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Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons

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Abstract

Objective—Abacavir use has been associated with cardiovascular risk, but it is unknown whether this association may be partly explained by patients with kidney disease being preferentially treated with abacavir to avoid tenofovir. Our objective was to compare associations of abacavir and tenofovir with cardiovascular risks in HIV-infected veterans.

Design—Cohort study of 10 931 HIV-infected patients initiating antiretroviral therapy in the Veterans Health Administration from 1997 to 2007, using proportional hazards survival regression.

Methods—Primary predictors were exposure to abacavir or tenofovir within the past 6 months, compared with no exposure to these drugs, respectively. Outcomes were time to first atherosclerotic cardiovascular event, defined as coronary, cerebrovascular, or peripheral arterial disease; and time to incident heart failure.

Results—Over 60 588 person-years of observation, there were 501 cardiovascular and 194 heart failure events. Age-standardized event rates among abacavir and tenofovir users were 12.5 versus 8.2 per 1000 person-years for cardiovascular disease, and 3.9 and 3.7 per 1000 person-years for heart failure, respectively. In multivariate-adjusted models, including time-updated measurements of kidney function, recent abacavir use was significantly associated with incident cardiovascular disease [hazard ratio 1.48, 95% confidence interval (CI) 1.08–2.04]; the association was similar but nonsignificant for heart failure (1.45, 0.85–2.47). In contrast, recent tenofovir use was significantly associated with heart failure (1.82, 1.02–3.24), but not with cardiovascular events (0.78, 0.52–1.16).

Conclusion—Recent abacavir exposure was independently associated with increased risk for cardiovascular events. We also observed an association between recent tenofovir exposure and heart failure, which needs to be confirmed in future studies.

Keywords

antiretroviral therapy; cardiovascular disease; heart failure; HIV

Introduction

Although the life expectancy of HIV-infected persons has increased steadily since the advent of combination antiretroviral therapy (ART), survival still falls short of the general population [1,2]. In practice, the full promise of ART has been difficult to achieve because of adverse drug effects, leading to medication nonadherence and injury to multiple end organs, such as the heart and the kidney. With recent consensus guidelines recommending the initiation of therapy early in the course of HIV infection, the average duration of exposure to ART will increase, and complications of treatment are expected to become more common [3,4].

Cardiovascular disease (CVD) is now a leading cause of death among HIV-infected persons in the USA [5,6], and represents a growing clinical concern among HIV-infected patients, providers, and the cardiology community [7]. The excess risk of CVD may be due to multiple causes, including a higher prevalence of traditional risk factors and kidney disease [8], the pathogenic effect of the virus itself, and potentially, specific antiretroviral drug toxicities [7]. Unfortunately, there have been too few cardiovascular events among participants of randomized controlled trials to address this issue with precision [9,10]. In an observational study, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study reported associations of protease inhibitors and nucleoside reverse transcriptase inhibitors with myocardial infarction (MI) [11–13]. The most debated finding has been the association of recent abacavir exposure with a 90% increased risk of MI [11]. Although observational studies do not usually have immediate impact on clinical decision-making, these results contributed to abacavir's demotion from a preferred to a second-line regimen and the issuance of a Food and Drug Administration warning within 6 months of publication [4].

Some concerns have been raised by critics of these studies. Since the evidence was based on observational studies, it is possible that results may have been subject to unmeasured confounding. In particular, a potential source of bias in the relationship between abacavir and MI is kidney disease, a potent risk factor for CVD not fully accounted for in the D:A:D study [8,14]. Nephrotoxicity is a well established complication of tenofovir, and patients with prevalent or incipient kidney disease may be preferentially treated with abacavir rather than tenofovir (i.e. 'channeling bias') [15]. Most prior studies evaluating abacavir and CVD have not fully controlled for kidney function and proteinuria as potential confounders [11,13,16]. Thus, several commentators have appealed for an analysis of CVD risk which accounts for longitudinal changes in kidney health [14,17].

We conducted this study to compare the effects of both abacavir and tenofovir on CVD and heart failure risk in a national sample of 10 931 HIV-infected persons who initiated ART between 1997 and 2007 within the Veterans Health Administration, which provides relatively uniform care. We included measurements of kidney function and proteinuria in our analyses and used time-dependent covariate modeling to adjust for changes in kidney health over time, which could cause changes in ART. We hypothesized that controlling for the effects of kidney disease on treatment selection and cardiovascular disease outcomes would attenuate the association between abacavir and CVD risk.

