Association Between Atazanavir-Induced Hyperbilirubinemia and Cardiovascular Disease in Patients Infected with HIV

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BACKGROUND: Serum bilirubin is inversely associated with cardiovascular risk. Atazanavir, an HIV protease inhibitor that competes with bilirubin conjugation, provides a unique opportunity to examine whether selectively increasing bilirubin is cardioprotective. We sought to determine whether patients receiving atazanavir manifest a reduced risk of cardiovascular disease compared with those receiving darunavir, an HIV protease inhibitor that does not increase serum bilirubin.

METHODS AND RESULTS: This was a retrospective cohort study of 1020 patients with HIV. The main outcome was time to myocardial infarction or ischemic stroke. Mean follow-up was 6.6±3.4 years, with 516 receiving atazanavir and 504 darunavir. Atazanavir patients exhibited significantly higher serum total bilirubin (1.7 versus 0.4 mg/dL; P<0.001) and longer mean time to ischemic event (10.2 versus 9.4 years; P<0.001). On Cox regression, atazanavir treatment (hazard ratio [HR], 0.38; 95% CI, 0.21–0.71; P=0.002) and serum bilirubin (HR, 0.60; 95% CI, 0.41–0.89; P=0.011) were independently associated with a lower risk of an ischemic event. Notably, when atazanavir and bilirubin were included together in the Cox regression model, atazanavir lost significance (HR, 0.55; 95% CI, 0.24–1.29; P=0.169) consistent with bilirubin being an intermediate variable on the causal pathway between atazanavir and its effect on cardiovascular disease. Patients on atazanavir also had a significantly lower risk of developing new cardiovascular disease (HR, 0.53; 95% CI, 0.33–0.86; P=0.010) and longer mean time to death (12.2 versus 10.8 years; P<0.001).

CONCLUSIONS: Patients with HIV on atazanavir manifest a decreased risk of cardiovascular disease when compared with those on darunavir, an effect that appears to be mediated by serum bilirubin.

Key Words: bilirubin ■ cardiovascular disease ■ HIV

Bilirubin is a potent endogenous antioxidant that has been shown to suppress inflammation by inhibiting leukocyte migration and cytokine signaling,1-3 and there is growing evidence that bilirubin exerts clinically significant anti-inflammatory effects. Studies have identified an inverse correlation between serum bilirubin concentrations and the development of such inflammatory conditions as cardiovascular disease (CVD), ulcerative colitis, multiple sclerosis, and cancer.4-10 In addition, individuals possessing the Gilbert’s polymorphism, which causes an increase in serum bilirubin through reduced activity of the UDP-glucuronosyltransferase 1A1 enzyme, exhibit a lower incidence of CVD, cancer, asthma, and Crohn’s disease.11-14 However, these association studies do not establish cause and effect, and it remains unclear whether selectively increasing serum bilirubin levels confers protection against inflammatory disorders.

Atazanavir is an HIV protease inhibitor that reliably causes an indirect hyperbilirubinemia by competitively inhibiting UDP-glucuronosyltransferase 1A1,15,16 thereby inducing a Gilbert’s phenotype. HIV infection increases the risk of CVD,17 and serum bilirubin is inversely associated with CVD in patients with HIV,18 which has prompted speculation that treatment with atazanavir may confer a protective effect against CVD.
In support of this proposition, a randomized clinical trial demonstrated a slower rate of carotid artery intima-media thickening in patients with HIV treated with atazanavir versus darunavir, a protease inhibitor that does not affect serum bilirubin. Other effects associated with bilirubin, including a reduction in markers of oxidative stress and inflammation, also have been demonstrated in atazanavir-treated patients.

