twenty-eight patients were analysed. Mean age was 41 years, 74% were male and 56% former IVDU. Median duration of previous ARV treatment was 64 months (IQR 28–98). Boosted PIs were used in preference to non-boosted (83% versus 15%). The most widely used PI was LPV/r (55%) followed by both

<table>
<thead>
<tr>
<th>Table 1. (Abstract P-71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>TDF + non-boosted PIs</td>
</tr>
<tr>
<td>group (n=216)</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
</tr>
<tr>
<td>Phosphate, mg/dl</td>
</tr>
<tr>
<td>GFR, CG/ml/min</td>
</tr>
<tr>
<td>TDF + boosted PIs</td>
</tr>
<tr>
<td>group (n=1,212)</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
</tr>
<tr>
<td>Phosphate, mg/dl</td>
</tr>
<tr>
<td>GFR, CG/ml/min</td>
</tr>
</tbody>
</table>
boosted (18%) and non-boosted (6%) ATV and FPV/APV (7%). Ten percent of patients had taken or were taking a nephrotoxic drug. There were 18 renal adverse events (1.3%), three when using TDF + non-boosted PIs (two renal function declines, one proteinuria/microhematuria) and 15 when using TDF + boosted PIs (11 renal function declines, two proteinuria/microhematuria, a renal colic due to IDV and a Fanconi syndrome). The rate of renal adverse event development was similar in both groups (1.4% TDF + non-boosted PIs and 1.2% TDF + boosted PIs). Only nine (0.6%) patients withdrew TDF treatment owing to renal adverse events, all of them with a combination of TDF + boosted PIs. Results are summarised in Table 1.

Conclusions: Consistent with previous studies, the rate of renal adverse events in this TDF + PI cohort is low, with or without ritonavir boosting. Although decrease in GFR is statistically significant at 12 months for both groups, the magnitude of change is the same and not clinically relevant (~4 ml/min). Additionally, we have not found alterations in serum phosphate levels at 12 months. Our data show that use of boosted PIs does not increase risk of renal adverse events or result in clinically relevant GFR changes.

ABSTRACT P-72
Antiviral Therapy 2007; 12 Suppl 2:L59

Low long-term incidence of tenofovir associated renal dysfunction as measured by creatinine clearance

CM Tsoukas1, J Falutz1, J Szabo1, J Cox1, B Rich1,2, and A Ciampi2

1McGill University Health Centre, Montreal General Hospital, Montreal, Canada; 2McGill University, Dept of Biostatistics, Montreal, Quebec, Canada

Objectives: Because renal dysfunction can occur during tenofovir disoproxil fumarate (TDF) use, we aimed to determine if changes in creatinine clearance (CrCl) over time could predict renal outcomes.

Methods: All 130 patients treated with TDF-containing HAART and 199 patients treated with non-TDF-containing HAART between January 19, 2001 and January 19, 2006 were studied. Baseline was defined as the beginning of the current TDF or non-TDF regimen, or January 19, 2001 (whichever came later). All clinic visits subsequent to baseline were included in the analysis. CrCl was estimated at every visit using both Cockcroft–Gault and MDRD formulas. Phosphate and urea were also evaluated. The primary outcome measured was change in GFR using CrCl. The analysis was done using a linear mixed-effects model for longitudinal data.

Results: Baseline age, gender, immune status and viral load were similar between both treatment groups. There was no significant difference in CrCl at baseline. Both groups showed an increase in CrCl with time. The rate of increase was slightly less for the TDF group than for the non-TDF group (difference=-0.008191 ml/min per year, 95% confidence interval [CI]: -0.01323–0.003149). The results were similar using both formulas. We conducted a small simulation to represent a hypothetical population of 10,000 males, age 45 at baseline on a TDF regimen by sampling CrCl values from our model at 6-month intervals up to 3 years. Median and (empirical) 95% CIs were computed at each time point. From the fitted model we extracted random coefficients and identified seven patients with a negative CrCl slope over time. Of these, only three had decreasing CrCl while on TDF (two of these three patients had pre-existing renal dysfunction). We found no significant changes in phosphate and urea over time, and no significant difference between the groups.

