HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2019 September 15.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2019 August 15; 81(5): e141–e147. doi:10.1097/QAI.0000000000002071.

Association between bilirubin, atazanavir, and cardiovascular disease events among people living with HIV across the US.

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Abstract

Objective—Bilirubin is an antioxidant that may suppress lipid oxidation. Elevated bilirubin is associated with decreased cardiovascular events in HIV-uninfected populations. We examined these associations in people living with HIV (PLWH).

Methods—Potential myocardial infarctions (MI) and strokes were centrally adjudicated. We examined MI types: Type 1 MI (T1MI) from atherosclerotic plaque instability and Type 2 MI (T2MI) in the setting of oxygen demand/supply mismatch such as sepsis.

We used multivariable Cox regression analyses to determine associations between total bilirubin levels and outcomes adjusting for traditional and HIV-specific risk factors. To minimize confounding by hepatobiliary disease we conducted analyses limited to bilirubin values<2.1 mg/dl; among those with Fibrosis-4 values<3.25; and among everyone. We repeated analyses stratified by hepatitis C status and time-updated atazanavir use.

Results—Among 25,816 PLWH, there were 392 T1MI and 356 T2MI during follow-up. Adjusted hazard ratios (HR) for the association of higher bilirubin levels with T1MI were not significant. Higher bilirubin levels were associated with T2MI. In contrast, among PLWH on atazanavir, higher bilirubin levels were associated with fewer T2MI (HR 0.56:0.33–1.00). Higher

Presented in part at the 18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV, New York

bilirubin levels among those on atazanavir were associated with fewer T1MI combined with ischemic stroke.

Limitations—Analyses were conducted with total rather than unconjugated bilirubin.

Conclusion—Among PLWH, higher bilirubin levels were associated with T2MI among some subgroups. However, among those on atazanavir, there was a protective association between bilirubin and T2MI. These findings demonstrate different associations between outcomes and elevated bilirubin due to diverse causes and the importance of distinguishing MI types.

Keywords

HIV; myocardial infarction; atazanavir; bilirubin; stroke; cardiovascular disease

Introduction

Bilirubin is the end product of heme catabolism and an effective antioxidant that may suppress lipid oxidation[1–3]. Bilirubin may also have anti-inflammatory, complement inhibitory, and possibly anti-thrombotic and lipid-lowering properties[4–6]. Elevated bilirubin, particularly mildly elevated levels[4], have been associated with fewer myocardial infarctions (MI) and strokes, and with reduced carotid atherosclerosis, in the general population and individuals with Gilbert's syndrome[2,3,7–11], although not always[12,13]. The nature and magnitude of the relationship between bilirubin levels and atherosclerotic events is undefined[9,10].

Relationships between bilirubin and atherosclerotic events are relevant to people living with HIV (PLWH), who have higher cardiovascular disease rates than the general population[14–17]; and may have abnormal bilirubin levels for several reasons. For example, the protease inhibitor atazanavir can cause hyperbilirubinemia due to inhibitor effects on UGT1A1 and has been a common component of HIV treatment regimens[18–20]. A relationship has been reported between mild hyperbilirubinemia and slower progression of atherosclerosis in PLWH[21]. It is unknown whether these associations translate into reduced risk of cardiovascular events such as MI with a recent study suggesting an association of higher bilirubin levels with lower CVD risk among PLWH[22]. However, this association was not statistically significant for MI.

These relationships may differ by the type of cardiovascular events. The Universal Definition of MI classifies MI into types according to the underlying mechanism of myocardial ischemia[23,24] with Type 1 MI (T1MI) and Type 2 MI (T2MI) being most common among PLWH. T1MI results spontaneously from atherosclerotic plaque instability. T2MI is related to oxygen demand-supply mismatch such as occurs with hypotension. Compared to the general population, where T2MIs comprise <10% of MIs[25–30], we found that half of MIs among PLWH were T2MI[31]. T2MI among PLWH are due to causes such as sepsis and cocaine-induced vasospasm[31]. Similarly, there are multiple types of strokes including ischemic and hemorrhagic with multiple subtypes of ischemic stroke[32], which are also associated with different predisposing causes and risk factors.