Three prior studies directly examined the influence of atazanavir on the development of CVD. The first identified a significantly lower risk of CVD in patients with elevated bilirubin levels who were taking atazanavir, but not in those taking other antiretroviral agents. The second analyzed a large Veterans Health Administration database and found that, during a mean follow-up of 1 year, the incidence of myocardial infarction (MI) and stroke were lower in atazanavir-treated patients compared with those administered alternative HIV medications, although the results were not correlated with serum bilirubin. A recent prospective study concluded that patients with HIV treated with darunavir exhibited an increased risk of cardiovascular events compared with those receiving atazanavir. Notably, in contrast with multiple prior reports, these investigators did not find an association between serum bilirubin levels and cardiovascular risk.

Speculating that induction of hyperbilirubinemia may reduce cardiovascular risk, in the present study we examined whether patients with HIV receiving atazanavir manifest a lower risk of CVD compared with those who received treatment with darunavir, a protease inhibitor that does not affect bilirubin levels.

**METHODS**

**Patients and Study Design**

This was a multicenter, retrospective cohort study of all patients with HIV who received outpatient care in the Partners HealthCare system and who received treatment with atazanavir or darunavir between 2003 and 2019. Patients were identified through the Partners Research Patient Data Registry, a centralized clinical data warehouse that gathers clinical information from the multiple hospital systems within Partners HealthCare. Patients were excluded if they were (1) younger than 18 years of age, (2) not on continuous treatment with either medication for at least 1 year, (3) did not receive care after the Epic electronic health record system was implemented in 2015, or (4) did not receive outpatient care in the Partners HealthCare system (Figure 1).

Approval was obtained from the Partners Human Research Committee. Given the retrospective nature of the study, consent for participation was waived. The data that support the findings of the study are available from the corresponding author upon reasonable request.

**Outcomes and Covariates**

The primary outcome was time to first ischemic event, which was defined as either an ischemic cardiac event or an ischemic stroke. An ischemic cardiac event was defined as the new development of unstable angina, ST-segment–elevation MI and non–ST-segment–elevation MI. Patients with type II MI (ie, demand ischemia) were not included in the primary outcome. Only patients with ischemic stroke were included (those with hemorrhagic stroke were excluded as the purpose of this study was to investigate events related to inflammation and atherosclerosis). Outcomes were determined through individual chart examination of Epic diagnosis codes and clinical notes and further validated by review of cardiac catheterization or brain imaging reports whenever possible (available in 87% of instances). Secondary outcomes were (1) all-cause mortality and (2) time to new diagnosis of CVD that, in addition to the primary outcomes, included coronary artery disease, peripheral vascular disease, carotid artery stenosis, and transient ischemic attack. The diagnosis of new CVD was established through a review of diagnosis codes and clinical notes as well as medications, imaging reports, stress test results, and catheterization reports.

Patients not reaching outcome were censored at termination of treatment, death, or last clinic visit. In addition to patients who were started on atazanavir or darunavir during the study period, those who were already receiving atazanavir or darunavir at the time of entry into the Partners HealthCare system were also included in the analyses, with the date of their first encounter in the Partners’ system considered to be the start date. Baseline demographic data included age, sex, ethnicity, smoking status, concomitant antiretroviral use, whether patients had been antiretroviral...
naive at study entry, diabetes mellitus, hyperlipidemia, pre-existing chronic kidney disease (defined as an estimated glomerular filtration rate below 60 mL/min per 1.73 m² for 3 months), and pre-existing CVD (defined and determined as previously described for secondary outcomes).

Clinical parameters (blood pressure, body mass index, virologic failure) and laboratory values (serum total and direct bilirubin, serum lipid levels [total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol], CD4 count, HIV viral load) obtained at the closest time point before study completion or treatment discontinuation to account for potential medication effects from long-term atazanavir or darunavir therapy. To account for the normal variance in serum bilirubin concentrations, if multiple bilirubin levels were available within the year before discontinuation of treatment, the median of the last 3 serum bilirubin values was used. Virologic failure was defined as viremia >200 copies per mL on at least 2 consecutive measurements. Serum bilirubin concentrations and virologic failure at the time of any primary event were used in the statistical analyses.

