CLINICAL STUDY

Switching to unboosted atazanavir improves glucose tolerance in highly pretreated HIV-1 infected subjects

Monica Guffanti¹, Andrea Caumo², Laura Galli¹, Alba Bigoloni¹, Andrea Galli¹, Geneviève Dagba¹, Anna Danise¹, Livio Luzi², Adriano Lazzarin^{1,3} and Antonella Castagna¹

¹Clinic of Infectious Diseases, San Raffaele Scientific Institute, Via Stamira d'ancona 20, 20127 Milan, Italy, ²Nutrition/Metabolism Unit, San Raffaele Scientific Institute, Milan, Italy and ³Università Vita-Salute, Milan, Italy

(Correspondence should be addressed to M Guffanti; Email: guffanti.monica@hsr.it)

Abstract

Objective: To evaluate the 24-week effects on glucose tolerance of switching from a protease inhibitor (PI)-based to an unboosted atazanavir-including regimen in highly pretreated HIV-1 infected subjects with metabolic alterations.

Design: Prospective, open-label, single-center, 24-week pilot study.

Methods: Twenty-one subjects underwent an oral glucose tolerance test (OGTT) at baseline (BL) and after 24 weeks of unboosted atazanavir. Insulin sensitivity and β -cell responsiveness were evaluated on the basis of static and dynamic data; fasting glucose, insulin, C-peptide, triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), TC/HDL-c ratio, CD4+ cell count and HIV-1 RNA were measured.

Results: After 24 weeks of unboosted atazanavir, the 120-min glucose level was significantly lower than the one measured at BL ($P=0.021$); there were no statistically significant differences in the insulin concentration profile. The SI_{oral} , an OGTT-based index of insulin sensitivity, was significantly higher at week 24 ($P=0.017$); the indices of first- and second-phase β -cell responsiveness did not significantly change. There was no significant difference between BL and 24-week fasting glucose, insulin or C-peptide levels, and consequently no change in fasting homeostasis model assessment indices of insulin sensitivity and β -cell function. There were significant improvements in TG ($P=0.009$), TC ($P=0.0001$), LDL-c ($P=0.019$) and TC/HDL-c ratio ($P=0.001$), and a similar trend in HDL-c levels ($P=0.069$). No significant changes in the immunological and virological parameters were detected.

Conclusions: Our results show that switching from a PI-based to an unboosted atazanavir-including regimen leads to a significant improvement in glucose tolerance in highly pretreated HIV-1 infected subjects with metabolic alterations.

European Journal of Endocrinology 156 503–509

Introduction

Insulin resistance (IR), impaired glucose tolerance (IGT), and type 2 diabetes mellitus (DM) are conditions that are increasingly described in HIV-1 infected subjects receiving highly active antiretroviral therapy (HAART) (1–2).

Insulin sensitivity (IS) and β -cell function are the cornerstones of glucose tolerance and their dysfunctions may progressively lead to IR, IGT and clinically established type 2 DM (2). Furthermore, they are inextricably linked insofar as changes in IS are compensated by inverse change in β -cell responsiveness (3) and, in order to obtain a complete picture of glucose homeostasis in a given subject, it is important to assess the individual contributions of both to glucose tolerance.

The introduction of HAART in the management of HIV infection, especially the use of protease inhibitor

(PI)-based regimens, has led to the greater emergence of metabolic complications such as dyslipidemia, IR, hyperglycemia and lipodystrophy (4–7).

Clinical studies have shown that treatments including indinavir, lopinavir/ritonavir and amprenavir cause IR and decreased glucose tolerance both in healthy HIV-seronegative and seropositive subjects (8–12). These *in vivo* observations are supported by *in vitro* studies showing that PIs dose-dependently differentially inhibit glucose transporter-4 (GLUT-4)-mediated glucose uptake in 3T3-L1 adipocytes (13–14).

The backbone therapy is similarly involved insofar as clinical studies indicate that exposure to nucleoside analogue reverse transcriptase inhibitors (NRTIs), particularly stavudine, is associated with the development of metabolic alterations (15–16).