We conducted this study to examine relationships between bilirubin and cardiovascular events among PLWH, whether these associations differ by MI type or among atazanavir users, and to evaluate the hypothesis that higher bilirubin levels may protect against T1MI.

Methods

Study setting:

Longitudinal observational study conducted in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a multisite clinical cohort of PLWH receiving HIV care[33].

Study participants:

PLWH ≥18 years of age receiving HIV care at six CNICS sites after adjudication of cardiovascular events began (dates varied by site, ~2000–2017). We started follow-up at 6 months after enrollment and excluded individuals with events before the start of follow-up to ensure incident events.

Data sources:

The CNICS Data Repository integrates comprehensive clinical data from outpatient and inpatient encounters including information on demographic characteristics, clinical and laboratory data, and medications. Laboratory data such as bilirubin values were collected as part of clinical care.

CNICS has an established state-of-the-art approach to cardiovascular outcome adjudication with MIs categorized by type[31,34]. Potential MIs were identified in the centralized CNICS data repository using a comprehensive set of diagnostic and procedure codes and elevated cardiac biomarker values. For all potential events, sites assembled de-identified packets that included provider notes, electrocardiograms, and imaging results. Two physicians with expertise in cardiac disorders and adjudicating events reviewed each packet, followed by a 3rd reviewer if discrepancies occurred. Reviewers categorized MIs by type, identified causes for T2MI, and also identified PLWH without an MI but with coronary interventions such as a coronary artery bypass graft (CABG) surgery, which were grouped with the T1MI. MI types beyond T1MI and T2MI are not discussed further due to low numbers (e.g. there were <10 Type 4 and 5 MIs associated with cardiac procedures in CNICS to date). We used a similar ascertainment and adjudication approach for strokes using provider notes, procedure reports, and imaging results in de-identified packets for centralized review. Reviewers categorized each stroke as ischemic vs. hemorrhagic. Ischemic strokes were further classified by whether concurrent infection or illicit drug use/intoxication was a predisposing factor when the stroke occurred.

Outcomes:

We examined MIs by type. We also conducted sensitivity analyses with a combined atherosclerotic outcome (T1MI plus ischemic strokes excluding strokes related to infection or illicit drug use).

Analyses:

Multivariable Cox regression analyses were used to determine associations between time-updated total bilirubin and outcomes, adjusting for traditional and HIV-specific risk factors: time-varying viral load and CD4 count, and baseline age, sex, race/ethnicity, HIV transmission risk factor, smoking status, hepatitis C virus (HCV) infection, diabetes, treated hypertension, statin use, kidney function (estimated GFR <30, 30–60, ≥60), calendar time, and site. HCV status was based on positive lab values (antibody, genotype, or viral load). Diabetes was based on any of the following: a) hemoglobin A1c≥6.5 OR b) use of a diabetes-specific medication such as insulin OR c) use of a diabetes-related medication not exclusively used to treat diabetes (e.g. biguanides) in the setting of also having a diabetes diagnosis[35].

Bilirubin values ≤30 days before outcomes were excluded to ensure outcomes or concurrent predisposing factors for T2MI such as sepsis were not impacting bilirubin values. To minimize confounding by hepatobiliary disease, we conducted analyses limited to bilirubin values <2.1 mg/dL as has been done in the general population[11], and repeated analyses limited to individuals who had Fibrosis-4 (FIB-4) values <3.25 at baseline. The FIB-4 index, derived from age, liver aminotransferases and platelet count, has been shown to predict liver-related events and death[36–38]. We also conducted analyses where we examined everyone, regardless of bilirubin or FIB-4 level. We examined associations in subgroups defined by HCV status. We examined the associations with total bilirubin as a continuous variable ($\log_2$ transformed), as a categorical variable (<0.6, 0.6–1.3, and ≥1.3 mg/dL, with cut points selected based on the normal adult range of up to 1.3 mg/dL) and using spline models to examine the association of a 0.1 mg/dL change in bilirubin within bilirubin categories.

We were particularly interested in any potential associations with atazanavir both to add clarity as to mechanisms as well as because of the potential clinical implications. We conducted stratified analyses examining person-time on or off atazanavir using time-updated models limited to those on ART and repeated these analyses stratified by HCV status for those on non-atazanavir containing regimens. All bilirubin values obtained while on ART were included. ART status varied over time based on whether individuals were currently receiving ART prescriptions.

