Impact of atazanavir-based HAART regimen on the carotid intima–media thickness of HIV-infected persons: a comparative prospective cohort

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\textbf{Objective}: With the advent of highly active antiretroviral therapy regimens, it is crucial to consider their long-term benefits to risk ratios among HIV-infected persons. The impact of protease inhibitors on the cardiovascular risk is controversial.

\textbf{Design}: This observational cohort was designed to investigate the cardiovascular impact of boosted atazanavir (ATV/r), a protease inhibitor that does not provide major dyslipidemia or insulin resistance.

\textbf{Setting}: This study was carried out at the University Hospital of Brest (France).

\textbf{Patients}: Among the 229 HIV-infected persons of the cohort, 33 cases treated by ATV/r-containing regimen since less than 6 months were compared to 99 age-matched and sex-matched ATV/r naive controls.

\textbf{Intervention}: None.

\textbf{Main outcome measure}: The main outcome measure was carotid intima–media thickness (cIMT) at the baseline, 6, 12, and 18 months.

\textbf{Results}: Although the cIMT was not different at inclusion (0.633 \pm 0.05 vs. 0.666 \pm 0.09, \( P = 0.07 \)), the cIMT course significantly decreased (\( P = 0.018 \)) in cases at 18 months. The differences remained significant even after adjustment on the variables that differed between cases and controls (\( P < 0.1 \)) at inclusion (high-density lipoprotein cholesterol, cardiovascular family history) and the cumulated and current exposure to the nucleosidic reverse transcriptase inhibitor, nonnucleosidic reverse transcriptase inhibitor, and protease inhibitor class.

\textbf{Conclusion}: Despite similar HIV and cardiovascular characteristics at baseline, cIMT decreased after 6 months of follow-up among the patients exposed to ATV/r, even after adjustment for the exposure to the three antiretroviral classes. Considering the shortcomings of this study, especially the absence of randomization and the heterogeneity of the control group, the benefit of ATV/r treatment in patients with high cardiovascular should be confirmed by randomized trials.

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\textbf{Keywords}: AIDS, atazanavir, atherosclerosis, HAART
Introduction

With the advent of HAART regimens, it is crucial to consider their long-term benefits to risk ratios in HIV-infected patients. If the high cardiovascular risk among these patients is no longer discussed [1,2], the mechanism is controversial:

1. the consequence of an HIV-associated chronic inflammation [3–7], of dysimmunity [8–10], or of co-infection [11];
2. a high frequency of standard risk factors (sex, smoking, etc.) among HIV-infected population [8,12,13]. However, the Framingham risk score underestimates subclinical atherosclerosis observed in HIV-infected population [14];
3. HAART-induced metabolic abnormalities [7,15], especially with protease inhibitor [16], even a metabolic syndrome [17,18], lipodystrophy [19], endothelial dysfunction [20,21], or acquired thrombophilia [22], even though the impact of confounders is discussed [13,23,24]. In this case, apart from the usual healthy lifestyle recommendations [25] (giving up smoking, diet, physical exercise), the interventional strategy is not clear: switching from a HAART regimen generally active and well accepted to a new regimen [26], which induces less metabolic abnormalities but without assurance of a favorable clinical impact [27]; giving a specific treatment (statins [28], salicylic acid [22,27]), or only cardiovascular monitoring.

Since 2003, thanks to atazanavir (ATV), a new protease inhibitor, it is possible to assess the impact of a protease inhibitor-containing HAART regimen that does not provide major dyslipidemia [29] or insulin resistance [30] thanks to a validated surrogate investigator of atherosclerosis: the carotid intima–media thickness (cIMT).

Methods

Design

This hospital-based single-center observational, comparative, prospective cohort study (AVATAR: atazanavir versus other antiretroviral therapy and atherosclerosis research) was approved by the institutional review committee and took place from January 2004 to January 2008.

First objective

To compare cIMT evolution between patients with and without ATV exposure.

Second objective

To adjust according to significantly different variables such as HIV, cardiovascular, or demographic status.