Atazanavir is a novel azapeptide PI that is characterized by a favorable effect on lipid profiles (17). *In vitro* data show that, unlike other PIs, it minimally inhibits

glucose transport by GLUT-4 (14). In line with this observation, studies comparing atazanavir (with and without ritonavir) and lopinavir/ritonavir in healthy HIV-seronegative adults found that treatment with atazanavir, unlike lopinavir/ritonavir, did not affect IS (18–19). Clinical trials involving antiretroviral (ARV)-naïve and experienced subjects have confirmed the better lipid profile of atazanavir in comparison with other treatments (17). However, atazanavir boosted with ritonavir may be less favorable than unboosted atazanavir in metabolic terms, as recently described (20–22).

At present, the management of highly pretreated HIV-1 infected subjects with metabolic disturbances is an important issue, since these complications may increase the risk of cardiovascular disease (23). Treatment options using drugs with less metabolic impact need to be investigated.

The aim of this study was to evaluate the 24-week effects on glucose tolerance of switching to unboosted atazanavir from a PI-based regimen in highly pretreated HIV-1 infected subjects with metabolic alterations.

Methods

We prospectively evaluated glucose and lipid metabolism in a subset of highly pretreated HIV-1 infected subjects attending the Clinic of Infectious Diseases – San Raffaele Scientific Institute, Milan, Italy – who were enrolled in the Atazanavir Early Access Program (AI424-900).

The subjects being treated with a PI-based regimen, who showed metabolic alterations including IR estimated by means of homeostasis model assessment (HOMA) method (24) and/or dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia) (25), and had HIV-1 RNA levels of <400 copies/ml were eligible.

We chose a HOMA-IR value ≥ 3.0 as indicative of IR in our population, according to similar values selected as the cut-off point to define IR in previous studies (26–27).

The criteria recommended by the American Diabetes Association were utilized to interpret glucose values (28).

The subjects were excluded if they had a diagnosis of DM or were being treated with an antidiabetic agent, reported the use of testosterone, estrogen, growth hormone or other steroids in the previous 6 months, were active alcohol or substance abusers, had experienced an acquired immune deficiency syndrome-related episode within the previous 3 months or showed poor treatment adherence.

This study was approved by San Raffaele Scientific Institute's Ethical Committee; the subjects gave their informed consent and were enrolled in accordance with the inclusion and exclusion criteria. Enrolment started in November 2003 and ended in December 2004.

Study design

This was a 24-week, prospective, open-label, single-center pilot study.

The primary objective was to assess whether switching from a PI-based to an unboosted atazanavir-including regimen significantly improves oral glucose tolerance in a group of highly pretreated HIV-1 infected subjects with metabolic alterations. The subjects underwent an oral glucose tolerance test (OGTT) at baseline (BL) and after 24 weeks of the study treatment; the primary endpoint was the 120-min glucose level.

The secondary objectives were the assessment of IS, β -cell function, lipid metabolism and the safety and efficacy of the HAART.

The subjects were instructed to remain fasting for at least 10-h before each study visit. Data regarding time of onset and stage of HIV-1 infection according to the 1993 Revised Classification System, concomitant diseases, previous ARV treatment and concomitant therapies were collected.

At BL the subjects were switched to receive unboosted atazanavir without any change in the NRTIs backbone of their ongoing regimen and were followed up as outpatients after 4, 12 and 24 weeks of study treatment. All visits were overseen by the same study physician. At each visit any change in diet, physical exercise or smoking habits was evaluated by direct questioning; fasting weight, treatment side-effects, intercurrent illnesses, concomitant therapies, self-reported adherence and pill count were recorded.

Blood samples were collected for clinical chemistry, lipid metabolism, immunological and virological analyses at BL and week 4, 12 and 24.