We conducted sensitivity analyses excluding those with diabetes. We conducted sensitivity analyses stratified by sex. In models stratified by sex, we adjusted for HCV but did not stratify by HCV due to insufficient numbers among subgroups of stratified analyses. We conducted sensitivity analyses among the subset with indirect (unconjugated) bilirubin values.

Results

We included 25,816 PLWH. Mean age at baseline was 40 years, 19% were female, 42% were White, and 18% had HCV (Table 1). There was a median of 9 total bilirubin values per person (interquartile range IQR 3–22). The median baseline total bilirubin was 0.6 mg/dL (IQR 0.4–0.8) among men and 0.5 mg/dL (IQR 0.3–0.6) among women. During an average of 5.8 years of follow-up, 392 PLWH had a T1MI, and 356 had a T2MI for an incidence rate

of 2.6 per 1000 person-years (95% confidence interval [95%CI]:2.4–2.9) for T1MI and 2.4 per 1000 person-years (95%CI:2.2–2.7) for T2MI. Of the T2MI, 127 (36%) were sepsis-related, 37 (10%) were related to cocaine-induced vasospasm, and 192 (54%) were related to a variety of other factors. There were 160 individuals with an ischemic stroke not related to infection or illicit drug use. There were 476 PLWH who had a combined outcome of a T1MI or ischemic stroke not associated with drug use or infection for an incidence rate of 3.2 per 1000 person-years (95%CI:2.9–3.5). Those with both an MI and stroke were categorized by their first event.

Type 1 MI:

In adjusted analyses, the hazard ratio (HR) for T1MI was <1.0 but not statistically significant (Table 2). For example, in analyses including bilirubin levels <2.1 mg/dL, the HR for the association of higher bilirubin levels with T1MI was 0.80 per 2-fold increase in bilirubin; 95%CI:0.49–1.53 with similar findings among groups stratified by HCV status. Findings were not statistically different than 1.0 in analyses limited to those with baseline Fib-4 values <3.25 and in analyses that included everyone. Similar results were seen with categorical approaches (e.g. bilirubin values between 1.3 and 2.1 vs. <0.6, HR 0.76; 95%CI: 0.33–1.72) and with spline models (data not shown). Similar patterns of non-significant findings were found in sensitivity analyses with an outcome of T1MI combined with ischemic strokes not associated with drug use or infection (Table 2).

Type 2 MI:

In adjusted analyses limited to bilirubin levels <2.1 mg/dL, higher bilirubin levels were significantly associated with T2MI overall (HR 1.70 per 2-fold bilirubin increase; 95%CI: 1.04–2.78) and in analyses stratified by HCV status, higher bilirubin levels were significantly associated with T2MI among those without HCV (HR 2.52 per 2-fold bilirubin increase; 95%CI:1.36–4.66) but not those with HCV (HR 1.01; 95%CI:0.45–2.30) (Table 2; interaction p-value, 0.01). Findings were similar in models limited to those with baseline Fib-4 values <3.25, but not in the models that included everyone (Table 2) where there was no difference by HCV status. In categorical analyses including bilirubin levels <2.1 mg/dL, higher categories of bilirubin were associated with T2MI and this was driven by those without HCV. Higher bilirubin levels (compared with bilirubin levels <0.6) were associated with T2MI (bilirubin levels 0.6–1.3: HR 1.61; 95%CI:1.15–2.27; bilirubin levels 1.3–2.1: HR 2.70; 95%CI:1.34–5.46) among those without HCV. In spline models among everyone, a bilirubin increase of 0.1 in the range of 0.6–1.3 was associated with an increased risk of T2MI (1.09; 95%CI:1.03–1.14), and this did not differ by HCV status (without HCV, HR 1.09; 95%CI:1.02–1.17; with HCV, HR 1.10; 95%CI:1.01–1.19).