Population

Among the 229 HIV-infected adults from the Brest Hospital University Cohort, 33 patients (cases) treated by HAART regimen including ritonavir-boosted ATV (ATV/r) were compared with 99 age-matched (<2 years) and sex-matched controls without ATV/r exposure.

Collected data

The data was collected blindly, cIMT included, and under informed consent.

Conventional atherosclerosis risk factors status

Age, sex, prior smoking (in pack-years), family history of cardiovascular disease (CVD) (in percentage of first-degree relatives), current cardiovascular therapy (hypolipemiant, antidiabetic, antiplatelet, or antihypertensive treatment), waist perimeter, BMI, SBP and DBP, and usual blood analysis, after overnight fasting (>12 h), of total and high-density lipoprotein (HDL) cholesterol, glucose, and triglycerides. The Framingham risk score [31] and the NCEP-ATP-III Metabolic Syndrome status [32] were calculated for each patient.

HIV status

The likely onset of infection, the CD4 cell count, the viral load, the current (HAART regimen at the baseline) and cumulated (addition of the cumulative time (in days) of exposure to all drugs of each class) exposure to nucleosidic reverse transcriptase inhibitors (NRTIs) or nonnucleosidic reverse transcriptase inhibitors (NNRTIs) and protease inhibitor (baby-dose not considered).

Measurement of carotid intima–media thickness

cIMT was measured at the baseline, 6, 12, and 18 months, using a bidimensional ultrasonography on an ATL HDI 5000 apparatus combined with a linear broadband transducer (L 12–7) (Philips, Eindhoven, the Netherlands). The measurement site was the common carotid artery posterior wall (left and right for each patient), 1 cm from the carotid bifurcation over at least a 1-cm-long distance, 35 mm deep. The measurement was carried out at the end of a diastole and the segment length, the mean IMT, and in addition, the minimal and maximal IMT values, the standard deviation, and a quality index were determined on a Metris station (Metris, Argenteuil, France) without manual correction. The intra-operator variability was characterized by an $R^2$ of 0.82 ($n = 57$).

Sample size estimation

When taking into account a cIMT increase of 0.05 mm/year [8], the impact of a ATV/r switch similar to statin use (–0.04 mm/year) [33] and a variance of 0.09 mm (as observed in SHIVA study conducted in the same population 1 year before [34]), 33 cases and 99 matched controls followed up over 18 months were required to obtain a power of 80% with an alpha risk of 5%.
Statistical analysis

After graphic analysis and confirmation by the Kolmogorov–Smirnov test, the main characteristics of cases and controls were compared by linear regression when the distribution was normal (age, BMI, waist perimeter, blood pressure, and CD4 cell count), otherwise by the Mann–Whitney test. The Student’s t-test was used for the binary variables.

We used the general linear model for repeated measurements (SPSS v17; SPSS Inc, Chicago, Illinois, USA) to compare the cIMT evolution. The missing intermediate cIMT values were substituted by their linear interpolation. The missing final values were not extrapolated and GLM analyses at 6, 12, and 18 months were performed. The same analysis was repeated after adjustment on the NRTI, NNRTI, and protease inhibitor cumulated and current exposure and the baseline variables when they differed between cases and controls (P < 0.1).

Results

At least two cIMT measures were available for 97 controls and 32 cases. The cIMT at 18 months was available for only 12 cases and 52 controls. The main characteristics at inclusion and during the study are summarized in Table 1. At the time of inclusion, among the cardiovascular risk factors, only the HDL–cholesterol level was significantly lower in the case group (1.23 vs. 1.62, P = 0.01). The percentage of the metabolic syndrome status (33.3 vs. 30.5) and the Framingham score (−3.32 vs. −3.36) were the same for cases and controls. No patient had previous or present CVD symptoms. As regards the current HAART regimen, two NRTI were associated with one protease inhibitor in 21 cases and in 25 controls (65.6 vs. 25.7%, P < 0.001), with one NNRTI in two cases and 42 controls (6.2 vs. 43.3%, P < 0.001). Two cases (6.2%) and 15 (15.4%) controls (P = 0.008) received only NRTI, two controls and one case had another HAART regimen. Six (18.7%) cases and 13 (13.4%) controls were not treated (P = 0.3). The control group had a lower cumulated and current protease inhibitor exposure than the case group and an increased exposure to the NNRTI class. However the results were not statistically significant as regards the NNRTI cumulated exposure (P = 0.35). The comparison between the 45 controls and the 16 cases, whose cIMT measure at 18 months was missing, gave the same results.

