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Effect of atazanavir versus other protease inhibitor-containing antiretroviral therapy on endothelial function in HIV-infected persons: randomised controlled trial

A J Flammer,¹ N T T Vo,² B Ledergerber,² F Hermann,¹ A Gämperli,² A Huttner,² J Evison,³ I Baumgartner,⁴ M Cavassini,⁵ D Hayoz,⁶ K Quitzau,¹ M Hersberger,⁷ I Sudano,¹ F Ruschitzka,¹ T F Lüscher,¹ G Noll,¹ R Weber²

¹ Cardiovascular Centre, Cardiology, University Hospital Zurich, Zurich, Switzerland; ² Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; ³ Division of Infectious Diseases, University Hospital Bern, Bern, Switzerland; ⁴ Division of Angiology, University Hospital Bern, Bern, Switzerland; ⁵ Division of Infectious Diseases, University Hospital Lausanne, Lausanne, Switzerland; ⁶ Division of Angiology, University Hospital Lausanne, Lausanne, Switzerland; ⁷ Institute of Clinical Chemistry, University Hospital Zurich, Zurich, Switzerland

Correspondence to: Professor R Weber, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland; Rainer.Weber@usz.ch

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ABSTRACT

Objective: Impaired endothelial function was demonstrated in HIV-infected persons on protease inhibitor (PI)-containing antiretroviral therapy, probably due to altered lipid metabolism. Atazanavir is a PI causing less atherogenic lipoprotein changes. This study determined whether endothelial function improves after switching from other PI to atazanavir.

Design: Randomised, observer-blind, treatment-controlled trial.

Setting: Three university-based outpatient clinics.

Patients: 39 HIV-infected persons with suppressed viral replication on PI-containing regimens and fasting low-density lipoprotein (LDL)-cholesterol greater than 3 mmol/l.

Intervention: Patients were randomly assigned to continue the current PI or change to unboosted atazanavir.

Main Outcome Measures: Endpoints at week 24 were endothelial function assessed by flow-mediated dilation (FMD) of the brachial artery, lipid profiles and serum inflammation and oxidative stress parameters.

Results: Baseline characteristics and mean FMD values of the two treatment groups were comparable (3.9% (SD 1.8) on atazanavir versus 4.0% (SD 1.5) in controls). After 24 weeks' treatment, FMD decreased to 3.3% (SD 1.4) and 3.4% (SD 1.7), respectively (all $p = \text{ns}$). Total cholesterol improved in both groups ($p < 0.0001$ and $p = 0.01$, respectively) but changes were more pronounced on atazanavir ($p = 0.05$, changes between groups). High-density lipoprotein and triglyceride levels improved on atazanavir ($p = 0.03$ and $p = 0.003$, respectively) but not in controls. Serum inflammatory and oxidative stress parameters did not change; oxidised LDL improved significantly in the atazanavir group.

Conclusions: The switch from another PI to atazanavir in treatment-experienced patients did not result in improvement of endothelial function despite significantly improved serum lipids. Atherogenic lipid profiles and direct effects of antiretroviral drugs on the endothelium may affect vascular function.

Trial registration number: NCT00447070.

The morbidity and mortality of HIV-infected persons with access to combination antiretroviral therapy (ART) have dramatically improved. However, there is a major concern that combination ART is associated with a premature manifestation of coronary artery disease (CAD).^{1,2} Protease inhibitors (PI) are among the key components of

combination ART and several studies propose a direct association between the use of PI and an increased risk of CAD,³⁻⁶ although this relationship has been questioned. Combination ART, particularly PI-containing regimens, is associated with hyperlipidemia, hyperglycemia, insulin resistance, central obesity and other metabolic factors known to promote vascular disease and premature CAD.⁷