Conclusion: TDF did not have a significant negative impact on renal function during long-term follow up. In fact, there was an average increase in CrCl over time in our patients. Because TDF can lead to renal dysfunction in some patients it would be of great interest to be able to identify these individuals a priori.

ABSTRACT P-73
Antiviral Therapy 2007; 12 Suppl 2:L59

Cystatin C underestimates glomerular filtration rate in HIV-infected individuals

S Mauss1, F Berger1, D Kuschak2, J Henke1, P Hegener1, C Athmann1, P Nemes2 and G Schmutz1

1Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; 2Medizinische Laboratorien Duesseldorf, Duesseldorf, Germany

Objectives: Serum cystatin C was proposed as a marker of renal function that is not affected by weight changes and may be more sensitive than formula calculations based on serum creatinine. In this study we matched antiretroviral naive HIV+ individuals with HIV-negative controls and followed them prospectively thereafter.

Methods: Caucasian HIV+ patients starting antiretroviral therapy (n=110) were followed prospectively and glomerular filtration rate (GFR) was estimated using MDRD formula and cystatin C. HIV-negative healthy volunteers (n=67) served as controls. For statistical analysis, Mann–Whitney, Wilcoxon and Spearman tests were used.

Results: Creatinine and MDRD based GFR did not differ between male and female individuals regardless of HIV status. However, cystatin C levels in HIV+ patients were significantly higher resulting in a mean GFR lower than the lower limit of normal in contrast to HIV-negative controls. Baseline HIV RNA was positively correlated with baseline cystatin C levels (r=0.35, P=0.004). At week 24 of antiretroviral therapy cystatin C decreased from 0.98 ±0.2
mg/l to 0.89 ±0.2 mg/l (P<0.001) resulting in an increase of GFR cystatin C from 82 ±25 to 98 ±30 ml/min (P<0.001). Creatinine was unchanged. Analysis according to use of tenofovir did not change these findings.

**Conclusions:** Our preliminary data suggest an interaction between HIV infection and cystatin C serum levels. Cystatin C is a cysteine protease inhibitor shown to be altered by immune modulating drugs, such as prednisolone or cyclosporine A. The positive correlation between HIV infection and cystatin C serum levels is altered by immune modulating drugs, such as prednisone or cyclophosphamide.

**ABSTRACT P-74**

*Antiviral Therapy 2007; 12 Suppl 2:60*

**Adverse reactions on switching from tenofovir/lamivudine (3TC) to the fixed-dose combination (FDC) of tenofovir/emtricitabine (FTC)**

**M Harris**, **J Toy**, **B Yip**, **R Hogg** and **J Montaner**

1AIDS Research Program, St. Paul’s Hospital, Vancouver, BC, Canada; 2Pharmacy, St. Paul’s Hospital, Vancouver, BC, Canada; 3British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

**Objectives:** To describe adverse reactions occurring early upon switching from tenofovir/3TC to tenofovir/FTC FDC.

**Methods:** The number of adults who switched from tenofovir/3TC (>1 month) to tenofovir/FTC was obtained from the BC Centre for Excellence in HIV/AIDS Drug Treatment Program database, starting from FDC availability in BC (19 June 2006) until 31 Dec 2006. Adverse events within 5 days after the switch are described.