Measurements

Blood samples were collected in the fasting state and all parameters were tested by standard routine procedures (Diagnostic Unit, San Raffaele Scientific Institute, Laboraf). Plasma glucose levels were measured by a hexokinase-G6PD method (Modular Roche Analyzer). Serum insulin and C-peptide levels were assayed with an immunofluorimetric method (AIA 1800 Tosoh Analyzer). Serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c) and low-density lipoprotein-cholesterol (LDL-c) levels were measured by an enzymatic colorimetric method (Modular Roche Analyzer) and the TC/HDL-c ratio was calculated. CD4⁺ cells ($\times 10^6/l$) were counted using flow cytometry (EPICS-XL Coulter, Beckman) and viral RNA was quantified in plasma using the Versant HIV-1 RNA Assay (bDNA; Bayer Health Care), with a lower quantification limit of 50 copies/ml. Co-infection with type B and C hepatitis was assessed by means of hepatitis B virus (HBV)-DNA (Real Time PCR HBV, Artus, Hamburg, Germany) and HCV-RNA (Amplicor Ver 2.0, Roche Diagnostics).

Oral glucose tolerance test

Seventy-five grams of dextrose in water was administered orally and blood samples were drawn from an indwelling intravenous catheter for glucose and insulin determination at 0, 30, 60, 90, 120 and 180 min after the ingestion of dextrose.

Glucose tolerance, insulin sensitivity and β -cell function

Glucose tolerance was evaluated by measuring glucose level 120 min after the start of the OGTT; IS and β -cell function were evaluated in two ways on the basis of the static (i.e. fasting) or dynamic (i.e. OGTT) data.

The HOMA2 method (29) was used to derive surrogate indices of IS (HOMA-S%) and β -cell responsiveness (HOMA-B%) from fasting glucose and insulin levels. The method proposed by Caumo *et al.* was used to calculate an index of IS, defined as SI_{oral} , from the OGTT data (30). Such an OGTT-based index has been shown to be well correlated with the IS measured by the glucose clamp technique (31). The equations proposed by Stumvoll *et al.* (32) were used to calculate two indices of β -cell responsiveness (first- and second-phase) from the OGTT data. Such OGTT-based indices have been shown to be well correlated with first- and second-phase insulin secretion during hyperglycemic clamp (33).

Statistical analysis

Absolute differences between BL and week 4, 12 and 24 values were calculated, and the non-parametric Wilcoxon signed rank test for paired data was used to detect their statistical significance. Bonferroni correction was considered.

Continuous variables are expressed as median values (interquartile range), unless otherwise indicated. The statistical analyses were made using SAS software (version 8.2; SAS Institute).

All of the significance tests were two-sided and $P < 0.05$ was considered statistically significant.

Results

Twenty-five subjects were enrolled in this study. Four were not eligible because of OGTT evidence of DM (1), BL OGTT insulin data unavailable because of specimen hemolysis (1), poor adherence (1) and discontinuation of atazanavir treatment before week 24 because of the occurrence of pregnancy (1). The analysis therefore included the 21 subjects (84%) for whom BL and week 24 data were available. The BL characteristics of the analyzed subjects are shown in Table 1.

The median (interquartile) BL body weight and body mass index (BMI) were 71 kg (63.5/77) and 24.8 kg/m^2 (22.0/26.6) respectively; by week 24

Table 1 Baseline characteristics of study subjects ($n=21$).

Variable	Value
Male sex (no. (%))	16 (76)
Median age (years (IQR))	42 (41/47)
Caucasian race (no. (%))	21 (100)
Median duration of HIV-1 infection (years (IQR))	8.56 (5.50/11.5)
AIDS-CDC stage C (no. (%))	9 (43)
Detectable HCV-RNA (no. (%))	6 (29)
Detectable HBV-DNA (no. (%))	0 (0)
Median exposure to ARV therapy (years (IQR))	6.42 (4.99/8.47)
Protease inhibitors withdrawn (no. (%))	21 (100)
Nelfinavir	10 (47)
Lopinavir/r	9 (43)
Amprenavir/r	1 (5)
Indinavir/r	1 (5)
Stavudine as NRTIs backbone (no. (%))	6 (29)
Median CD4 cell count $\times 10^6/\text{l}$ (IQR)	528 (382/806)
Median HIV-RNA $\log_{10}$ copies/ml (IQR)	1.69 (1.69/1.69)

IQR, interquartile range; ARV, antiretroviral.

these had increased to 71 kg (64.7/80; change_{w24-w0} 1.2 (0.5/2.7); $P=0.006$) and 23.6 kg/m^2 (22.4/27.7; change_{w24-w0} 0.415 (0.173/0.978); $P=0.005$). No change in diet, physical exercise or smoking habits occurred during the study.