Endothelial function, a powerful surrogate marker of early atherosclerosis,⁸ has been found to be reduced in treated HIV-infected persons,⁹ even in young children,¹⁰ when compared with uninfected individuals. Recent reports have demonstrated impaired endothelial function, especially in HIV-infected persons on PI, probably due to an altered lipid metabolism.^{10,11} In contrast, an improvement of endothelial function was measured in HIV-infected persons on PI-containing combination ART who started lipid-lowering therapy with statins, although this could also be attributed to their pleiotropic effect.¹² In comparison with other PI, atazanavir is a PI causing less atherogenic lipoprotein changes.¹³ Whether this feature of atazanavir leads to preserved endothelial function and subsequently to a lower incidence of cardiovascular complications, however, is unclear at present because long-term observations are missing.

This randomised controlled multicentre study aimed prospectively to evaluate endothelial function, serum lipid profiles and serum inflammatory and oxidative stress surrogate parameters over a period of 24 weeks in persons on PI-containing combination ART with suppressed viral replication who either continued the current PI or switched to atazanavir-containing combination therapy.

METHODS

Patient characteristics, inclusion and exclusion criteria

Eligible participants were male and female HIV-infected individuals between 18 and 65 years of age on stable combination ART with two nucleoside reverse transcription inhibitors and one PI (other than atazanavir) for at least 12 weeks, with two consecutive viral load assessments below 50 copies/ml within 60 days before study entry, CD4 lymphocyte counts above 100 cells/ μl , a treatment history and results of previous resistance

Table 1 Patient characteristics

	Atazanavir (n = 20)	Continued PI (n = 19)	p Value
Men, no (%)	15 (75%)	15 (79%)	1.0
Mean age, years (SD)	46 (7.5)	47 (12.5)	0.80
Current smokers, n (%)	9 (45%)	7 (37%)	0.61
Mean body mass index, kg/m ² (SD)	23 (3.0)	24 (2.3)	0.37
Mean (SD) duration of HIV seropositivity, years	10 (5.5)	7.6 (4.7)	0.14
Mean (SD) duration of antiretroviral therapy, years	7.7 (3.7)	5.7 (3.1)	0.07
PI at time of randomisation*			0.426
Lopinavir/ritonavir	5 (25.0)	3 (15.8)	
Nelfinavir	13 (65.0)	16 (84.2)	
Ritonavir, therapeutic dose	1 (5.0)	0 (0)	
Indinavir/ritonavir	1 (5.0)	0 (0)	
Clinical HIV CDC stage C, no (%)	5 (25%)	5 (26%)	0.45
Mean (SD) systolic blood pressure, mm Hg	125 (13)	125 (17)	0.96
Mean (SD) diastolic blood pressure, mm Hg	77 (8.8)	77 (9.0)	0.91
Mean (SD) pulse, 1/min	75 (7.4)	74 (9.5)	0.64
No (%) with HIV-1 RNA <50 copies/ml	20 (100%)	19 (100%)	1.0
Mean (SD) CD4 cell count, cells/ μ l	539 (250)	520 (324)	0.84
Mean (SD) total cholesterol, mmol/l	6.5 (0.95)	6.5 (1.1)	0.78
Mean (SD) LDL, mmol/l	4.0 (0.96)	4.2 (0.9)	0.52
Mean (SD) HDL, mmol/l	1.2 (0.4)	1.2 (0.3)	0.85
Mean (SD) triglycerides, mmol/l	3.2 (1.6)	2.3 (1.0)	0.04
Mean (SD) fasting glucose, mmol/l	5.1 (0.6)	5.0 (0.5)	0.57
Mean (SD) insulin, mIU/l	16.5 (18)	10.5 (8.4)	0.19

*The reverse transcriptase inhibitor backbone in the atazanavir and continued protease inhibitor (PI) groups, respectively, were statistically not different: zidovudine plus lamivudine, 14 and 13 patients; abacavir plus lamivudine, 0 and 4 patients; stavudine plus lamivudine, 2 and 1 patients; didanosine plus lamivudine, 1 and 1 patients; lamivudine plus tenofovir, 1 and 0 patients; zidovudine plus tenofovir, 1 and 0 patients; didanosine plus stavudine, 1 and 0 patients, respectively.
CDC, Centers for Disease Control and Prevention; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

testing allowing replacement of the current PI by unboosted atazanavir, and low-density lipoprotein (LDL)-cholesterol above 3.0 mmol/l.