**Results:** During a 6.5 month period, 420 patients in BC switched from tenofovir/3TC to tenofovir/FTC FDC with no concomitant changes to their regimen. Two experienced an adverse reaction within 5 days. The first was a 45-year old white man with a previous diagnosis of AIDS and a current CD4 cell count of 680/mm³. He had been taking tenofovir, 3TC, nevirapine, and lopinavir/ritonavir since Oct 2003. On 24 Nov 2006 he discontinued tenofovir/3TC and started tenofovir/FTC. After the second dose he awoke with severe periorbital, facial, and perioral erythema and edema. He was treated with oral diphenhydramine and diclofenac eye drops. Tenofovir/FTC was stopped after the second dose and he resumed tenofovir/3TC on 27 Nov 2006. Symptoms resolved by 05 Dec 2006. The second patient was a 42-year old white man who started tenofovir, 3TC, and atazanavir/ritonavir on 09 June 2006. On 08 Aug 2006 he discontinued tenofovir/3TC and commenced tenofovir/FTC, at which time his CD4 count was 170 cells/mm³. On 13 Aug 2006 he developed purplish spots on his legs, which gradually increased in number and spread to his thighs, arms and trunk. A diagnosis of Henoch–Schonlein purpura was made. In Sept 2006 he developed mild lower leg edema and haematuria. Renal biopsy showed active glomerulonephritis with IgA deposits. On 21 Nov 2006 he had ongoing haematuria and proteinuria and new skin lesions. FTC was discontinued and 3TC was restarted. At his last assessment on 23 Jan 2007 his edema and vasculitic lesions were resolving, but urine sediment remained abnormal. He received a prescription for prednisone and cyclophosphamide.

**Conclusions:** Patients switching from tenofovir/3TC to tenofovir/FTC FDC should be monitored for possible allergic-type reactions, though these events were infrequent (0.5%) in our population.

**ABSTRACT P-75**

*Antiviral Therapy 2007; 12 Suppl 2:60*

**Effectiveness and safety profile of TDF+ddI+EFV. Results from the DIDITEN cohort.**

**A Antela**, **F Gutierrez**, **P Viciana**, **C Miralles**, **FJ Rodriguez**, **JC López**, **C Martin**, **ML Alvarez** and **S Moreno**

1Complejo Hospitalario Universitario de Santiago de Compostela, Spain; 2Hospital de Elche, Spain; 3Hospital Virgen del Rocio, Sevilla, Spain; 4Hospital Xeral de Vigo, Spain; 5Hospital Nuestra Señora de Aranzazu, Donostia, Spain; 6Hospital Gregorio Marañón, Madrid, Spain; 7Hospital Nuestra de la Montaña, Cáceres, Spain; 8Gilead Sciences, Madrid, Spain; 9Hospital Ramón y Cajal, Madrid, Spain

**Objectives:** To describe the effectiveness and safety outcomes of the combination of TDF+ddI+EFV in a non-clinical trial setting.
Methods: The DIDITEN cohort included data from 67 different HIV units in Spain, including 749 patients treated with different TDF+ddI combinations. We have selected from this cohort only those patients who received TDF+ddI+EFV and analysed the data for effectiveness and safety with particular attention to the immunological outcome.

Results: Two-hundred and five patients were analysed. Mean age was 41 years, 71% were male and 40% former IVDU. At baseline, mean CD4 cell count was 438 cells/μl (SD=291). Mean duration of previous ARV treatment was 5.3 years (SD=2.8). Simplification (42%) was the most common reason to start the TDF+ddI+EFV combination. After a median follow-up of 15 months, the mean CD4 cell count increase was 50 cells/ml; however, different patterns of CD4 response were observed after stratifying by reason of treatment initiation with virological failure (+128 cells/μl; P<0.05) and treatment initiation (+107 cells/μl; P<0.05) groups behaving differently to simplification (+6 cells/μl; P=N.S.). Mean creatinine clearance (CrCl) (MDRD formula) at baseline, 12 and 24 months was 97, 93 and 93 ml/min, respectively (P=N.S.). Mean serum creatinine (SCr) level at baseline was 0.90 mg/dl (SD=0.22) and remained unchanged during the follow-up. In this cohort 33 episodes of adverse events were reported, which were principally attributed to the use of ddI (52%) and EFV (39%). However, only 11 patients (5.4%) after a mean exposure of 283.5 patient-years discontinued treatment due to toxicities.

Conclusions: In our highly pre-treated cohort, the combination of TDF, ddI and EFV was shown to be efficacious and safe. A deleterious effect in the CD4 count was not observed in any of the groups treated with this combination within this cohort.