Atazanavir and ART:

In models limited to those on ART, we stratified by atazanavir use (Table 3). During ART that did not include atazanavir, the pattern of findings was similar to the overall findings, showing a not significant decreased risk of T1MI (HR 0.70; 95%CI:0.43–1.15] and a significantly increased risk of T2MI associated with higher bilirubin levels (HR 2.00:95%CI:1.52–2.62). During ART that included atazanavir, the association with T1MI was similar to the main analyses with a HR <1.0 but not statistically significant. Higher

bilirubin levels were associated with significantly fewer of the combined outcome of T1MI and ischemic stroke (HR 0.64;0.41–0.99). However, the association with T2MI was different than among those not on atazanavir: higher bilirubin levels were associated with significantly fewer T2MI events (HR 0.56; 95%CI:0.33–1.00).

Sensitivity analyses:

For the analysis shown in Table 2, findings did not differ in analyses that excluded those with diabetes. In adjusted analyses adjusting for HCV status and stratified by sex limiting to those with bilirubin values <2.1, associations with T1MI were not significant, while for T2MI higher bilirubin levels were associated with increased risk for women only (4.58; 95%CI:2.06–10.1); p-value for bilirubin*sex interaction term, 0.02). Findings were also similar but not significant in analyses among the subset of 4,963 with indirect bilirubin values (data not shown).

Discussion

In a large cohort of PLWH with carefully adjudicated cardiovascular outcomes we found that overall, mildly elevated levels of total bilirubin (<2.1mg/dL) were associated with increased risk of T2MI, particularly among those without HCV. Interestingly, among those on ART and including all bilirubin values, bilirubin levels were not associated with increased T2MI among those currently taking atazanavir, in fact the opposite was the case. In the subset of individuals currently on atazanavir, elevated bilirubin levels were associated with reduced T2MI risk. Among those currently on atazanavir, elevated bilirubin levels were also associated with reduced risk of the combined outcome of T1MI and ischemic stroke. Mildly elevated bilirubin levels (<2.1mg/dL) had a HR for the association with T1MI that was <1 consistent with protective findings seen in the general population, however this association was not significant. To our knowledge, these analyses are one of the largest to date evaluating the relationship between bilirubin and cardiovascular outcomes among PLWH and the first to do so distinguishing T1MI and T2MI.

PLWH with T2MI have previously been shown to have more severe HIV disease on average than those with T1MI[31]. Elevated bilirubin in this setting possibly represents the greater burden of underlying comorbidity. However, we adjusted for HIV disease severity as measured by time-varying CD4 count and viral load and still found higher bilirubin levels were associated with T2MI. We hypothesized that liver disease might be a driver of this association; however, the association between higher bilirubin and T2MI was particularly notable in those without HCV. Heavy alcohol use and alcohol-related liver injury may also be a potential confounding factor but our findings remained consistent in analyses that eliminated those with higher baseline Fib-4 values or with more elevated bilirubin levels, who likely comprise the majority of patients with alcoholic hepatitis. We were concerned that higher bilirubin levels and T2MI may be surrogates for the same thing, such as sepsis that caused widespread organ ischemia, therefore, all analyses excluded bilirubin levels ≤30 days before the MI to minimize this.

These findings add to the limited literature on bilirubin, atazanavir, and cardiovascular disease outcomes in PLWH. A cross-sectional case-control study examining carotid intimal

media thickness found little difference by bilirubin level, but the small sample size (N=78) limited the conclusions that could be drawn[39]. A study compared those on atazanavir (N=11) versus those not on atazanavir (N=51) and found that both atazanavir use and higher baseline total serum bilirubin level were associated with slower mean carotid intima media thickness progression[40]. Another study of 145 PLWH on atazanavir vs. efavirenz-based regimens found oxidative stress measured by lipoprotein-associated phospholipase A2 and oxidized low-density lipoprotein was reduced in those on atazanavir and was correlated with elevated bilirubin levels[41]. One of the more compelling studies (ACTG 5260s) was a trial of ART-naïve individuals randomized to atazanavir vs. darunavir vs. raltegravir-based regimens. Those on atazanavir had slower carotid intima media thickness progression than those on darunavir, and in some analyses, raltegravir. This was associated in part with bilirubin levels >0.6 mg/dL[21], although bilirubin levels may also serve as a marker of good ART adherence for those on atazanavir[42]. A recent large study conducted in the Veterans Affairs (VA) Health Care System suggested that higher bilirubin levels are associated with decreased cardiovascular events such as heart failure and ischemic stroke among PLWH although associations with MI were not statistically significant and that study did not distinguish MI type[22]. Another large study from the VA was conducted in 9,500 PLWH[43]. A study strength was that it examined the association of atazanavir with MI and stroke rather than intermediate outcomes. However, MI and stroke were not adjudicated raising concerns about accuracy, and surprisingly there were higher rates of strokes than MI, raising questions about MI capture completeness. The VA study reported a lower incidence of MI and stroke among PLWH on atazanavir compared with other regimens; however, because this study was unable to distinguish T1MI from T2MI, it is not clear whether the findings were similar to ours.