During the study, only the glucose level was significantly higher in the case group (5.95 vs. 5.51, P = 0.03). Of

Table 1. Main characteristics of atazanavir versus other antiretroviral therapy and atherosclerosis research study population.

<table>
<thead>
<tr>
<th>Cardiovascular status</th>
<th>At inclusion</th>
<th>During the follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female [n (%)]</td>
<td>Not included</td>
<td>Controls P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>25 (25)</td>
<td>NS 31 (32)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.0 (0.9)</td>
<td>0.06 44.6 (0.9)</td>
</tr>
<tr>
<td>Smoking (packets-years)</td>
<td>22.0 (2.4)</td>
<td>NS 21.4 (2.3)</td>
</tr>
<tr>
<td>First degree CVD history (%)</td>
<td>12 (2)</td>
<td>NS 9 (2)</td>
</tr>
<tr>
<td>Glycemia (mmol/l)</td>
<td>5.22 (0.07)</td>
<td>NS 5.95 (0.23)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.93 (0.13)</td>
<td>NS 5.21 (0.13)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.80 (0.06)</td>
<td>0.01 1.62 (0.09)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.20 (0.33)</td>
<td>NS 2.07 (0.18)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>112 (3)</td>
<td>&lt;0.001 117 (23)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 (2)</td>
<td>&lt;0.001 77 (16)</td>
</tr>
<tr>
<td>Waist perimeter (cm)</td>
<td>87.9 (1.2)</td>
<td>0.03 83.2 (1.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.9 (3.1)</td>
<td>NS 23.1 (6.2)</td>
</tr>
<tr>
<td>CVD treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>6 (6.1)</td>
<td>NS 1 (3.1)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>10 (10.3)</td>
<td>NS 2 (6.2)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (6.1)</td>
<td>NS 1 (3.1)</td>
</tr>
<tr>
<td>Antiangiagreent, n (%)</td>
<td>5 (5.1)</td>
<td>NS 2 (6.2)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of HIV (years)</td>
<td>10 (1)</td>
<td>NS 11 (1)</td>
</tr>
<tr>
<td>CD4 cell count (cells/µl)</td>
<td>483 (27)</td>
<td>NS 513 (30)</td>
</tr>
<tr>
<td>Nadir (cells/µl)</td>
<td>288 (225)</td>
<td>0.005 210 (163)</td>
</tr>
<tr>
<td>Viral load (log₁₀ copies/ml)</td>
<td>4.5 (4.0)</td>
<td>NS 5.2 (5.0)</td>
</tr>
<tr>
<td>Maximum (log₁₀ copies/ml)</td>
<td>4.8 (1.2)</td>
<td>NS 4.8 (1.2)</td>
</tr>
<tr>
<td>Antiretroviral exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulated protease inhibitor (days)</td>
<td>491 (89)</td>
<td>0.09 751 (104)</td>
</tr>
<tr>
<td>Cumulated NRTI (days)</td>
<td>2918 (300)</td>
<td>NS 4503 (302)</td>
</tr>
<tr>
<td>Cumulated NNRTI (days)</td>
<td>497 (78)</td>
<td>NS 761 (85)</td>
</tr>
<tr>
<td>Protease inhibitor current [n (%)]</td>
<td>23 (23.7)</td>
<td>0.001 23 (23.7)</td>
</tr>
<tr>
<td>NRTI current [n (%)]</td>
<td>83 (85.5)</td>
<td>NS 26 (21.2)</td>
</tr>
<tr>
<td>NNRTI current [n (%)]</td>
<td>49 (50.5)</td>
<td>0.001 26 (21.2)</td>
</tr>
</tbody>
</table>

