HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2017 February 20.

Published in final edited form as:

AIDS. 2016 February 20; 30(4): 672–674. doi:10.1097/QAD.0000000000000970.

Atazanavir use and CIMT progression in HIV: Potential influence of bilirubin

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Keywords

Atazanavir; CIMT progression; HIV; Bilirubin

To the editor - Cardiovascular disease (CVD) deaths are an important cause of mortality in HIV infected patients. As a prediction of cardiovascular outcome, carotid intima media thickness (CIMT) has been shown as an independent predictor of CVD events [1]. We read with great interest the study by Stein et al. in which they report that treatment-naïve HIV-infected individuals randomized to an initial ART regimen including atazanavir/ritonavir (ATV/r) experienced slower progression of CIMT than those assigned darunavir/ritonavir (DRV/r), or raltegravir (RAL) [2]. Accordingly, we conducted retrospective analysis of the longitudinal Hawaii Aging with HIV - Cardiovascular Study to assess the relationship of ATV/r on CIMT in a cohort of HIV infected individuals on stable antiretroviral therapy (ART). Additionally, the baseline plasma biomarkers and total serum bilirubin were analyzed for differences between participants currently receiving ATV/r compared to participants not on ATV/r. Group differences between participants receiving ATV/r versus those not taking ATV/r were assessed using multivariable regression.

A total of 62 subjects enrolled in the Hawaii Aging with HIV-Cardiovascular Study had available CIMT measures at baseline and year 2. Eleven subjects (18%) were receiving ATV/r and 51 (82%) were not receiving ATV/r (non-ATV/r). In the non-ATV/r group, 55% were on a Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), 18% were on a Protease Inhibitors (PIs) other than ritonavir as a booster and none were on an integrase inhibitor. Entry criteria for the cohort required subjects to be on stable ART for at least 3 months, and 82% of these subjects were virologically suppressed with a plasma HIV RNA level of < 50 copies/mL on ATV/r and 82% were suppressed on non-ATV/r. The median CD4 count was 370 cells/μL (Q1: 249, Q3:612) for the ATV/r group and 502 (349, 660) cells/μL for the non-ATV/r group (p=0.10). Baseline median Framingham Risk Score were: ATV/r 0.03 (0.01, 0.14), NNRTI 0.04 (0.02, 0.14) and PI 0.08 (0.04, 0.20) (p=0.53). Median duration on antiretroviral therapy did not differ between the ATV/r and non-ATV/r groups, 14.2 years (6.4, 14.6) verses 12.6 (7.8, 16.2) respectively. The median increase in CIMT

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over 2 years was 0.009 mm (0.005, 0.022) for the ATV/r group compared to 0.022 mm (0.013, 0.034) in the non-ATV/r group ($p<0.001$). ATV/r use continued to be associated with slower CIMT progression compared to the non-ATV/r group after adjusting for age, gender, hypertension, diabetes mellitus, current smoking status, LDL cholesterol and systolic blood pressure ($p=0.012$) (Table).

The rate of CIMT change was similar to the findings presented by the A5260 study. Interestingly, we also found a significant correlation between increasing baseline total serum bilirubin level and reduced CIMT progression (Table). The A5260 study reported a significant reduction in CIMT with bilirubin as a binary cut point of 0.6 mg/dL at weeks 4 and 24, with similar trends seen for higher cut points. Bilirubin has an antioxidant effect as well as an association with reduced inflammation [3]. The antioxidant and anti-inflammatory effects of bilirubin metabolism have been reported with lower serum IL-6, CRP, SAP level [4–6]. In our study, log total bilirubin levels correlated with log SAP ($r= -0.329$, $p=0.009$) and log CRP ($r= -0.288$, $p=0.023$) but not with other biomarkers such as IL-6, MMP-9, TPAI-1, sICAM, sVCAM, MPO, MCP-1, SAA, IL-1, TNFα, or VEGF. Total bilirubin was also negatively correlated with the intermediate (CD14++CD16+) monocyte subset ($r= -0.267$, $p=0.048$). None of these baseline biomarkers or intermediate monocyte subsets were associated with change in CIMT [7]. The article by Stein et al. did not report on the correlations between bilirubin, biomarkers and monocyte subsets. Although there were no direct associations with biomarkers and monocyte subsets, we still speculate a potential role of total bilirubin in slowing CIMT progression. Hereditary conditions such as Gilbert syndrome, where serum bilirubin levels in these individuals are elevated, are reported to have much lower rates of ischemic heart disease compared to the general population [8]. A cardioprotective role of bilirubin, heme oxygenase (HO), and UDP-glucuronosyltransferase (UGT1A1) has been speculated [9]. This retrospective study is limited by its small sample size and non-randomized design. Despite these differences, our findings have important implications and suggestions for future research. Our data demonstrated similar CIMT findings with ATV/r as in the A5260 study. The exact mechanism of ATV/r on CIMT progression remains unclear but total serum bilirubin may play a potential role in modifying CVD risk.

Acknowledgments

Sources of Support: This work was supported by the National Institutes of Health grants U54RR026136, U54MD007584, and R01HL095135.

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Table

Multivariable linear regression of 2 year change in carotid intima media thickness of the common carotid artery predicted by atanazavir use and separately for baseline total bilirubin as a continuous variable.

Predictor of Interest	β	S.E.	P value
Current atanazavir use	−0.269	0.103	0.012
Total bilirubin (mg/dL)	−0.123	0.056	0.031

Change in CIMT has been log-10 transformed to adjust for normality. A p-value ≤ 0.05 was regarded as statistically significant. Risk factors adjusted for in both models include: age, gender, hypertension, diabetes mellitus, current smoking status, LDL cholesterol and systolic blood pressure.