ABSTRACT P-76
Antiviral Therapy 2007; 12 Suppl 2:L61
Effect of nucleoside reverse transcriptase inhibitors (NRTIs) on CD4 recovery for individuals on long-term, fully suppressive antiretroviral therapy (ART)

H Byakwaga1, J Zhou2, M Law3, S Emery4, P Mallon5 and DA Cooper6
1National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia; 2National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia; 3National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia; 4National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia; 5National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia; 6National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia

Background and objectives: In vitro studies of lymphocytes demonstrated NRTI-induced mitochondrial dysfunction to be associated with decreased lymphocyte proliferation. The in vivo consequences of this are not yet clear. The purpose of this study was to describe associations between exposure to individual NRTIs and CD4 outcomes for individuals on long-term, fully suppressive ART.

Methods: In a retrospective study, HIV-infected patients after starting ART with fully suppressed HIV viral load (HIVVL<400 copies/ml) were included. Patients not undetectable by week 60 or with virological failure were excluded. Linear regression analysis was used to determine relationships between time-weighted change from baseline CD4+ T-cell count at 48, 96 or 144 weeks and age, baseline CD4+ T-cell count, CD4% and HIVVL, time to fully suppressed virus, and exposure to different classes, combinations or individual antiretroviral agents.

Results: One-hundred and thirty-four patients were recruited: 3% female mean age 42 years (standard deviation [SD] 10.9], baseline CD4+ T-cell count was 242 [SD 198 cells/mm³]. Baseline VL >10,000 copies/ml was associated with greater increases in CD4+ T-cell counts from baseline at week 48 and 96. A trend towards smaller rises in CD4+ T-cells from baseline was observed in patients exposed to didanosine: 127 cells/mm³ versus 88 cells/mm³, 171 cells/mm³ versus 130 cells/mm³ and 202 cells/mm³ versus 153 cells/mm³ at weeks 48, 96 and 144, respectively, although this did not reach statistical significance. No significant association was found between exposure to individual NRTI, thymidine analogue or the combination of stavudine and didanosine, even when corrected for protease inhibitor and non-NRTI exposure.

Conclusion: Exposure to individual NRTI was not shown
to affect the recovery of CD4+ T-cell counts from baseline for individuals on long-term ART with fully suppressed viral load.

**ABSTRACT P-77**

*Antiviral Therapy 2007; 12 Suppl 2*:L62

Updated clinical characteristics and clinical risk factor analysis for suspected hypersensitivity (HSR) to abacavir (ABC) comparing ABC once daily (QD) versus ABC twice daily (BID)

AG Cutrell1, LL Curtis2, CH Brothers1, TM Davis1, CM Stainsby2 and JE Hernandez1

1GlaxoSmithKline Research and Development, Research Triangle Park, NC USA; 2GlaxoSmithKline Research and Development, Greenford, UK

**Background:** Abacavir (ABC) is an effective drug for HIV-1 therapy. The main adverse event associated with ABC is a hypersensitivity reaction (HSR). We performed an updated retrospective analysis of data from 39 trials using ABC to identify potential determinants of suspected HSR to ABC, and assessed the clinical syndrome described with ABC once daily (QD) compared with ABC twice daily (BID).

**Methods:** All GSK-sponsored trials with ≥24 weeks of ABC exposure and an authorized database by March 2006 were analysed. Cases had documentation of a clinical syndrome compatible with HSR or were reported using the ABC HSR case report form (CRF) module. Variables analysed for association with suspected HSR included baseline (BL) demographics and HIV disease characteristics, prior ART, frequency of ABC dosing, concurrent medications and laboratory results. After univariate analyses, multivariable models with stepwise selection were used to control for confounders. Two models were constructed, one with and one without BL laboratory data. Variables were retained if the significance level was <0.05.

**Results:** Among the 39 protocols, the incidence of suspected HSR ranged from 0% to 14%. Data from 10,888 subjects were analysed, of which 590 (5.4%) reported HSR to ABC, and assessed the clinical syndrome described with ABC once daily (QD) compared with ABC twice daily (BID).