We hypothesized that among PLWH on atazanavir, higher bilirubin levels would be associated with reduced MI risk, particularly T1MI. Instead, we found that higher bilirubin levels were associated with reduced risk of both types of MI, reaching statistical signifiance for T2MI risk or risk of the combined outcome of T1MI and ischemic stroke. Interestingly, this is in direct contrast to individuals on ART that did not include atazanavir, in whom higher bilirubin levels were significantly associated with increased T2MI risk. These findings are intriguing and suggest that the impact of bilirubin levels on cardiovascular disease in PLWH may differ compared with the general population. The difference in overall findings among those with and without HCV, and in particular the protective association of elevated bilirubin levels among those on atazanavir, where presumably many of the higher bilirubin levels are due to atazanavir rather than illness, highlights the diverse causes of elevated bilirubin levels among PLWH. We suspect that bilirubin elevations due to benign causes such as atazanavir may be protective, similar to the protective associations seen with Gilbert's syndrome in the general population. However, other factors such as liver disease including related to HIV-disease itself, viral hepatitis, and hazardous alcohol use may all contribute to bilirubin elevation and may not necessarily have protective associations with either T1MI or T2MI.

We considered whether associations between atazanavir, bilirubin, and T2MI were due to channeling bias. There is always a concern about medication channeling, where the healthier participants are selectively prescribed a particular pharmacotherapy (e.g. atazanavir).

However, we suspect that if the protective association between bilirubin and T2MI among patients on atazanavir versus those on other regimens was due to health status differences and not direct effects of the atazanavir and bilirubin metabolism, we would have seen differences between those on atazanavir vs. those on other ART regimens with T1MI. The hazard ratios for the association of bilirubin with T1MI are very similar among those on atazanavir vs. other regimens (HR 0.68 vs 0.70). This difference in the bilirubin association by atazanavir use between MI type makes it less likely that the protective association between T2MI and bilirubin in the atazanavir group is due to channeling of healthier participants towards atazanavir.

A key finding is the importance of distinguishing T1MI and T2MI. The distinct associations by MI type adds to prior studies demonstrating substantial differences in demographic and clinical characteristics and outcomes among PLWH who experienced a T1MI vs. T2MI[31,44]. These differences in risk factors combined with the diverse pathophysiologies and concomitant comorbidities associated with different MI types adds to the compelling argument that MI type in PLWH should be distinguished rather than combined[31].

Strengths.

The large sample size and well-defined outcomes are strengths. The careful adjudication, including distinguishing T1MI and T2MI, is of value, particularly as we found that the association between bilirubin and atherosclerotic T1MI differs from the association with T2MI. We evaluated outcomes separately. We used several different bilirubin parameterizations based on the recommendations from studies not conducted in PLWH[9,10,45].

An additional strength is that we excluded bilirubin values ≥2.1 mg/dL from some models to minimize the impact of hepatic pathology. While higher bilirubin levels have been associated with decreased atherosclerotic disease in the general population, this association has not always been found or different patterns such as u-shaped associations have been seen. This may be due to liver disease[9] which would likely have as big if not bigger impact among PLWH. However, excluding values ≥2.1 mg/dL may impact being able to evaluate a potential protective effect of hyperbilirubinemia associated with atazanavir, as 2.1 mg/dL is not much higher than mean values on atazanavir[46]. Therefore, we repeated analyses using a FIB-4 cut-off and among everyone. We included all bilirubin values for the atazanvir analyses. We used time-updated models to examine atazanavir vs. other drugs, and did not limit people to baseline regimens but allowed them to contribute whenever they were on ART.