All the subjects were on a PI-based regimen (as showed in Table 1) with a backbone of at least two NRTIs: lamivudine in 19 subjects (90%), didanosine in 13 (62%), stavudine in six (29%), and zidovudine in five (24%).

Fasting measures of glucose and lipid metabolism

Table 2 shows that there were no significant differences between the fasting glucose, insulin or C-peptide levels measured at BL and after 24 study weeks; consequently, there was no significant change in the fasting HOMA2 indices of IS and β -cell function. Nevertheless, a positive median change value of HOMA-S% and negative median change value of HOMA-B% were observed.

Table 3 shows the fasting values of lipid metabolism in 17 subjects; the remaining four were excluded from the analysis because they were taking lipid lowering agents at BL. No other subjects started lipid lowering therapy during the study. There were significant improvements in TG, TC, LDL-c and TC/HDL-c ratio between BL and week 24. HDL-c showed a similar (but not statistically significant) trend.

OGTT

The OGTT data are shown in Table 2 and Fig. 1.

Figure 1 shows the average time courses of glucose and insulin concentrations during the BL and 24-week OGTT. Plasma glucose concentration at every time point was lower after 24 weeks of treatment than at BL, with

Table 2 Twenty-four-week changes from baseline in glycemic parameters in 21 HIV-1 infected subjects.

Parameter	Baseline ^a	Week 24	Δ_{w24-w0}	$P(\Delta_{w24-w0})^b$
Fasting measurements				
Glucose (mg/dl)	95 (87/100)	95 (87/98)	-2 (-6/6)	0.724
Insulin (μ U/ml)	14 (7/17)	10 (5/21)	-2 (-6/7)	0.721
C-peptide (ng/ml)	3.25 (2.32/3.96)	2.41 (2.24/4.6)	-0.09 (-0.95/0.64)	0.731
HOMA-S%	53.2 (45.6/107)	77.1 (37.3/149.9)	19 (-18.3/42.9)	0.202
HOMA-B%	100.2 (72.4/197.1)	111.3 (60/145.4)	-12.4 (-37.9/71.4)	0.675
OGTT				
Glucose at 30 min	158 (138/177)	155 (133/180)	-5 (-27/25)	0.712
Insulin at 30 min	82 (28/138)	50 (17/112)	-22 (-47/11)	0.308
Glucose at 120 min	108 (81/126)	91 (82/107)	-13 (-21/-3)	0.021
Insulin at 120 min	37 (24/106)	17 (8/69)	-25 (-39/0)	0.112
SI _{oral} ($\times 10^4$)	7.87 (4.05/21.47)	20.18 (3.56/56.45)	5.13 (-0.497/17.68)	0.017
Stumvoll-first phase	1281 (514/2299)	893 (422/1606)	-127 (-456/386)	0.511
Stumvoll-second phase	325 (170/572)	244 (142/399)	-29.5 (-105.7/102.3)	0.408

OGTT, oral glucose tolerance test; HOMA-S%, homeostasis model assessment2-insulin sensitivity; HOMA-B%, homeostasis model assessment2- β -cell function; SI_{oral}, index of insulin sensitivity from oral glucose tolerance test; Stumvoll-first phase and Stumvoll-second phase, indices of β -cell responsiveness from oral glucose tolerance test.

^aBaseline = w0.

^bWilcoxon signed rank test. Data are presented as median (interquartile range).

the 120 min value being significantly lower. The serum insulin concentrations measured after 24 weeks were also always lower than at BL, but no statistically significant differences were detected.

The SI_{oral} index was significantly higher after 24 study weeks than at BL, whereas the indices of first- and second-phase β -cell responsiveness were not significantly different.

Safety and efficacy

The only grade III/IV adverse event was a grade III transaminase alteration in one subject with hepatitis C virus co-infection observed in week 24. No intercurrent illnesses occurred during the study.