**Conclusions:** The overall HSR rate was 5.4%. Black race and male gender were associated with a reduced risk of HSR; the prevalence of HLA-B*5701 differs among racial groups and is low in people of black race, which could partially explain this finding. Year since HSR CRF module introduction was associated with lower odds of reporting HSR. ABC dosing frequency was not associated with HSR or with a difference in incidence, clinical presentation or severity of suspected HSR to ABC.

**ABSTRACT P-78**

*Antiviral Therapy 2007; 12 Suppl 2*:L62

One-year bone mineral density changes in antiretroviral-naïve HIV-infected patients treated by a triple, versus a single-agent regimen, with Lopinavir/ritonavir in the Monark Trial

K Briot1, S Kolta1, P Flandre2, F Boué3, P Ngo Van4, I Cohen-Codar4, F Emery Salbert4, J P Chauvin5, M Norton5, YJ Delfraissy6 and C Roux1

1Paris-Descartes University, Medicine Faculty, UPRES-EA 4058, Assistance Publique-Hôpitaux de Paris, Cochin Hospital, Paris, France; 2INSERM Unité 720, CHU Pitié-Salpêtrière, France; 3A. Béclère Hospital, Clamart, France; 4Abbott, France; 5Abbott Laboratories; 6Bicêtre Hospital, Le Kremlin Bicêtre, France

**Background:** Antiretroviral therapy (ART) usually combine at least three drugs, including frequently a protease inhibitor (PI). However, ART causes long term problems, especially metabolic complications such as bone disease. Osteoporosis can be associated with either the HIV disease by itself, or to the therapy. Several trials evaluate the strategy of ART simplification into single class regimen, especially with lopinavir/ritonavir.

**Objectives:** To assess and to compare the one-year bone mineral density (BMD) relative (%) changes in HIV-infected patients treated with a triple drug versus a single drug lopinavir/ritonavir-based antiretroviral regimen.

**Patients and methods:** In the MONARK trial, 136 antiretroviral-naïve patients were randomized to receive either a lopinavir (400 mg)/ritonavir (100 mg) single-drug regimen (n=83) or lopinavir/ritonavir in combination with lamivudine (3TC) and zidovudine (AZT; n=53). Lumbar spine and total hip BMD were assessed by dual-energy X-ray absorptiometry (DEXA) at baseline and week 48; all the scans were analysed in a central facility by a single observer blinded to the treatment arms. The BMD changes after 1 year were expressed as a percentage of the baseline value. Wilcoxon rank-sum test and Wilcoxon signed-rank test were used.

**Results:** BMD data at baseline and Week 48 were available for 35 patients (mean age 37 years ±1.5) in the single-drug group and for 22 patients (37 years ±1.6) in the triple group. At week 48, lumbar spine BMD significantly decreased by 4.1% (interquartile range: -5.15–-2.1; P<0.001) in the lopinavir/ritonavir group and by -3.32%
HIV proteins modulate osteogenesis in a phase-specific manner

EJ Cotter, N Chew, PP Doran and WG Powderly

General Clinical Research Unit, School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland

Objective: A high incidence of decreased bone mineral density (BMD) has been associated with HIV infection. Normal skeletal homeostasis is controlled, at least in part, by the production and activity of mature osteoblasts. Previous studies by our group have demonstrated the ability of HIV proteins to perturb osteoblast function, and the degree of osteogenesis in differentiating mesenchymal stem cells (MSCs). Having shown effects on both terminally differentiated osteoblasts and MSCs undergoing osteoblastic differentiation, we sought to determine the mechanisms by which these proteins perturb total osteoblast number and activity, the cellular hallmarks of osteoporosis.

Methods: MSCs were cultured under both osteogenic (15 days culture in osteoblast differentiation medium) and quiescent (15 days culture in basal medium) conditions. Both cell populations were exposed to HIV p55-gag and HIV rev (100 ng/ml, 24 h). Cell function and the activity of the key MSC transcription factor RUNX-2 were determined post-exposure. Cellular levels of β-catenin were analysed using whole-cell ELISA.