Exclusion criteria were known CAD, hypertension, peripheral artery disease, cerebrovascular disease and diabetes mellitus. Furthermore, patients with serious illness requiring systemic treatment and/or hospitalisation within 14 days before study entry, current drug or alcohol addiction or patients participating in other studies were excluded, as well as patients with previous virological failure on PI-containing regimens and previously documented protease resistance mutations. The use of non-nucleoside reverse transcriptase inhibitors, testosterone or anabolic steroids, systemic glucocorticoids, long-acting inhaled steroids or other immunomodulators at study entry or during the study led to exclusion, as did the use of any lipid-lowering drugs within 4 weeks before study entry. Pregnancy was ruled out by pregnancy test.

Study protocol

A total of 41 patients were enrolled in this observer-blinded, randomised controlled multicentre study using a parallel group design between 4 August 2004 and 24 October 2005. During the screening period, two assessments of endothelial function by flow-mediated dilation (FMD) were performed (at least one week apart) and the mean of the two assessments was the baseline value. Because FMD is dependent on many factors including gender, smoking, alcohol consumption, degree and duration of hypertension or dyslipidemia, the participants were stratified by the FMD operator after the two baseline measurements into two groups: persons with mean FMD below 2.0% and persons with mean FMD equal to or above 2.0%. The allocation schedule for the two treatment arms,

including the two different strata with randomly permuted block sizes of 2 and 4, was generated in advance with the program RandList version 1.0.0.107, and two separate series of sealed envelopes were prepared for the two FMD strata.

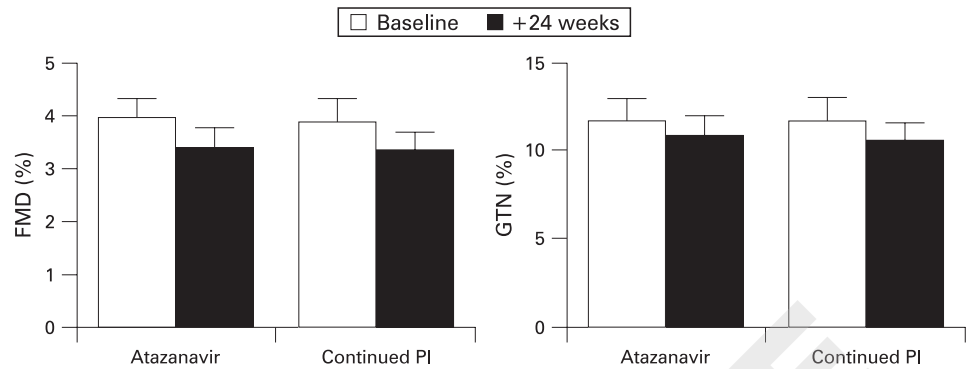
Participants were then randomly assigned by the study nurse of the HIV outpatient clinic to receive either 400 mg open-label unboosted atazanavir a day, instead of the current PI, or to continue the currently used PI. Both groups maintained the two reverse transcriptase inhibitors unaltered. Clinical visits were performed after 4, 12 and 24 weeks. At weeks 12 and 24 measurement of FMD was repeated. The patient's compliance with treatment and procedures were assessed at each visit. Returned study medications were counted to determine whether they were consistent with the number prescribed.