No significant variation in the median (interquartile) immunological or virological values was observed between BL and week 24 (CD4 cell count ($\times 10^6$ /l) 528 (382/806) at BL vs 477 (370/809) at week 24; change_{w24-w0} 3 (-74/52); $P=0.776$ and HIV-1 RNA ($\log_{10}$ copies/ml) 1.69 (1.69/1.69) at BL vs 1.69 (1.69/1.69) at week 24; change_{w24-w0} 0 (0/0); $P=0.812$).

Twenty subjects (95%) showed HIV-1 RNA level <50 copies/ml at BL and the undetectability had lasted a median (interquartile) of 23.82 months (12.99/38.81).

Only one subject previously treated with amprenavir/ritonavir experienced a virological rebound (930 copies/ml) at week 24.

Discussion

In the present study, we observed that switching to unboosted atazanavir from a PI-based regimen improved glucose tolerance in a group of pretreated HIV-1 infected subjects, as assessed by 120 min glucose concentration during an OGTT. Glucose tolerance was measured before the switch and up to 24 weeks afterwards, when not only was glucose tolerance significantly higher, but also the entire glycemic curve was below the BL curve at each time point, thus indicating an improved ability to dispose of the oral glucose load. Interestingly, this was accompanied by a trend towards a lower insulin profile at week 24, as

Table 3 Lipidemic parameters at baseline, and 4, 12 and 24 weeks after switching to unboosted atazanavir, and changes from baseline, in 17 HIV-1 infected subjects^a.

Parameters	Baseline ^b	Week 4	Week 12	Week 24	Δ_{w24-w0}	$P(\Delta_{w24-w0})^c$
Triglycerides (mg/dl)	190 (138/411)	156 ^{*c} (77/189)	130 ^{*c} (89/199)	119 (87/176)	-65 (-144/-14)	0.009
TC (mg/dl)	220 (209/260)	195 ^{†c} (169/234)	192 ^{†c} (175/229)	205 (175/226)	-34 (-45/-17)	0.0001
HDL-c (mg/dl)	47 (40/50)	49 ^{†c} (40/51)	53 ^{†c} (39/57)	53 (43/58)	6 (3/8)	0.069
LDL-c (mg/dl)	144 (120/154)	123 ^{§c} (94/162)	128 ^{§c} (108/162)	134 (104/150)	-18 (-35/-7)	0.019
TC/HDL-c ratio	5.0 (3.8/5.9)	4.4 ^c (3.8/4.8)	4.2 ^c (3.3/5.1)	4.0 (3.2/4.5)	-1.1 (-1.5/-0.5)	0.001

TC, total cholesterol; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; TC/HDL-c, total cholesterol/high-density lipoprotein-cholesterol ratio. ^{*} $P(\Delta_{w4-w0})$:0.0008; ^{*} $P(\Delta_{w12-w0})$: <0.0001 . [†] $P(\Delta_{w4-w0})$: <0.0001 ; [†] $P(\Delta_{w12-w0})$:0.0002. [‡] $P(\Delta_{w4-w0})$:0.720; [‡] $P(\Delta_{w12-w0})$:0.311. [§] $P(\Delta_{w4-w0})$:0.046; [§] $P(\Delta_{w12-w0})$:0.101. ^{||} $P(\Delta_{w4-w0})$:0.0009; ^{||} $P(\Delta_{w12-w0})$:0.006. Data are presented as median (interquartile range).

^aFour subjects were excluded because on treatment with lipid lowering agents at baseline.

^bBaseline = w0.

^cWilcoxon signed rank test with Bonferroni correction.

Figure 1 Glycemic and insulin curves during oral glucose tolerance test at baseline and after 24 weeks of treatment with unboosted atazanavir, in 21 HIV-1 infected subjects. Data are presented as mean $\pm$ S.E.M. *Baseline=w0.

shown by the negative median change value and the related interquartile range at 120 min. The finding of improved glucose disposal with less insulin strongly suggests enhanced IS, which was confirmed by the significant increase in the SI_{oral} index following the switch to unboosted atazanavir. In order to obtain a more detailed picture of glucose metabolism in our subjects, the indices of first- and second-phase insulin secretion were also calculated. This was not significantly different at BL compared to week 24, but a trend towards a reduced β -cell responsiveness was detected, as shown by the negative median change value, which can be interpreted as a reduced need for β -cells to supply insulin due to the enhancement of IS.