Results: Exposure of MSCs cultured in basal media to HIV proteins had no significant effect on osteogenesis. However, changes in osteogenesis were revealed in cells cultured in osteoblast differentiation media. These data suggest that the effect of HIV proteins on osteoblast production are dependent on MSC differentiation status. RUNX-2 activity was significantly changed in cells grown under basal conditions, a pattern that was also observed in cells grown in osteoblast differentiation medium (p55 inducing a decrease of 41 ±1.5% and rev an increase of 47 ±3% [n=3, P≤0.05]). RUNX-2 is a transcription factor associated with the development and maintenance of an osteoblastic phenotype. These data suggest that whilst HIV proteins do not effect the differentiation of MSCs grown under basal conditions, they do activate the signalling mechanisms that drive final cell phenotype. In addition, the HIV proteins altered expression of protein levels of β-catenin, a signalling protein associated with osteogenesis.

Conclusions: These data demonstrate that the effect of HIV proteins on bone is dependent on the differentiation status of the cells that they are in contact with. The effect on bone cell signalling provides insights into the mechanism of HIV-induced decreases in bone mineral density.
13.14–26.35) per 100 person-years. Eight (9.5%) patients with significant fibrosis versus one (3.4%) of those with <F2 showed TE (P=0.51). TE was observed in two (8.3%) cirrhotic patients and in three (5.3/58) subjects with a fibrosis measurement and no cirrhosis (P=0.63). TBE was more common among cirrhotics (8 [35%] versus 7 [13%], P=0.05). Forty-five (25%) patients had values of APRI and Forns indexes consistent with significant fibrosis at entry. This percentage did not change significantly throughout the follow-up.

Conclusions: Atazanavir/ritonavir including combinations are safe in HIV patients with viral hepatitis, including those with cirrhosis. The presence of significant fibrosis does not increase the risk of TE in this setting.

**ABSTRACT P-81**

*Antiviral Therapy* 2007; 12 Suppl 2:L64

**Association of hyperlipidaemia with advanced liver fibrosis in HIV* patients**

**E Blanco, P García-Gascó, P Ryan, J García-Merchán, C Carapeto, A Alcolea, J González-Lahoz and V Soriano**

Hospital Carlos III, Madrid, Spain

**Objectives:** Liver fibrosis (LF) in HIV* patients (pts) may be the final consequence of several causes, steatohepatitis being one condition that is potentially involved. Hepatic elastometry (FibroScan) and ultrasonography (US) are non-invasive procedures with high accuracy of detecting advanced LF and severe liver steatosis (SLS), respectively. The aim of this study is to explore which factors might be related to LF.

**Methods:** Cross-sectional study of all HIV* outpatients who underwent liver US and FibroScan assessment during 2003–2007 at our institution. Demographics, immunological, virological and biochemical parameters, as well as chronic hepatitis B/C, alcohol abuse (>60 g/day), diabetes, hyperlipidaemia (cholesterol and/or triglycerides levels >200 mg/dl), BMI, and time on antiretrovirals were recorded. Univariate and multivariate analyses were performed.

**Results:** In 781 out of 2,300 HIV* patients on regular follow-up, hepatic US was performed and SLS was diagnosed in 78 (10%). Among those patients who underwent US, LF was assessed by FibroScan in 111 individuals. Of those: mean age 42 ±2 years, male 83%, mean CD4 count 564 ±311 cells/μl, HIV-RNA <50 copies/ml 77%, pos HCV RNA 57%, HbsAg* 12%, alcohol abuse 19%, diabetes 16%, and hyperlipidaemia 36%. SLS was seen in 63 pts (57%) and advanced LF (Metavir F3–F4) in 25 pts (22.5%). Association of US and FibroScan findings are shown in Table 1. Of 25 pts with advanced LF, 16 (64%) had SLS; of 48 pts with no SLS, 39 (81%) did not show advanced LF. In the univariate analysis, differences were found between patients with and without advanced LF (F3–F4) for chronic hepatitis C (76% versus 51%, P=0.04) and hyperlipidaemia (52% versus 31%, P=0.09).