Statistical Analysis
Baseline patient demographics and covariates are reported as means and standard deviations for continuous normal data, medians and interquartile ranges for continuous non-normal data, and frequencies and percentages for categorical data. Univariable analyses were performed using a 2-sided Student \( t \) test or Wilcoxon rank sum test for continuous variables, \( \chi^2 \) test for categorical variables, and Kaplan–Meier analysis for time-to-event data. Multivariable analysis using Cox proportional hazards regression was employed to control for potential confounders. As missing data were rare for any specific variable apart from direct bilirubin, then any missing values were excluded from statistical analysis. A mediation analysis was performed to test whether any relationship between atazanavir exposure and cardiovascular outcomes was attributable to total bilirubin as an intermediate variable on the causal pathway.25,26 For survival analysis, patients were censored at the time of last follow-up, death, or medication discontinuation. Statistical significance was defined as \( P \leq 0.05 \). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS
A total of 937 patients treated with atazanavir and 844 patients treated with darunavir were identified in the initial search of the Research Patient Data Registry, of which 761 met at least 1 of the exclusion criteria (Figure 1). The remaining 516 patients who received atazanavir and 504 who received darunavir were included in the analysis. Table 1 lists the baseline
Table 1. Demographics of Patient Cohorts

| Characteristic                                         | Atazanavir (n=516) | Darunavir (n=504) | P Value |
|--------------------------------------------------------|--------------------|-------------------|---------|
| Age at enrollment, y                                   | 45.4±9.2           | 47.5±10.6         | <0.001  |
| Age at end of study, y                                 | 52.9±9.8           | 53.2±11.0         | 0.664   |
| Follow-up, y                                           | 7.5±3.5            | 5.7±2.9           | <0.001  |
| Patients with ambulatory infectious diseases follow-up | 492 (95.4)         | 482 (95.6)        | 0.826   |
| Patients lost to follow-up                            | 10 (1.9)           | 20 (4.0)          | 0.055   |
| Patients censored because of medication discontinuation| 440 (85.3)         | 283 (56.2)        | <0.001  |
| Males                                                  | 351 (68.0)         | 330 (65.5)        | 0.388   |
| Ethnicity                                              |                    |                   |         |
| White                                                  | 268 (52.0)         | 222 (44.1)        | 0.041   |
| Black                                                  | 157 (30.4)         | 177 (35.1)        |         |
| Hispanic                                               | 83 (16.1)          | 89 (17.7)         |         |
| Other/unknown                                          | 8 (1.6)            | 16 (3.2)          |         |
| Body mass index                                        | 27.7±5.6           | 27.6±6.1          | 0.674   |
| Systolic blood pressure                               | 126.9±16.5         | 126.9±16.4        | 0.969   |
| Diastolic blood pressure                              | 78.5±10.6          | 77.4±10.3         | 0.100   |
| Lipids                                                 |                    |                   |         |
| Cholesterol, mg/dL                                     | 179.5±41.5         | 179.6±46.7        | 0.968   |
| Triglycerides, mg/dL                                   | 161.6±104.4        | 160.8±101.5       | 0.900   |
| HDL, mg/dL                                             | 47.2±16.3          | 47.5±17.7         | 0.755   |
| LDL, mg/dL                                             | 100.6±35.4         | 101.4±37.3        | 0.712   |
| Serum bilirubin                                        |                    |                   |         |
| Total bilirubin, mg/dL                                 | 1.7 (1–2.5)        | 0.4 (0.3–0.5)     | <0.001  |
| Direct bilirubin, mg/dL                                | 0.2 (0.2–0.3)      | 0.1 (0.1–0.2)     | <0.001  |
| Cardiovascular risk factors                            |                    |                   |         |
| Smoking                                                | 214 (41.5)         | 181 (35.9)        | 0.068   |
| Hypertension                                           | 259 (50.2)         | 228 (45.2)        | 0.113   |
| Diabetes mellitus                                      | 76 (14.7)          | 87 (17.3)         | 0.270   |
| Hyperlipidemia                                         | 232 (45.0)         | 205 (40.7)        | 0.167   |
| Pre-existing chronic kidney disease                    | 59 (11.4)          | 76 (15.1)         | 0.086   |
| Pre-existing cardiovascular disease                    | 28 (5.4)           | 39 (7.7)          | 0.136   |
| HIV parameters                                         |                    |                   |         |
| CD4 count, per µL                                      | 603.1±333.6        | 534.1±340.4       | 0.001   |
| Viral load, copies/mL                                  | 20 (0–50)          | 20 (0–30)         | 0.140   |
| Below detectable viral load                            | 367 (71.3)         | 371 (73.6)        | 0.402   |
| Virologic failure                                      | 66 (12.8)          | 45 (9.0)          | 0.050   |
| Antiretroviral naive                                   | 62 (12.0)          | 30 (5.0)          | 0.001   |
| Atazanavir/daranavir initiated at enrollment           | 412 (79.8)         | 406 (80.6)        | 0.776   |
| Other HIV medications at enrollment                   |                    |                   |         |
| Ritonavir                                              | 466 (90.3)         | 478 (94.8)        | 0.006   |
| Truvada                                                | 314 (60.9)         | 338 (67.1)        | 0.039   |
| Abacavir                                               | 24 (4.7)           | 14 (2.8)          | 0.114   |
| Outcomes                                               |                    |                   |         |
| Myocardial infarction                                  | 12 (2.3)           | 19 (3.8)          | 0.179   |
| Ischemic stroke                                        | 6 (1.2)            | 20 (4.0)          | 0.005   |
| New diagnosis of cardiovascular disease                | 35 (7.1)           | 43 (9.2)          | 0.243   |
| Death                                                  | 6 (1.2)            | 22 (4.4)          | 0.002   |