It is worth making some comments about the assessments of glucose metabolism made using the OGTT and HOMA2 method. It is well known that it is important to assess IS and β -cell responsiveness simultaneously because their interdependence is fundamental to glucose tolerance (3). The OGTT is a simple physiological test that directly assesses glucose tolerance and provides validated, model-based assessment of insulin sensitivity (SI_{oral}) and β -cell responsiveness (Stumvoll's first- and second-phase indices) based on dynamic glucose and insulin concentrations (30, 33), whereas the HOMA provides estimates of IS (HOMA-S%) and β -cell responsiveness (HOMA-B%) based on fasting glucose and insulin concentrations (29). The HOMA indices refer to static, unstimulated conditions and have been validated against the clamp technique (31). In the present study we found that the HOMA-based picture of glucose metabolism and the OGTT were substantially concordant; the OGTT revealed a significant improvement in IS and a modest, non-significant reduction in β -cell responsiveness, whereas the HOMA detected a slight, non-significant improvement in IS and a slight, non-significant reduction in β -cell responsiveness. This substantial agreement is reassuring, but it is worth pointing out that the OGTT seems to be more capable of detecting changes in IS than the HOMA2 method, probably because the dynamic conditions as determined by an oral glucose load allow a more accurate assessment of insulin action.

A secondary aim of our study was to investigate the effect of the switch on lipid metabolism. Our data showed a significant improvement in the parameters of fasting TG, TC and the TC/HDL-c ratio by week 4, which was maintained until week 24, when there was a significant decrease of LDL-c and a trend towards an increase in HDL-c.

In the present study we administered unboosted atazanavir, thus allowing a selective investigation of the impact of the switch without the potential confounding effect of ritonavir. It has been recently shown that a low dose of ritonavir can worsen the metabolic status (20–22) and a significant increase of TG and insulin area under the curve during OGTT has been detected in healthy HIV-negative subjects (34).

In our opinion, there is a need for randomized studies comparing unboosted and boosted atazanavir to evaluate the effect of ritonavir in heavily pretreated HIV-1 infected subjects with metabolic disturbances.

The overall results of our study are consistent with the idea that the improvement in glucose and lipid metabolism is a result of replacing PIs with a drug having few, if any, effects on these parameters, however they do not allow any comment on the possibility that long-term treatment with unboosted atazanavir may actually be beneficial.

Moreover, we found that the switch to unboosted atazanavir effectively controlled HIV replication and immune status for 24 weeks in this group of HIV-1 infected subjects, with sustained virological control, who had been exposed to HIV-1 virus and ARV treatment for a long time.

Our study has a number of limitations. It is a pilot, non-randomized study that enrolled a limited number of subjects who were followed-up for 24 weeks. The previous treatment regimens were based on different PIs, and we cannot exclude a possible difference in the impact of the switch depending on the previous PI, as a drug-specific effect is involved in the development of metabolic disturbances (14).

We did not make a full assessment of fat redistribution by means of dual-energy X-ray absorptiometry/single-cut computed tomography scan in order to evaluate the

contribution of body changes, although we excluded weight loss as a possible cause of the improvement in glucose tolerance. Finally, we did not measure free fatty acids as indices of lipolysis.

In summary, our results show that switching from a PI-based to an unboosted atazanavir including regimen leads to a significant improvement in glucose tolerance, insulin sensitivity and fasting lipidemic parameters in highly pretreated HIV-1 infected subjects with metabolic alterations.

These encouraging results are helpful indications for assessing the effectiveness of a switch to unboosted atazanavir in pretreated HIV-1 infected subjects affected by glucose intolerance or DM.

Acknowledgements

We are indebted to the patients who took part in this study, without whom this work would not have been possible. We would like to thank Bristol-Mayer Squibb for providing atazanavir (Expanded Access Program AI424-900).