Methods

We conducted an analysis of CVD in a national sample of HIV-infected US veterans. The data sources used to assemble the analytic cohort have been described in detail previously [8]. In brief, the Department of Veterans Affairs (VA) HIV Clinical Case Registry (CCR) actively monitors all HIV-infected persons receiving care in the VA nationally and extracts

demographic, clinical, laboratory, pharmacy, utilization, and death information entered in the VA electronic medical record to a centralized database through an automated process [18]. The CCR is validated in three stages. First, an extensive review is conducted of initial data received from every facility in every field. Second, monthly, facility-level data field counts are assessed with the goal of quickly identifying missing data. Third, validation is conducted within all aspects of national quality and safety initiatives for veterans with HIV infection [18].

The HIV CCR was linked to the VA National Patient Care Database, the VA Beneficiary Identification and Records Locator Subsystem Death File, and Medicare claims to augment demographic, comorbidity, and vital status data, and to capture clinical events outside of the VA system [19,20]. The US Renal Data System, a comprehensive, national end-stage renal disease (ESRD) registry, was used to ascertain ESRD status, defined by receipt of chronic dialysis treatment or kidney transplant [21].

Patients

The target population for this analysis was all HIV-infected veterans who were ART treatment naive at study entry and subsequently received ART with regular care and laboratory monitoring in the Veterans Health Administration [11,16]. There were 59 479 HIV-infected persons treated in the Veterans Health Administration between 1985 and 2007. Among these patients, 19 715 patients initiated ART in the modern era of combination ART (after 1997). In order to delineate a cohort that was receiving treatment in the VA, we also excluded patients who did not have at least one viral load, CD4 cell count, outpatient visit, and assessment of kidney function, leaving 10 931 patients in the analytic cohort.

Outcomes

The primary outcomes for the study were time to first atherosclerotic cardiovascular event, defined as hospitalization for coronary, cerebrovascular, or peripheral arterial disease; and time to hospitalization for heart failure. Outcomes were defined using primary discharge diagnoses and procedural codes entered into VA and Medicare databases based on validated algorithms defined previously [22,23]. Coronary heart disease (CHD) was defined by an acute presentation for MI or unstable angina, or by a coronary revascularization procedure (angioplasty or bypass surgery). Cerebrovascular disease (CVA) was defined by ischemic or hemorrhagic stroke. Chronic heart failure (CHF) was defined as hospitalization for acute heart failure treatment, and peripheral vascular disease (PVD) was defined by surgical procedures for lower extremity revascularization or amputation. We also performed secondary analyses examining each of the above categories of cardiovascular outcomes, the outcomes of MI alone and other CHD events separate from one another, and ischemic stroke.

Independent variables

We ascertained drug utilization in the CCR medication files for ART, diabetes therapy, antihypertensive therapy, and cholesterol-lowering medications based on pharmacy fill information. Medication exposure was used to define the primary ART predictor variables, and to identify individuals with chronic diseases based on validated algorithms. Previous work has shown that VA pharmacy data are comprehensive and reliable for assessing medication use [24–28]. To replicate the D:A:D analysis [11], abacavir and tenofovir therapy was modeled in terms of cumulative exposure (total years of use), as well as mutually exclusive indicators for any past exposure (last use more than 6 months prior) and any recent exposure (current use, or use within the previous 6 months).

Demographic information including age, sex, and race was obtained from the CCR and supplemented with Medicare database information. Kidney function was defined as the estimated glomerular filtration rate (eGFR), calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula based on age, sex, race, and serum creatinine [29]. Chronic kidney disease (CKD) was defined by an eGFR below 60 ml/min per 1.73 m². Proteinuria was defined as urine dipstick measurements greater than 30 mg/dl.

We defined comorbid conditions based on a combination of physician problem lists, procedures, ambulatory diagnoses, hospitalization discharge diagnoses, laboratory results, and medication prescriptions. We applied previously validated algorithms to define the following conditions: diabetes, hypertension, hyperlipidemia, hepatitis B and C virus co-infection, chronic obstructive lung disease, liver disease, substance abuse, and smoking [22,23,30,31]. Hypertension was defined based on two outpatient ICD-9 codes or a combination of diagnostic codes and antihypertensive treatment [22,32]. Diabetes was defined by any prescription for insulin or an oral hypoglycemic agent, or two or more diagnoses from inpatient or outpatient visits [31]. Tobacco use was defined by inpatient or outpatient diagnostic codes; questions regarding tobacco use are mandatory in VA clinical care. Drug abuse was defined using inpatient and outpatient diagnostic codes [25]. Dyslipidemia was based on outpatient diagnosis OR use of lipid-lowering therapy [32]. Cancer was defined as gastro-intestinal, lung, urogenital, hematological, skin (melanoma, Kaposi and nonepithelial skin cancer), or other (including history of cancer, eye cancer, brain cancer, soft tissue cancer, thyroid cancer, endocrine cancer, ill-defined cancer). Hepatitis B virus infection was defined by positive surface antigens or a detectable hepatitis viral load. Clinical information such as blood pressure, body mass index (BMI), CD4 T-cell counts, HIV RNA level, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and serum glucose were included in statistical models or used to define clinical characteristics. At any given time, the most recent previous measurement was used to define time-dependent covariates.