Data are mean±SD, median (interquartile range), or number (percentage). HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.
characteristics by cohort, which were generally well matched. Notable differences between those receiving atazanavir versus darunavir were mean age at the start of treatment (45.4 versus 47.5 years; \(P<0.001\)), mean follow-up (7.5 versus 5.7 years; \(P<0.001\)), rates of medication discontinuation (85.3% versus 56.2%; \(P<0.001\)), ethnicity \((P=0.041\)), CD4 count (603.1 versus 534.1; \(P=0.001\)), proportion who were antiretroviral naïve (12.0% versus 6.0%; \(P<0.001\)), and virologic failure at end of follow-up (12.8% versus 9.0%; \(P=0.050\)). As expected, the median serum total bilirubin concentration was higher in the atazanavir compared with the darunavir cohort (1.7 versus 0.4 mg/dL; \(P<0.001\)), with a marked broadening of the bilirubin distribution among atazanavir-treated patients (Figure 2).

Consistent with previous studies, \(^8,^27\) total bilirubin was higher in men compared with women in the atazanavir (1.8 versus 1.4 mg/dL; \(P<0.001\)) and darunavir (0.4 versus 0.3 mg/dL; \(P<0.001\)) groups and was also higher in White patients compared with Black patients (2.0 versus 1.3 mg/dL \(P<0.001\) in the atazanavir group and 0.4 versus 0.3 mg/dL \(P<0.001\) in the darunavir group).

Regarding outcomes in the total study population, 31 patients experienced a new ischemic cardiac event, 26 patients were diagnosed with an ischemic stroke, 78 patients developed new CVD, and 28 patients died during the entire follow-up period. Crude incidence rates per thousand patient-years in the atazanavir versus the darunavir cohort for ischemic cardiac events and ischemic stroke were significantly lower in the atazanavir group (4.65 versus 13.55; incidence rate ratio, 0.34; 95% CI, 0.20–0.60; \(P<0.001\)). On survival analysis, the atazanavir cohort had a significantly longer time to first MI or stroke than did the darunavir cohort (log-rank \(P<0.001\); Figure 3A).