Funding

This study was supported by a grant from the Fondazione San Raffaele del Monte Tabor.

References

- 1 Lumpkin MM. Reports of diabetes and hyperglycemia in patients receiving protease inhibitors for the treatment of human immunodeficiency virus (HIV). *FDA Public Health Advisory*. Washington, DC:US Food and Drug Administration, 1997.
- 2 Dubè MP. Disorders of glucose metabolism in patients infected with human immunodeficiency virus. *Clinical Infectious Diseases* 2000 **31** 1467–1475.
- 3 Bergman RN, Finegood DT & Kahn SE. The evolution of β -cell dysfunction and insulin resistance in type 2 diabetes. *European Journal of Clinical Investigation* 2002 **32** 35–45.
- 4 Walli R, Herfort O, Michl GM, Demant T, Jäger H, Dieterle C, Bogner JR, Landgraf R & Goebel FD. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired glucose tolerance in HIV-1 infected patients. *Acquired Immunodeficiency Syndrome* 1998 **12** F167–F173.
- 5 Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ & Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *Acquired Immunodeficiency Syndrome* 1998 **12** F51–F58.
- 6 Behrens G, Dejam A, Schmidt H, Balks HJ, Brabant J, Körner T, Stoll M & Schmidt RE. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *Acquired Immunodeficiency Syndrome* 1999 **13** F63–F70.
- 7 Woerle HJ, Mariuz PR, Meyer C, Reichman RC, Popa EM, Dostou JM, Welle SL, Gerich JE, Welle SL & Gerich JE. Mechanism for the deterioration in glucose tolerance associated with HIV protease inhibitor regimen. *Diabetes* 2003 **52** 918–925.
- 8 Noor MA, Lo JC, Mulligan K, Schwarz JM, Halvorsen RA, Schambelan M & Grunfeld C. Metabolic effects of indinavir in healthy HIV-seronegative men. *Acquired Immunodeficiency Syndrome* 2001 **15** 11–18.
- 9 Dubè MP, Edmondson-Melançon H, Qian D, Aqeel R, Johnson D & Buchanan TA. Prospective evaluation of the effect of initiating indinavir-based therapy on insulin sensitivity and B-cell function in HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes* 2001 **27** 130–134.
- 10 Noor MA, Seneviratne T, Aweeka FT, Lo JC, Schwarz JM, Mulligan K, Schambelan M & Grunfeld C. Indinavir acutely inhibits insulin-stimulated glucose disposal in humans: a randomized, placebo-controlled study. *Acquired Immunodeficiency Syndrome* 2002 **16** F1–F8.
- 11 Lee GA, Seneviratne T, Noor MA, Lo JC, Schwarz JM, Aweeka FT, Mulligan K, Schambelan M & Grunfeld C. The metabolic effects of lopinavir/ritonavir in HIV-negative men. *Acquired Immunodeficiency Syndrome* 2004 **18** 641–649.
- 12 Dubè MP, Qian D, Edmondson-Melançon H, Sattler FR, Goodwin D, Martinez C, Williams V, Johnson D & Buchanan TA. Prospective, intensive study of metabolic changes associated with 48 weeks of amprenavir-based antiretroviral therapy. *Clinical Infectious Diseases* 2002 **35** 475–481.
- 13 Murata H, Hruz PW & Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *Journal of Biological Chemistry* 2000 **275** 20251–20254.
- 14 Parker RA, Flint OP, Mulvey R, Elosua C, Wang F, Fenderson W, Wang S, Yang WP & Noor MA. Endoplasmic reticulum stress links dyslipidemia to inhibition of proteasome activity and glucose transport by HIV protease inhibitors. *Molecular Pharmacology* 2005 **67** 1909–1919.
- 15 Hadigan C, Borgonha S, Rabe J, Young V & Grinspoon S. Increased rates of lipolysis among human immunodeficiency virus-infected men receiving highly active antiretroviral therapy. *Metabolism* 2002 **51** 1143–1147.
- 16 Brambilla AM, Novati R, Calori G, Meneghini E, Vacchini D, Luzi L, Castagna A & Lazzarin A. Stavudine or indinavir-containing regimens are associated with an increased risk of diabetes mellitus in HIV-infected individuals. *Acquired Immunodeficiency Syndrome* 2003 **17** 1193–1195.
- 17 Swainston Harrison T & Scott LJ. Atazanavir: a review of its use in the management of HIV infection. *Drugs* 2005 **65** 2309–2336.
- 18 Noor MA, Parker RA, O'Mara E, Grasela DM, Currie A, Hodder SL, Fiedorek FT & Haas DW. The effect of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. *Acquired Immunodeficiency Syndrome* 2004 **18** 2137–2144.
- 19 Noor MA, Flint OP, Maa J-F & Parker RA. Effects of atazanavir/ritonavir and lopinavir/ritonavir on glucose uptake and insulin sensitivity: demonstrable differences *in vitro* and clinically. *Acquired Immunodeficiency Syndrome* 2006 **20** 1813–1821.
- 20 Möbius U, Lubach-Ruitman M, Castro-Frenzel B, Stoll M, Esser S, Voigt E, Christensen S, Rump J, Fätkenheuer G, Behrens G & Schmidt RE. Switching to atazanavir improves metabolic disorders in antiretroviral-experienced patients with severe hyperlipidemia. *Journal of Acquired Immune Deficiency Syndromes* 2005 **39** 174–180.
- 21 Malan N, Krantz E, David N, Kastango K, Frederick D, Matthew M, Schnittman S, Hammond J & the -089 Study Group. Efficacy and safety of atazanavir-based therapy in antiretroviral naïve HIV-1 infected subjects, both with and without ritonavir: 48-week results from AI424-089 (Abstract 107LB). Presented at: *XIII Conference on Retroviruses and Opportunistic Infections*. Denver, February 2006.
- 22 Samson P, Rutstein R, Fenton T, Kiser J, Fletcher C, Schnittman C, Mofenson L, Smith E, Graham B, Aldrovandi G & PACTG 1020 Study Team. Changes in cholesterol and triglyceride level among pediatric patients treated with atazanavir, with or without ritonavir boosting: the 1020A NIH PACTG Protocol (Abstract 689). Presented at: *XIII Conference on Retroviruses and Opportunistic Infections*. Denver, February 2006.