Comorbidities were set up using the last-observation-carry-forward principle, meaning once the patient has the condition, he/she has it until death. Other variables, such as lab measurements, are time-updated at each observation. All variables were available in the vast majority of patients. If a variable was never measured, we used a 'missing' indicator so that the patient could remain in our analysis. The frequency of missing measures is as follows: creatinine, CD4 cell count, viral load (0%), glucose (0.2%), blood pressure levels (1.8%), serum albumin (1.9%), BMI (4.1%), total cholesterol (6.3%), and urine protein (9.7%).

Statistical analysis

Our primary objectives were to estimate the effects of abacavir and tenofovir on cardiovascular outcomes. We calculated incidence rates for each outcome standardized to the age distribution of the source population. We estimated abacavir and tenofovir treatment effects using two Cox proportional hazards regression models: adjusted for demographic characteristics only; and adjusted for demographics and time-dependent prognostic covariates. Using the Cox proportional hazards regression models, we replicated the D:A:D abacavir analysis [10]. Tests for interaction were performed using cross-product terms between tenofovir or abacavir and characteristics of interest defined at baseline. Patients were censored at the time of death or the last day of follow-up (31 December 2007).

Assumptions of the Cox regression models were checked by comparing plots of log [−log(survival)] versus log of survival time and the Schoenfeld test. Analyses were conducted using Stata version 10.1 (Stata Corp, College Station, Texas, USA). This study was approved by the Committee on Human Research at the San Francisco VA Medical Center and the VA Public Health Strategic Healthcare Group on 18 July 2008.

Results

We initially compared characteristics of the 10 931 HIV-infected persons at the time they initiated abacavir, tenofovir, or other ART. The frequency of use of antiviral agents with ART initiation was as follows, in decreasing order of frequency: lamivudine ($n=6559$, 71.90% of other ART), zidovudine (4792, 52.53%), stavudine (2225, 24.39%), nelfinavir (1672, 18.33%), efavirenz (1665, 18.25%), indinavir (1557, 17.07%), nevirapine (744, 8.16%), didanosine (634, 6.95%), ritonavir (598, 6.56%), saquinavir (404, 4.43%), kaletra (208, 2.28%), atazanavir (80, 0.88%), zalcitabine (71, 0.78%), amprenavir (58, 0.64%), delavirdine (30, 0.33%), and fosamprenavir (13, 0.14%). Demographic characteristics were similar across these three groups. Only 24 and 22% of abacavir and tenofovir new users, respectively, were ART-naïve at the time these therapies were initiated. As a result, CD4 cell counts were higher and viral loads lower at the time abacavir and tenofovir were started compared with other antiretroviral regimens. Abacavir and tenofovir new users were similar to each other in most chronic conditions, CD4 cell count and viral load (Table 1); however, they differed somewhat in the prevalence of CKD, defined by an eGFR below 60 ml/min per 1.73 m^2 (10 and 6% of individuals receiving abacavir versus tenofovir had CKD, respectively). In contrast, the proportion of those with proteinuria (defined by urinalysis protein 30 mg/dl or greater) was approximately equal among new users of abacavir and tenofovir.

There were 194 heart failure events in 60 588 person-years of follow-up and 501 atherosclerotic cardiovascular events over 59 578 person-years of follow-up. The median period of observation per individual was 4.5 years (maximum 11.1 years).