After adjusting for established cardiovascular risk factors (ie, hypertension, hyperlipidemia, diabetes mellitus, smoking, sex, ethnicity) as well as differences in baseline characteristics of the cohorts (ie, virologic failure, ritonavir use, age) (Table 2), using Cox regression analysis, atazanavir treatment was significantly associated with a decreased risk of ischemic cardiac event or stroke when compared with darunavir (hazard ratio [HR], 0.38; 95% CI, 0.21–0.71; \(P=0.002\)). Similarly, when the serum total bilirubin level was substituted for atazanavir as a continuous variable in the regression model (Table 2), it also was significantly associated with a decreased risk of MI or stroke (HR, 0.60; 95% CI, 0.41–0.89; \(P=0.011\)). To test the hypothesis that atazanavir exerts a protective effect against CVD by augmenting serum bilirubin levels, both atazanavir and serum bilirubin were included simultaneously as variables in the regression model in a mediation analysis (Figure 2). After the addition of bilirubin to the model, atazanavir treatment was no longer significantly associated with a decreased risk of ischemic events (HR, 0.55; 95% CI, 0.24–1.29; \(P=0.169\)), which is consistent with bilirubin serving as an intermediary in the causal pathway between atazanavir and CVD.\(^26\)

**Figure 2.** Distribution of serum total bilirubin in patients receiving atazanavir or darunavir

Overlay histogram indicating number of patients at each serum bilirubin concentration.
Notably, a Cox regression model built using a stepwise forward-selection technique eliminated age, sex, smoking, and diabetes mellitus as covariates, but did not meaningfully alter the findings; atazanavir treatment remained strongly associated with a diminished risk of ischemic cardiac events or stroke (HR, 0.38; 95% CI, 0.21–0.71).

Table 2. Cox Regression Models and Time to Ischemic Event

| Covariate                | Model Excluding Bilirubin, HR (95% CI) | P Value | Model Excluding Atazanavir, HR (95% CI) | P Value | All-Inclusive Model, HR (95% CI) | P Value |
|--------------------------|----------------------------------------|---------|-----------------------------------------|---------|---------------------------------|---------|
| Atazanavir treatment     | 0.38 (0.21–0.71)                       | 0.0022  | ...                                     | ...     | 0.55 (0.24–1.29)                | 0.1694  |
| Total bilirubin          | ...                                    | ...     | 0.58 (0.39–0.86)                       | 0.0067  | 0.77 (0.47–1.28)                | 0.3113  |
| Hyperlipidemia           | 4.40 (2.05–9.42)                       | 0.0001  | 4.34 (2.02–9.30)                       | 0.0002  | 4.34 (2.02–9.33)                | 0.0002  |
| Chronic kidney disease   | 2.17 (1.19–3.96)                       | 0.0114  | 2.25 (1.23–4.09)                       | 0.0082  | 2.19 (1.20–3.98)                | 0.0102  |
| Virologic failure        | 2.97 (1.25–7.03)                       | 0.0135  | 1.94 (0.83–4.57)                       | 0.1286  | 2.42 (0.97–6.06)                | 0.0586  |
| Ritonavir                | 3.60 (1.29–10.06)                      | 0.0143  | 4.26 (1.58–11.54)                      | 0.0043  | 3.63 (1.30–10.13)               | 0.0138  |
| Hypertension             | 2.02 (1.02–3.99)                       | 0.0445  | 1.81 (0.91–3.58)                       | 0.0888  | 1.80 (0.91–3.59)                | 0.0929  |
| Cardiovascular disease   | 2.05 (1.01–4.19)                       | 0.0474  | 1.93 (0.94–3.96)                       | 0.0750  | 1.98 (0.97–4.07)                | 0.0619  |
| Black                    | 0.59 (0.31–1.10)                       | 0.0963  | 0.56 (0.30–1.05)                       | 0.0706  | 0.93 (0.63–1.37)                | 0.7060  |
| Male sex                 | 0.75 (0.40–1.41)                       | 0.3650  | 0.78 (0.41–1.47)                       | 0.4345  | 0.83 (0.44–1.57)                | 0.5710  |
| Age at start of study    | 1.01 (0.98–1.05)                       | 0.0430  | 1.01 (0.98–1.05)                       | 0.3879  | 1.01 (0.98–1.05)                | 0.4738  |
| Diabetes mellitus        | 0.88 (0.47–1.68)                       | 0.7064  | 0.89 (0.47–1.68)                       | 0.7076  | 0.89 (0.47–1.69)                | 0.7197  |
| Smoking                  | 1.04 (0.58–1.86)                       | 0.8897  | 0.98 (0.55–1.74)                       | 0.9370  | 1.05 (0.59–1.88)                | 0.8750  |