In the logistic regression analysis, chronic hepatitis C (OR 8.4, P=0.01) and hyperlipidaemia (OR 7, P=0.01) were independently associated with advanced LF.

**Conclusions:** Advanced LF in HIV* patients is associated with chronic hepatitis C and with hyperlipidaemia. The association of SLS with advanced LF supports the hypothesis that lipid increases can cause liver damage throughout liver steatohepatitis. Therefore, control of lipid abnormalities might help minimize liver damage in HIV* patients.

**Table 1. (Abstract P-81)**

<table>
<thead>
<tr>
<th>FibroScan (n=111)</th>
<th>Not severe liver steatosis in ultrasonography (n=48)</th>
<th>Severe liver steatosis in ultrasonography (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0–F2 (n=86)</td>
<td>39</td>
<td>47</td>
</tr>
<tr>
<td>F3–F4 (n=25)</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>P=NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ABSTRACT P-82**

*Antiviral Therapy* 2007; 12 Suppl 2:L64

**Metabolic syndrome and progression of liver fibrosis in HIV/HCV-coinfected patients on HAART**

**P Barreiro1, E Blanco1, C de Mendoza1, N Zakhonero1, I. Martín-Carbonero1, E Melián2, G Fernández-Vázquez2, F Sánchez-Franco2, J González-Lahoz1 and V Soriano1**

1Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain; 2Department of Endocrinology, Hospital Carlos III, Madrid, Spain

**Objectives:** Besides immune suppression, other factors can influence liver fibrosis progression in HIV/HCV-coinfected patients. The aim of this study is to identify which factors might be involved in liver fibrosis.

**Methods:** All HIV/HCV-coinfected patients (HCV-RNA*) on regular follow-up at our institution underwent liver fibrosis assessment using elastometry (FibroScan). Advanced liver fibrosis (ALF) was defined as liver stiffness >9.5 Kpa. Total exposure to distinct antiretroviral (ARV) drugs was estimated using the pharmacy-computerized database. Demographics, immunological, virological and biochemical parameters, as well as alcohol abuse (>60 mg/day) were recorded. Univariate and multivariate analyses were performed.

**Results:** A total of 489 HIV/HCV-coinfected patients on HAART were identified, of whom 37% had ALF. In the
univariate analysis, older age (44 versus 42 years), male gender (76% versus 67%), prior episodes of ALT >100 IU/ml (25% versus 7%), increased alcohol consumption (55% versus 34%), mean CD4 (486 versus 553 cells/ml), mean HCV RNA (6.4 versus 6 log IU/ml), mean glucose (102 versus 98 mg/dl), HOMA index (4.5 versus 3.2) and mean triglycerides (176 versus 148 mg/dl) were all significantly associated with ALF, as compared with patients without ALF.

A total of 3,291 HCV/HIV-coinfected patients years of ARV exposure were further analysed. Overall, 34.7%, 48.7% and 74.1% had received prior NVP, EFV or PI, respectively. There was an association between greater liver fibrosis and duration of PI exposure (rho: 0.11; P=0.01), even more pronounced for RTV-boosted PI (rho: 0.18; P<0.001). No such correlation was found for distinct nucleoside analogues nor for NVP or EFV.

In the multivariate analysis, factors (OR [95% CI]) significantly associated with ALF were age (2.1 [1.1–4] per decade), alcohol abuse (2.3 [1.3–4]), episodes of ALT >100 IU/ml (1.04 [1.03–1.06]), CD4 counts (0.8 [0.7–0.9] per 100 cells/ml), glucose levels (1.1 [1–1.2] per 10 mg/dl) and HOMA index (1.2 [1.1–1.4]).

Conclusions: The influence of HAART on the progression of liver fibrosis in HIV/HCV-coinfected patients may be a ‘double-edged sword’. While increased CD4 counts could slow liver fibrosis progression, episodes of ALT elevations, insulin resistance and hypertriglyceridaemia might accelerate liver damage.