- 23 Grinspoon S & Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *New England Journal of Medicine* 2005 **352** 48–62.
- 24 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF & Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985 **28** 412–419.
- 25 Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association* 2001 **285** 2486–2497.
- 26 Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, Alberiche M, Bonadonna RC & Muggeo M. Prevalence of insulin resistance in metabolic disorders: the Bruneck study. *Diabetes* 1998 **47** 1643–1649.
- 27 Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A & Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* 2003 **26** 3320–3325.
- 28 The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003 **26** S5–S20.
- 29 Wallace TM, Levy JC & Matthews DR. Use and abuse of HOMA modelling. *Diabetes Care* 2004 **27** 1487–1495.
- 30 Caumo A, Bergman RN & Cobelli C. Insulin sensitivity from meal tolerance tests in normal subjects: a minimal model index. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 4396–4402.
- 31 Mari A, Pacini G, Brazzale AR & Ahrén B. Comparative evaluation of simple insulin sensitivity methods based on the oral glucose tolerance test. *Diabetologia* 2005 **48** 748–751.
- 32 Stumvoll M, Van Haeften T, Fritsche A & Gerich J. Oral glucose tolerance test indexes for insulin sensitivity and secretion based on various availabilities of sampling times. *Diabetes Care* 2001 **24** 796–797.
- 33 Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Järvinen H, Van Haeften T, Renn W & Gerich J. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care* 2000 **23** 295–301.
- 34 Noor MA, Flint OP, Parker RA, Maa J, Witek J & Hodder SL. Evaluation of insulin sensitivity in healthy volunteers treated with low-dose ritonavir combined with atazanavir (ATV/RTV) or lopinavir (LPV/RTV): a prospective, randomized study using a hyperinsulinaemic, euglycaemic clamp and oral glucose tolerance testing (Abstract 16). *Antiviral Therapy* 2005 **10** L11.

Received 30 October 2006

Accepted 16 January 2007