HR indicates hazard ratio.
0.39; 95% CI, 0.21–0.71; P=0.002). The addition of bilirubin to the model was again found to negate this association (HR, 0.57; 95% CI, 0.25–1.32; P=0.191). Although some studies have suggested that abacavir may alter cardiovascular risk, 28,29 the addition of abacavir to the regression models did not substantially alter the results. As it has previously been suggested that it is unconjugated, rather than conjugated, bilirubin that exerts a protective effect against CVD, we performed an analysis of the subset of 469 patients (230 in the atazanavir cohort and 239 in the darunavir cohort) in whom serum bilirubin levels were fractionated. When either direct (conjugated) or indirect (unconjugated) serum bilirubin were substituted for total bilirubin in the Cox regression model, indirect bilirubin was significantly associated with lower risk of MI or ischemic stroke (HR, 0.51; 95% CI, 0.31–0.84; P=0.008), whereas direct bilirubin was not (HR, 0.12; 95% CI, 0.01–3.40; P=0.216). These data support that the observed effect of bilirubin on CVD is primarily attributable to the unconjugated fraction. In addition, when indirect bilirubin and atazanavir were jointly included in the Cox regression model, atazanavir again lost significance with respect to risk of an ischemic event (HR, 0.47; 95% CI, 0.17–1.30; P=0.145) consistent with indirect bilirubin serving as an intermediary in the causal pathway between atazanavir and CVD.

When examining the secondary outcomes of time to diagnosis of new CVD and time to all-cause mortality, log-rank testing demonstrated that the atazanavir cohort had significantly longer time to CVD (P=0.030; Figure 3B) and to all-cause mortality (P<0.001; Figure 3C) than did the darunavir cohort. On Cox regression analysis using the same covariates as in our primary model (apart from the exclusion of pre-existing CVD), atazanavir treatment was associated with a significantly lower risk of developing new CVD compared with darunavir (HR, 0.53; 95% CI, 0.33–0.86; P=0.010) as was bilirubin itself (HR, 0.73; 95% CI, 0.56–0.95; P=0.017). After accounting for bilirubin, atazanavir no longer significantly decreased this risk (HR, 0.69; 95% CI, 0.35–1.34; P=0.267), again supporting that bilirubin lies on the causal pathway between atazanavir treatment and decreased risk of CVD. Although multivariable analysis of time to death was constrained by the low number of deaths (28 total) in the overall study, using a simplified Cox regression model adjusting only for age, atazanavir treatment was associated with a significantly decreased risk of death (HR, 0.19; 95% CI, 0.07–0.49; P=0.001), as was bilirubin when examined separately (HR, 0.37; 95% CI, 0.18–0.74; P=0.005). Once again after accounting for bilirubin, the atazanavir effect on risk of death was negated (HR, 0.33; 95% CI, 0.10–1.16; P=0.085).