Screening and study visits were performed at specialised HIV outpatient clinics of three tertiary care university hospitals in Switzerland (Zurich, Bern and Lausanne). The local ethics committees of these university hospitals approved the study protocol and all procedures were in accordance with institutional guidelines and the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Assessment of endothelial function

Assessments were performed in dedicated cardiovascular ultrasound laboratories of the university hospitals, maintaining a standardised protocol. Physicians from these centres and the FMD operator remained blinded throughout the study and data analysis. FMD examinations were performed in a temperature controlled, quiet room in the morning. Patients were examined in the fasting state and were asked to quit smoking at least 2 h before examination and to refrain from coffee, tea, fruits and chocolate for at least 24 h. FMD and glycerol-trinitrate

Figure 1 Vascular function. Left, Endothelial function measurement. Flow-mediated dilation (FMD) did not change after atazanavir as well as after continued protease inhibitor (PI)-containing therapy (from 4.0% (SD 1.5) to 3.4% (SD 1.7), $p = 0.4$ and from 3.9% (SD 1.8) to 3.3% (SD 1.4), $p = 0.37$, respectively). Right, Similarly, endothelial-independent, glycerol-trinitrate (GTN)-mediated vasodilation did not change during the study (from 11.7% (SD 5.1) to 10.8% (SD 4.6), $p = 0.64$ and from 11.7% (SD 5.3) to 10.6% (SD 3.8), $p = 0.45$).



(GTN)-induced vasodilation (0.4 mg sublingual; Nitrolingual Spray, Pohl-Boskamp, Germany) of the brachial artery were assessed by a high-resolution ultrasound vessel wall tracking device with a 10-MHz linear array transducer, according to guidelines.^{14, 15} Flow-mediated reactive hyperemia reflects endogenous nitric oxide formation, resulting in endothelium-dependent vasodilation, whereas GTN acts as an exogenous nitric oxide donor directly on vascular smooth muscle cells, inducing endothelium-independent vasodilation. FMD of the brachial artery was induced by the release of a wrist cuff inflated to 220 mm Hg pressure for 5 minutes. After release, we recorded the arterial diameter every 15 s for 2 minutes. After GTN application, we recorded the diameter every 30 s for 6 minutes.

Serum inflammation and oxidative stress parameters

Malondialdehyde was derivatised and measured on a high-performance liquid chromatography system with a fluorescence detector with a limit of detection of 0.01 $\mu\text{mol/l}$ and a coefficient of variation of 3% (Chromsystems, Munich, Germany). Highly sensitive C-reactive protein (hsCRP) was measured on an Immulite 2500 immunoanalyser using commercial assays with a limit of detection of 0.1 mg/l and a coefficient of variation of 6% (DPC, Los Angeles, California, USA). The oxidised LDL was measured by ELISA with a limit of detection of 1 mU/l and a coefficient of variation of 8% (Mercodia, Uppsala, Sweden) and the total antioxidative capacity (TAOC) was measured using Trolox as a standard with a limit of detection of 0.04 mmol/l and a coefficient of variation of 3.4% (Cayman Chemicals, Ann Arbor, Michigan, USA).

Statistical analysis

The authors had full access to the data and take responsibility for its integrity. Statisticians remained blinded throughout the predefined primary data analysis. For comparison of baseline characteristics between treatment groups, *t* tests or Fisher's exact tests were used. Primary endpoints were changes of endothelial function at the end of the 24-week study period comparing the two treatment arms using *t* tests and individual changes using paired *t* tests. The sample size of 38 participants was calculated to detect a 20% difference in the change of FMD (power of 80%; $\alpha = 0.05$). The following secondary endpoints were analysed: changes in lipid profiles, serum inflammatory and oxidative stress parameters. Repeating the analyses with non-parametric methods yielded comparable results and

therefore we only report results from two-sided parametric tests. We used STATA version 9.2.

RESULTS

Study participants

Two of 41 enrolled patients dropped out before random assignment. We therefore report results on 39 participants (20 in the atazanavir arm and 19 in the continued PI arm). Baseline characteristics including PI treatment at enrollment are presented in table 1. Except for the baseline serum triglycerides, which were significantly higher in the atazanavir group, both treatment arms were equally balanced. The mean duration of HIV seropositivity as well as the duration of ART and PI therapy tended to be slightly longer in the atazanavir group (ns). HIV surrogate markers did not differ between the two treatment arms.