Abacavir

There were 123 cardiovascular and 56 heart failure events over a total of 15 142 person-years of current or recent (<6 months) abacavir use. Incidence rates for the composite outcome of any atherosclerotic CVD event were higher in the setting of recent abacavir use compared with recent tenofovir use or other ART (13.4 versus 9.4 per 1000 person-years for abacavir and tenofovir, respectively, $P < 0.01$; see Fig. 1). Results were consistent for the individual outcomes of coronary and CVA, but no difference was observed for peripheral arterial disease. In multivariate Cox proportional hazard models, recent abacavir exposure was associated with approximately a 50% increase in risk of the composite outcome of any atherosclerotic cardiovascular event, compared with those who used neither abacavir nor tenofovir in the previous 6 months (Table 2). The association of recent abacavir exposure with increased risk of atherosclerotic cardiovascular events was similar (1.49, 95% CI 1.09–2.05) in multivariate analysis that excluded time-updated kidney function covariates. This indicates that kidney health was not a major confounder. We found similar findings for the association of recent abacavir use with acute MI (1.64, 95% CI 0.88–3.08) and other coronary heart disease events (1.53, 95% CI 0.97–2.43) in multivariate analyses. The risk of ischemic stroke was similar in adjusted analyses to that for the combined CVA outcome (2.05, 95% CI 1.00–4.19). Cumulative abacavir exposure (0.93, 95% CI 0.79–1.10) and less recent abacavir exposure (1.38, 95% CI 0.95–1.99) were not significantly associated with cardiovascular events. Among the individual outcomes, abacavir use had associations with coronary disease, CVA, and heart failure, but only CVA had statistically significant associations. Cumulative exposure to abacavir was not significantly associated with atherosclerotic CVD or heart failure in models without recent or past exposure.

We evaluated the association of recent abacavir exposure with CVD after stratifying on 13 baseline variables (Fig. 2). Abacavir was consistently associated with higher CVD risk in the majority of subgroups. Only one of the 13 subgroups was found to have a significant P value for interaction (<0.05); abacavir had a stronger association with CVD in those without

dyslipidemia compared with those with dyslipidemia. This suggests that the abacavir association was not mediated through any harmful effects on lipoproteins. The association appeared somewhat stronger among those without CKD compared with persons with CKD, based on eGFR less than 60 ml/min per 1.73 m²; however, this was not a significant interaction. These findings were nearly identical by proteinuria status.

Tenofovir

There were 90 cardiovascular and 53 heart failure events over 22 551 person-years of current or recent (<6 months) tenofovir use. In adjusted Cox models, recent tenofovir use was not statistically significantly associated with CVD, or its component outcomes of coronary, cerebrovascular, or peripheral arterial disease (Table 2), compared with those not exposed to tenofovir in the prior 6 months.

The incidence of heart failure (Fig. 1) in tenofovir compared with abacavir users and other ART users was similar (3.7 versus 3.9 and 3.6 events per 1000 person-years, respectively). In a multivariable adjusted Cox model, tenofovir was associated with an 82% increase in heart failure (as compared to non-tenofovir use).

In subgroup analyses, hazard ratios consistently supported a higher adjusted risk of heart failure associated with tenofovir; however, CIs were wide (Fig. 3). None of the *P* values for interaction was statistically significant; however, the strength of the association between tenofovir with heart failure appeared to be somewhat larger in those with CKD marked by an eGFR less than 60 ml/min per 1.73 m², and in subgroups with risk factors for CKD such as diabetes and hypertension.

Discussion

In this national sample of 10 931 HIV-infected persons receiving relatively uniform care in the Veterans Health Administration, we found that recent abacavir exposure was independently associated with an increased risk for the composite outcome of atherosclerotic cardiovascular events. The risk appeared to be relatively consistent across patient subgroups and for the individual outcomes of coronary and CVA, but not for peripheral arterial disease. In contrast to abacavir, tenofovir did not appear to be substantially associated with the development of atherosclerotic vascular events. However, we found that recent tenofovir exposure was associated with a significantly higher adjusted risk of heart failure. Although the magnitude of these increases in the absolute risk of adverse cardiovascular events were relatively small, these findings indicate the need to evaluate comprehensively the potential harms and benefits of these agents.

Abacavir and cardiovascular disease

Contrary to our initial hypothesis, adjustment for kidney disease marked by either low eGFR or proteinuria did not strongly attenuate the association of recent abacavir exposure with CVD risk. Although the link between abacavir and CVD has been controversial, our results are generally consistent with several published studies identifying an association between recent abacavir use and higher risk of MI. In addition to the D:A:D study, a recent nested case-control study by Lang *et al.* [33] found elevated MI risk in association with recent, but not cumulative, exposure to abacavir. These investigators did not account for certain potential confounders such as renal function, and they were not able to adjust for changing covariates over time because of the case-control design of the study. In both the D:A:D study and our current analysis, the majority of abacavir users had previously received ART, whereas in the study by Lang *et al.*, three-quarters of all patients were antiretroviral naive at

the beginning of the study [16,33]. We do not know whether this biases in favor or against our finding associations of abacavir and tenofovir with CVD.