**DISCUSSION**

A number of epidemiological analyses have consistently demonstrated an inverse association between serum bilirubin levels and the risk of CVD, 5-7 with some investigations additionally correlating the presence of the Gilbert’s polymorphism with these findings. 11,12,30 What is less well established is whether the induction of a sustained increase in circulating bilirubin levels can result in a beneficial therapeutic effect on cardiovascular risk. In the present study involving a large, diverse HIV cohort, patients treated with atazanavir exhibited a sustained increase in serum bilirubin levels in conjunction with a significantly decreased risk of ischemic events when compared with those receiving darunavir, even after adjusting for established cardiovascular risk factors. Moreover, atazanavir treatment also was significantly associated with improved survival. As most HIV parameters including viral load and percent of patients with undetectable viral loads were no different between the atazanavir and darunavir cohorts (in line with previously published studies 31-33), we speculate that the lower rate of death in patients receiving atazanavir results from a protective effect of this medication against CVD and potentially other comorbidities associated with chronic HIV infection.

As bilirubin has been shown to prevent atherosclerosis in animal models by inhibiting inflammatory cell migration into sites of vascular injury, 33 we speculate that the cardioprotective effects of atazanavir are mediated by its ability to effectively increase the concentration of bilirubin in the systemic circulation. Support for this hypothesis is derived from our finding that inclusion of bilirubin in Cox regression models negates the influence of atazanavir on CVD, consistent with bilirubin acting as at least a partial intermediary of this phenomenon. We further show that the protective effect of bilirubin is specifically associated with the unconjugated fraction, which is consistent with experimental data demonstrating that conjugated bilirubin does not regulate leucocyte migration. 3 On the other hand, it is important to point out that the HR for bilirubin also does not remain significant when atazanavir is included in the Cox regression model and that the HR for atazanavir is only partially mitigated from 0.38 to 0.55 and does not approach 1 (although notably losing significance with bilirubin in the model). These observations raise the possibility that hyperbilirubinemia is not the sole determinant of the protective effect of atazanavir against CVD and that there may be an as of yet unidentified cardioprotective mechanism of atazanavir that is not related to its effect on bilirubin. Alternatively, it could reflect that darunavir exerts a deleterious cardiovascular effect, as postulated by Ryom et al. 24 The results also could be confounded by the high prevalence of the Gilbert’s polymorphism.
on atazanavir. LaFleur et al23 retrospectively examined stress and inflammation are decreased in individuals receiving an atazanavir-containing versus non-atazanavir cohort and found a reduced incidence of MI and stroke, but not mortality, in patients with HIV-2 infection in the United States is rare it is unlikely that it is a clinically meaningful confounder. Furthermore, there were some differences in the study population notably with atazanavir-exposed patients being younger and having longer follow-up. Although these raise the possibility of indication bias, we speculate that the age difference is attributable to atazanavir patients being more frequently treatment naïve (which is consistent with darunavir being an option for treatment-resistant disease) and that the difference in follow-up time is attributable to atazanavir being approved by the US Food and Drug Administration 3 years earlier than darunavir. Significantly more patients receiving atazanavir had their medication discontinued compared with darunavir (85.3% versus 56.2%), which would also raise concern for residual confounding except that this observation is consistent with prior reports of higher discontinuation rates with atazanavir.31 This higher discontinuation rate has been attributed to atazanavir-induced hyperbilirubinemia and, in more recent clinical practice, by perceived better compliance with the single-pill formulation of darunavir, which is not available for atazanavir. Indeed, there was significantly more virologic failure in patients receiving atazanavir versus darunavir (12.8% versus 9.0%; P=0.05; see Table 1), which could be explained by lower compliance in the atazanavir cohort. Finally, events that occurred outside of the Partners system were captured through reviews of outpatient notes and Care Everywhere (a national interoperability system that links our electronic health record to other Epic-based electronic health records), although the possibility exists that events could have been missed if the data were not accessible through these methods.

In summary, patients with HIV treated with atazanavir were found to have a reduced incidence of CVD and improved survival compared with those receiving darunavir. Our data support that bilirubin is a mediator of this effect and suggest that the induction of a sustained increase in serum bilirubin may represent a viable therapeutic approach to reducing cardiovascular risk.

**ARTICLE INFORMATION**

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