Course of treatment

Of the 39 patients, 38 (97%) completed the 24-week trial. One patient in the atazanavir arm stopped the assigned treatment after 2 months. There were no serious adverse events or new AIDS-defining illnesses throughout the study. However, four patients (21%) in the continued PI arm experienced virological failure compared with none in the atazanavir arm.

Endothelial function

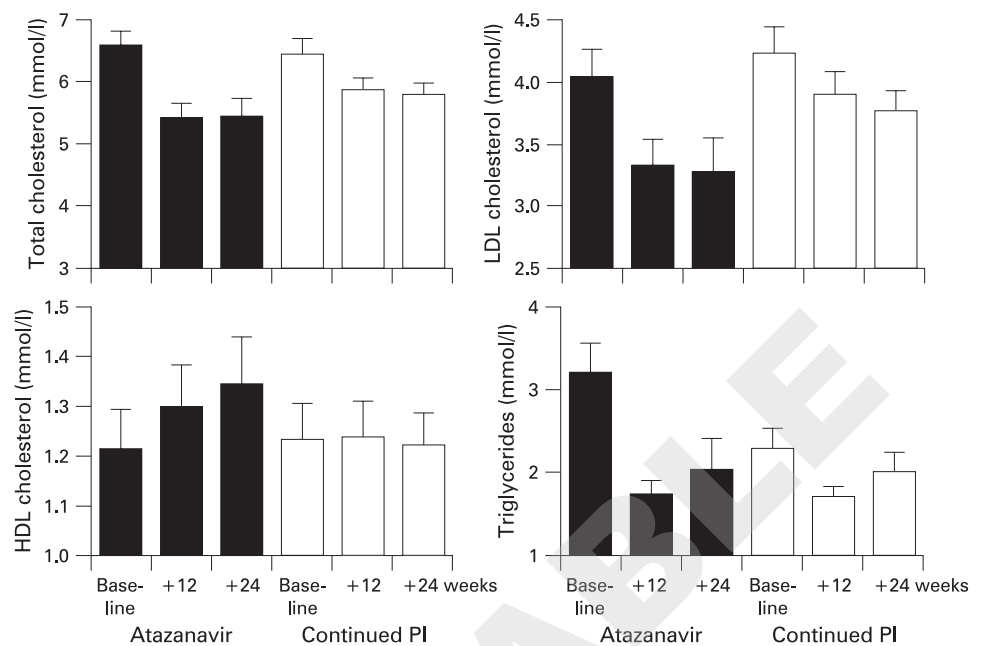
Baseline brachial artery diameter matched well at baseline and did not significantly change during the 24-week study period (from 4.60 mm (SD 0.78) to 4.56 mm (SD 0.76), $p = 0.90$, in the atazanavir group, and from 4.68 mm (SD 0.61) to 4.74 mm (SD 0.61), $p = 0.78$, in the continued PI group). FMD did not change after the switch to atazanavir or during continued PI therapy (from 4.0% (SD 1.5) to 3.4% (SD 1.7), $p = 0.40$, and from 3.9% (SD 1.8) to 3.3% (SD 1.4), $p = 0.37$, respectively; fig 1). The atazanavir and continued PI arms combined showed FMD changes from 3.9% (SD 1.6) to 3.4% (SD 1.5) ($p = 0.22$) during the study period. Also, GTN-mediated vasodilation and blood flow did not change during the study (all $p = \text{ns}$).