Limitations:

We analyzed total bilirubin which combines conjugated and unconjugated bilirubin values and does not distinguish between elevated bilirubin caused by hepatic pathology or by benign deficiency in excretory capacity[4]. Some associations between bilirubin and reduced cardiovascular risk have been in the context of elevated unconjugated bilirubin levels such as with Gilbert's syndrome[6]. In our analysis the overall results were similar in the subset with unconjugated bilirubin levels available, it was a small subset and no associations were

significant. Additionally, we did not limit bilirubin levels to fasting values; associations may be stronger in studies using fasting bilirubin levels[10] as fasting may impact bilirubin levels[47]. Our study is observational, so causality cannot be inferred. This limitation has also been noted in general population studies regarding whether relationships between bilirubin levels and cardiovascular disease may be causal or due to confounding and reverse causality[10,48]. We stratified overall results by HCV status to better understand the influence of liver disease, but due to low numbers were unable to stratify by hepatitis B.

More research seems warranted with carefully adjudicated T1M1 versus T2MI to better understand the mechanism of the associations between bilirubin and T2MI, the complicated relationships between bilirubin and cardiovascular outcomes in general, and whether there is a protective effect of mildly elevated bilirubin levels not due to liver disease and the role of specific antiretroviral medications, potentially done with unconjugated bilirubin levels rather than total bilirubin. Differences in associations between those with and without HCV and receiving or not receiving atazanavir suggest the need for a nuanced approach to evaluating bilirubin that considers causes of elevated levels among PLWH. In addition, the larger risk of T2MI associated with a 2-fold increase in bilirubin among women than men raises questions regarding reasons for differences between men and women worthy of future study.

Conclusions:

In this large cohort, the hazard ratio for the association of higher bilirubin with T1MI was <1, consistent with general population studies, but not statistically significant. If the antioxidant effect of bilirubin reduces cardiovascular risk among PLWH, the impact may be small and difficult to detect even with large samples. Higher bilirubin levels were associated with increased T2MI risk, particularly among those without HCV, raising questions about potential mechanisms. In contrast, among patients on atazanavir, higher bilirubin levels were associated with lower risk of T2MI. Among those on atazanvir, higher bilirubin levels were associated with lower risk of the combined outcome of T1MI and ischemic stroke. These findings demonstrate differences in impact of elevated bilirubin levels due to diverse causes on outcomes among PLWH and highlights the importance of carefully validated outcomes including MI types and looking at individual outcomes rather than composite outcomes where relationships differ.

Acknowledgements

We wish to acknowledge the patients, staff, and providers throughout CNICS.

Conflicts of Interest and Source of Funding

This work was supported by Brystol-Myers Squibb. Additional support came from the National Institute of Allergy and Infectious Diseases (CNICS R24 AI067039, UW CFAR NIAID Grant P30 AI027757; UNC CFAR grant P30 AI50410, JHU CFAR grant P30 AI094189, and UAB CFAR grant P30 AI027767), the National Institute of Drug Abuse (U01DA036935) and the National Heart, Lung, and Blood Institute [R01HL126538] at the National Institutes of Health and from the American Heart Association (13GRNT14560022).

The following have received grant support or served as consultants or advisors: Dr. Hunt with Merck and Gilead, Dr. Burkholder with DefiniCare, Dr. Saag with BMS, Gilead, Merck, and ViiV, Dr. Moore with Medscape, Dr. Eron with Merck, ViiV, BMS, Abbvie, Gilead, Tibotec/Janssen, Dr. Drozd with Gilead, Dr. Crane with ViiV, and Dr. Budoff has consulted for General Electric. The following are affiliated with BMS: C Ritchings, L Rosenblatt.

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Table 1.

Demographic and clinical characteristics overall (N=25,816) and by myocardial infarction status

Baseline	Overall	No MI	Type 1 MI	Type 2 MI
N	25,816	25,068	392	356
Age (mean)	40	40	47	45
Female	19%	19%	14%	29%
Race				
White	42%	42%	49%	24%
Black	40%	40%	38%	65%
Hispanic	13%	13%	10%	8%
Other/Missing	5%	5%	3%	3%
Hepatitis C	18%	18%	21%	40%
VL ≤400	61%	61%	61%	51%
CD4 cell count cells/mm^3 (mean)	445	446	407	366
Bilirubin mg/dL (mean)	0.72	0.72	0.72	0.72

MI: myocardial infarction

VL: viral load

Percentages are the percent in each column with a particular characteristic. For example, overall 19% of the included participants are female. However, among those with a type 2 MI, 29% are female.