Comparison of main characteristics between 97 not included and 132 included (data not showed) patients at the baseline, and between 33 boosted Atazanavir (cases) and 99 not Atazanavir (age (<2 years) and sex matched controls) exposed patients at the baseline and during the follow-up. Except if specified, the data were expressed as mean and standard deviation (in brackets). CVD, cardiovascular disease; NNRTI, nonnucleosidic reverse transcriptase inhibitor; NRTI, nucleosidic reverse transcriptase inhibitor; NS, not significant (P > 0.05).
course, the protease inhibitor and NNRTI exposure were different between both groups, the cases being exclusively exposed to ATV/r, while the NRTI exposure was the same. Nevertheless, the use of a once-a-day drug (didanosine or tenofovir) was more frequent with ATV/r-based regimen than with zidovudine (Table 2, http://links.lww.com/QAD/A92). Ten controls (10.1%) did not receive HAART during the study; the three others were treated by boosted ATV/r and NRTI, 162, 186, and 504 days after inclusion, respectively. For two of them, two cIMT measures were missing.

Exposure to cardiovascular drugs was the same before and during the study (Table 2, http://links.lww.com/QAD/A92).

Although not different at inclusion \((0.633 \pm 0.05\) in cases vs. \(0.666 \pm 0.09\) in controls, \(P = 0.07\)), the cIMT significantly decreased at 12 \((0.636 \pm 0.676; P = 0.05)\) and 18 months \((0.611 \pm 0.675; P = 0.018)\), but not at 6 months \((0.642 \pm 0.660)\) in cases when compared to controls (Fig 1). After adjustment by the variables that differed between cases and controls \((P < 0.1)\) at inclusion (HDL-c, cardiovascular family history) and the protease inhibitor, NRTI, and NNRTI cumulated and current exposures, the differences remain significant.

**Discussion**

The cIMT, a well known and validated surrogate marker of atherosclerosis, decreased significantly among patients on the HAART regimen including ATV/r, whereas a slight increase is observed in the control group. This difference in the cIMT course appeared after 6 months of follow-up, when the cases had been ATV/r exposed since 289 days. The HIV and cardiovascular baseline characteristics were similar and these results did not change after the planned adjustments. The glycemia, the only parameter significantly different during the study \((\sim 0.44 \text{ mmol/l in case group})\), had no impact on the cIMT difference observed between cases and controls.

However, this study has some limitations. First, the study was not randomized. Thus, it is impossible to exclude the hypothesis that the ATV/r regimen may have been especially prescribed to patients with a high vascular risk, even though the cardiovascular baseline characteristics, including the Framingham score, the metabolic syndrome status, cardiovascular treatments, and cIMT were not significantly different. Incidently, with larger samples, the baseline characteristics might have been different. Moreover, this modification in the HAART regimen could have been brought about by diet or physical activity recommendations, two relevant parameters, which were not collected in our study.

On the contrary, the heterogeneity of the control group should lead to sub-analyses according to the different HAART regimens. However, sufficient statistical power cannot be attained due to the small size of the samples. Moreover, the insufficient number of cases and controls, particularly at the end of the study, could explain why the mechanisms of the positive impact of ATV/r remain unclear. In fact, a major metabolic change is not obvious.

Thus, if an interventional correction of the cardiovascular risk is necessary, the results of the AVATAR study favor a switch to a low cardiovascular impact HAART regimen, like HAART including ATV/r, which amounts to the usual cardiovascular prevention. Of course, these data must be confirmed by further randomized studies.

**Acknowledgements**

AVATAR study was approved by the CCPPRB (Ethics committee). The CNIL and the Health Department were informed of the study (2003). L.d.S.-M. has been a member of French regional board of BMS since 2009.

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