Serum lipid levels and liver enzymes

During the study period, serum lipid levels improved both in the atazanavir and continued PI arm (table 2, fig 2). In the atazanavir group, however, the improvement was more pronounced. Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were significantly improved after 24 weeks of atazanavir treatment, whereas triglycerides and HDL did not change in the continued PI arm. Liver enzymes

Endothelial function

Figure 2 Serum lipids. Top left, Total cholesterol decreased from 6.5 (SD 0.95) to 5.5 mmol/l (SD 1.2), less than $p < 0.001$, in the atazanavir group, and from 6.5 (SD 1.1) to 5.8 mmol/l (SD 0.8), $p = 0.007$, in the control group. The effect of atazanavir on total cholesterol was significantly more pronounced than the control protease inhibitor (PI) ($p = 0.48$). Top right, Low-density lipoprotein (LDL) decreased from 4.0 (SD 1.0) to 3.3 mmol/l (SD 1.2), $p < 0.001$, in the atazanavir group and from 4.2 (SD 0.9) to 3.8 mmol/l (SD 0.7), $p = 0.02$, in the control group. Bottom left, High-density lipoprotein (HDL) increased from 1.2 (SD 0.4) to 1.3 mmol/l (SD 0.4), $p = 0.03$, in the atazanavir group, whereas HDL remained unchanged in the control group (1.2 (SD 0.3) and 1.2 mmol/l (SD 0.3)). Bottom right, Triglycerides were significantly lowered in the atazanavir group (from 3.2 (SD 1.6) to 2.0 mmol/l (SD 1.6), $p = 0.003$) but remained stable in the control group (from 2.3 (SD 1.0) to 2.0 mmol/l (SD 1.0)).



were slightly but statistically significantly higher after 24 weeks of atazanavir treatment compared with baseline values, whereas the liver enzymes remained stable on continued PI therapy.

changes were in parallel with LDL, therefore no conclusion concerning oxidative stress can be reached.

Serum inflammation and oxidative stress parameters

The inflammation parameter hsCRP as well as the oxidative stress parameters malondialdehyde and TAOC did not change significantly during the course of the study (table 2). Oxidised LDL changed significantly in the atazanavir group; however, the

DISCUSSION

In this randomised, controlled study we found that a switch from another PI to unboosted atazanavir-containing combination ART did not result in an improvement in endothelial function after 24 weeks, despite a significantly improved lipid profile.

Table 2 Comparison of the two treatment groups at baseline and at 24 weeks

	Atazanavir arm			Continued PI arm				
	Baseline (n = 20)	Week 24 (n = 19) [§]	p Value*	Baseline (n = 19)	Week 24 (n = 19)	p Value*	p Value [†]	p Value [‡]
SBP, mm Hg	125 (13)	121 (13)	0.08	126 (17)	120 (17)	0.18	0.95	0.84
DBP, mm Hg	77 (9)	77 (9)	0.94	77 (9)	73 (7)	0.04	0.19	0.15
Pulse, 1/min	75 (7)	72 (7)	0.19	74 (10)	69 (6)	0.02	0.21	0.67
No (%) with HIV-1 RNA <50 copies/ml	20 (100%)	19 (100%)	0.15	19 (100%)	15 (78.9%)	0.32	0.31	0.30
HIV-1 RNA [¶] , log ₁₀ copies/ml	0.03 (0.15)	0.17 (0.4)	0.15	0.32 (0.6)	0.58 (1.5)	0.32	0.24	0.30
CD4 lymphocyte count, cells/ μ l	539 (250)	543 (247)	0.14	520 (324)	489 (382)	0.61	0.62	0.38
ALT, U/l	31.7 (14.6)	40.4 (17.4)	0.002	28.4 (14.7)	30.4 (12.3)	0.70	0.05	0.02
AST, U/l	31.5 (12.1)	37.4 (20.1)	0.02	29.2 (12.5)	29.0 (10.5)	0.95	0.12	0.09
Total cholesterol, mmol/l	6.5 (0.95)	5.5 (1.2)	<0.001	6.5 (1.1)	5.8 (0.8)	0.007	0.29	0.048
LDL, mmol/l	4.0 (0.96)	3.3 (1.2)	<0.001	4.2 (0.9)	3.8 (0.7)	0.02	0.13	0.13
HDL, mmol/l	1.2 (0.4)	1.3 (0.4)	0.03	1.2 (0.3)	1.2 (0.28)	0.77	0.29	0.07
Triglycerides, mmol/l	3.2 (1.6)	2.0 (1.6)	0.003	2.3 (1.0)	2.0 (1.0)	0.13	0.97	0.03
Fasting glucose, mmol/l	5.1 (0.6)	5.2 (0.5)	0.28	5.0 (0.45)	5.0 (0.54)	0.78	0.17	0.36
Insulin, mIU/l	16.5 (18)	12.3 (13.6)	0.35	10.5 (8.4)	7.9 (5.0)	0.14	0.20	0.69
hsCRP, mg/l	2.0 (1.8)	2.5 (3.3)	0.58	1.5 (1.3)	1.8 (1.5)	0.45	0.43	0.87
oxLDL, U/l	68.9 (15.6)	55.1 (14.6)	<0.001	77.7 (16.1)	70.2 (14.2)	0.048	0.003	0.16
Malondialdehyde, μ mol/l	0.12 (0.04)	0.12 (0.02)	0.85	0.13 (0.05)	0.12 (0.05)	0.47	0.93	0.62
TAOC, mmol	2.7 (0.65)	2.7 (0.67)	0.82	2.6 (0.64)	2.7 (0.75)	0.12	0.76	0.18