Table 2.

Associations of bilirubin levels with cardiovascular outcomes limited to bilirubin values <2.1 mg/dL, limited to those with FIB-4 values <3.25, and among everyone stratified by hepatitis C virus co-infection status in adjusted analyses*

	Hazard Ratio per 2-fold increase in bilirubin [95% confidence interval]		
Outcome	**HCV-uninfected and infected (combined)**	**Stratified by HCV status**	
		HCV-uninfected	**HCV-infected**
N (Limited to bilirubin values <2.1 mg/dL)	20,604	17,127	3,477
Type 1 MI	0.80 [0.49, 1.33]	0.78 [0.45, 1.37]	0.88 [0.29, 2.72]
Type 2 MI	1.70 [1.04, 2.78]	2.52 [1.36, 4.66]	1.01 [0.45, 2.30]
Type I MI and ischemic stroke	0.87 [0.56, 1.34]	0.98 [0.60, 1.58]	0.53 [0.19, 1.47]
N (Limited to those with FIB-4 values <3.25 at baseline)	24,205	20,190	4,015
Type 1 MI	1.01 [0.80, 1.28]	1.04 [0.80, 1.35]	0.90 [0.50, 1.61]
Type 2 MI	1.35 [1.07, 1.72]	1.56 [1.19, 2.06]	1.00 [0.63, 1.60]
Type I MI and ischemic stroke	0.99 [0.79, 1.23]	0.99 [0.78, 1.26]	0.97 [0.59, 1.60]
N (All)	25,816	21,111	4,705
Type 1 MI	0.98 [0.78, 1.23]	0.99 [0.77, 1.29]	0.93 [0.56, 1.56]
Type 2 MI	1.47 [1.19, 1.82]	1.53 [1.17, 2.00]	1.42 [1.02, 1.98]
Type I MI and ischemic stroke	0.98 [0.79, 1.20]	0.94 [0.74, 1.20]	1.06 [0.70, 1.61]

FIB-4: Fibrosis-4 index

HCV: hepatitis C virus

MI: myocardial infarction

*Analyses adjusted for time-varying viral load and CD4 count, and baseline age, sex, race/ethnicity, HIV transmission risk factor, smoking status, hepatitis C virus status, diabetes, treated hypertension, statin use, kidney function (estimated GFR <30, 30–60, ≥60), calendar time, and site. Analyses stratified by HCV not adjusted for HCV. Analyses included all bilirubin levels obtained on ART.

Table 3.

Associations of bilirubin levels with cardiovascular outcomes among those on antiretroviral therapy stratified by atazanavir use and by hepatitis C virus co-infection status in adjusted analyses *

	Hazard Ratio per 2-fold increase in bilirubin [95% confidence interval]		
Outcome	**HCV-uninfected and infected (combined)**	**Stratified by HCV status**	
		HCV-uninfected	**HCV-infected**
N (Limited to those on ART not including atazanavir)	20,305	16,706	3,599
Type 1 MI	0.70 [0.43, 1.15]	0.65 [0.36, 1.17]	0.82 [0.33, 2.04]
Type 2 MI	2.00 [1.52, 2.62]	2.11 [1.37, 3.25]	2.03 [1.40, 2.95]
Type I MI and ischemic stroke	0.91 [0.61, 1.35]	0.69 [0.41, 1.16]	1.29 [0.75, 2.22]
N (Limited to those on ART including atazanavir)	5,671		
Type 1 MI	0.68 [0.43, 1.09]	**	**
Type 2 MI	0.56 [0.33, 1.00]		
Type I MI and ischemic stroke	0.64 [0.41, 0.99]		

HCV: hepatitis C virus

MI: myocardial infarction

* Analyses adjusted for time-varying viral load and CD4 count, and baseline age, sex, race/ethnicity, HIV transmission risk factor, smoking status, hepatitis C virus status, diabetes, treated hypertension, statin use, kidney function (estimated GFR <30, 30–60, ≥60), calendar time, and site. Analyses stratified by HCV not adjusted for HCV.

** Atazanavir analyses not stratified due to small outcome numbers

*** Note that ART use and atazanavir user are time-varying