Data are presented as mean \pm SD.

*p Values within groups from a paired = matched t test.

[†]p Values between groups from two-sided t tests: intergroup groups at week 24.

[‡]p Values between groups from two-sided t tests: intragroup (changes from baseline to week 24).

[§]No data at week 24 for one patient.

[¶]Values below the limit of detection are coded as 1 copy/ml (ie, log₁₀(1) = 0).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL, high-density lipoprotein; hsCRP, highly sensitive C-reactive protein; LDL, low-density lipoprotein; oxLDL, oxidised LDL; PI, protease inhibitor; TAOC, total antioxidative capacity.

This result is intriguing as dyslipidemia is associated with endothelial dysfunction and, vice versa, the improvement of blood lipids ameliorates endothelial vascular function,^{16 17} as previously demonstrated in HIV-infected persons on PI who received pravastatin treatment.¹² Therefore, an improvement in endothelial function after atazanavir therapy was expected. However, because serum lipids not only improved in the atazanavir arm, as expected, but also—less profound—in the control group (although the addition of lipid-lowering drugs was not allowed during the 24-week study period), the course of lipid levels might have influenced the results of endothelial function in favour of the control group. In previous studies, treatment with PI was associated with impairment in serum lipid profiles as well as impaired endothelial function,¹⁸ however, such an effect has been seen after initiating the drug. In contrast, our patients were already on stable PI treatment for months or years before they were enrolled in the study. The improvement in serum lipids during the study could be explained by the adherence of patients and physicians to treatment guidelines, which recommend changes in lifestyle and behaviour in order to reduce cardiovascular risks. The fact that at the end of the study systolic blood pressure tended to be lower in both groups and diastolic blood pressure and heart rate were significantly lower in the control group after 24 weeks compared with baseline is suggestive of such a healthier lifestyle. However, lower blood pressure is also associated with an ameliorated endothelial function, an effect not seen in our study.

The lacking improvement of vascular function after the replacement of another PI with atazanavir may also be explained by a direct effect of the nucleoside reverse transcription inhibitor plus PI-containing combination ART on the endothelium. Based on in-vitro experiments as well as clinical investigations in HIV-infected patients and in persons not infected with HIV, toxic effects and other direct effects on the endothelium have been postulated, including a decrease in endothelium-dependent vasorelaxation, inhibition of the nitric oxide synthase system, increase in oxidative stress and activation of mitogen-activated protein kinases.^{11 18–20} Direct effects on the endothelium, as for example increased oxidative stress or an inflammatory response of the vessel wall, were mainly associated with PI. Nevertheless, results of animal models also indicate that reverse transcriptase inhibitors can directly affect the vascular endothelium.²¹ As a consequence, not only PI inhibitors but rather combination therapy with reverse transcriptase inhibitors plus PI could counterbalance the expected beneficial effect of an improved lipid profile associated with, eg, atazanavir, or other single drugs that do not influence lipid profiles. The participants of the trial presented here were already on long-term ART before enrolment, namely for a mean of 6.7 years on any antiretroviral drugs, and a mean of 5.6 years on combination drug regimens, which may have affected vascular endothelial function. Although patients were randomly assigned, the mean duration of previous ART among the atazanavir group was 2 years longer than in the continuing PI group.

The results of FMD in our study participants indicated endothelial dysfunction compared with healthy individuals not infected with HIV, but we do not have any indices of increased inflammation or oxidative stress at baseline or after 24 weeks of treatment. The surrogate serum biomarkers of inflammation and oxidative stress, including hsCRP, malondyaldehyde, oxidised LDL, or TAOC, were not significantly influenced by atazanavir or continued PI, although earlier reports suggested increasing oxidative stress due to PI therapy.²²

Antiretroviral drugs can cause drug-induced liver injury.^{23 24} In our study, liver enzymes increased mildly but significantly after switching to atazanavir treatment, possibly indicating some toxic effect of this drug, which might also affect the endothelium. A recent study in patients with diabetes mellitus type 2 showed an inverse correlation between liver enzymes and FMD.²⁵ Moreover, toxic effects to the liver might lead to an inflammatory response, not only affecting liver enzymes but also leading to complex inflammatory responses possibly affecting endothelial function. However, we did not observe hsCRP serum concentrations to increase after atazanavir treatment.

The strengths of our study include the random assignment of individuals with suppressed viral replication and the stratification based on baseline FMD, which may control for the various cardiovascular risk factors in the different treatment arms. Possible limitations include the sample size and the probably too short duration of the study. Despite the fact that randomisation balanced the two groups quite well, HIV-infected persons have heterogeneous co-morbidities, co-medication, different lifestyles including heterogeneous cardiovascular risk behaviour and a high prevalence of smoking, all factors known to influence endothelial function. Therefore, such confounding factors may have influenced our study endpoints. Furthermore, although unlikely, the higher baseline triglyceride levels might have contributed to a false low endothelial function in the atazanavir group, thus confounding our results.

In conclusion, we found marked endothelial dysfunction—a powerful surrogate for atherosclerosis—among our study participants who were on ART for a mean of 6.7 years. We now demonstrate that switching PI therapy to atazanavir, a new PI not negatively altering lipid profiles and therefore considered to be less atherogenic, has no beneficial impact on the vascular endothelium, thus probably not solving the important problem of vascular dysfunction in these patients. However, the clearly demonstrated positive effect on the lipid profile may, in the long term, still be beneficial with respect to cardiovascular morbidity and mortality. Therefore, further long-term observations are needed to determine whether the incidence of clinical endpoints of cardiovascular diseases will decrease among persons on atazanavir-containing antiretroviral regimens. Changing current (effective) PI therapy to atazanavir merely in the hope of reduced cardiovascular risk may not be appropriate at present as definitive data are lacking. It is, however, important to take other preventive measures and to treat cardiovascular risk factors strictly in this patient group.

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Competing interests: RW has received travel grants or speakers honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dome, Pfizer, Roche, TRB Chemedica and Tibotec. BL has received travel grants or honoraria from Abbott, Aventis, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dome, Roche and Tibotec. TFL and KQ have received grants for the conduct of clinical studies from Bristol-Myers Squibb.

Ethics approval: The local ethics committees of the three university hospitals approved the study protocol and all procedures were in accordance with institutional guidelines and the Declaration of Helsinki.

Patient consent: Obtained.

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