All of these studies finding an association between abacavir and CVD have been conducted in 'real world' populations, which were older and carried a greater risk of CVD [11,16,33,34], compared with clinical trials, populations with relatively low CVD risk, shorter follow-up time, and smaller sample sizes [9,10]. On the contrary, our study was observational, and therefore may be inherently confounded by characteristics influencing treatment. Because individuals with kidney dysfunction would be less likely to use tenofovir, we thought they might be 'channeled' to abacavir treatment, thereby confounding through a 'channeling bias'. Therefore, we accounted for history of other ART use and time-dependent measures of kidney health; however, adjusting for these covariates did not affect our results. Only further confirmation of these results in additional study populations and the elucidation of underlying pathogenesis can resolve the abacavir controversy.

Potential mechanisms of abacavir cardiovascular toxicity

Since the publication of the D:A:D study, a number of possible mechanisms have emerged as potential mediators of the abacavir effect. In ACTG 5202, participants receiving abacavir in the low viral load stratum (<100 000 copies/ml) had higher rates of cholesterol elevations compared with controls. In addition, abacavir has been implicated in a number of processes which may lead to accelerated vascular disease such as platelet activation [35], hyperlipidemia [36], T-lymphocyte activation [37], abnormal endothelial function [38] and vascular inflammation [16,39]. Hypersensitivity reaction and concomitant inflammatory processes may affect platelet and endothelial function. Of note, HLAB5701 testing to prevent abacavir hypersensitivity reactions was not the standard of care during the conduct of this study. Therefore, it is possible that the risk of CVD may be lower in contemporarily treated patients who are unlikely to experience abacavir hypersensitivity reactions.

Tenofovir and heart failure

We observed that recent tenofovir exposure was associated with a statistically significant increase in the adjusted risk of heart failure, but the absolute increase in risk appeared to be small and the CIs were relatively wide. Although this observation raises concern about the potential risk of heart failure associated with tenofovir exposure, we consider these results hypothesis generating and urge replication studies in other patient populations.

Despite the need for replication, the link between tenofovir and heart failure is biologically plausible. Several studies report that chronic tenofovir therapy is associated with accelerated loss of kidney function over time compared with controls [40–45]. Generally, the observed changes in eGFR have been small and within the range of normal; therefore, they have been thought to be clinically insignificant [46]. However, it is possible that these reductions in kidney function may predispose certain individuals to heart failure, as observed in HIV-uninfected individuals [47]. Alternatively, tenofovir may cause heart failure via pathways not accounted for in this analysis. It is known that tenofovir can cause injury to renal tubular epithelial cells which are responsible for activation of vitamin D and homeostasis of calcium and phosphate. Studies of renal mineral bone disease, marked by abnormalities of vitamin D, calcium, and phosphate metabolism in both animals and humans, support its critical role in the pathogenesis of CVD [48–54]. These findings indicate an urgent need to investigate the potential link between tenofovir-related tubular toxicity, disordered mineral metabolism, and heart failure.

Strengths and limitations

We present a 'real world' comparison of antiretroviral effectiveness by including patients who are often systematically excluded from clinical trials and who do not qualify or volunteer for cohort studies. Strengths of this study are the ability to replicate the D:A:D analysis, our large sample size, and our vigorous analytical approach. As in all observational studies, we cannot exclude the possibility of residual confounding, also known as 'selection bias' or 'confounding by indication'. We have attempted to adjust for the cardiovascular risk profile, but we could not account for certain factors like family history. However, to be an actual confounder, clinicians would have to prescribe abacavir disproportionately to patients with a family history of CVD. In addition, it is possible that our findings of antiretroviral use with cardiovascular events were due to chance, particularly as we had several comparisons in our study. Another limitation is that we could not account for out-of-hospital cardiovascular deaths; if abacavir was more or less likely than other ART agents to cause sudden death, then our analysis would be biased. In addition, our results may not be generalizable to nonveterans, women, or uninsured patients not receiving regular clinical care.

Conclusion

In this large, national registry of over 10 000 HIV-infected persons receiving care in a relatively uniform healthcare system, recent abacavir exposure was significantly associated with higher risk of atherosclerotic vascular events, and recent tenofovir exposure was significantly associated with heart failure. These findings suggest a need for raising the level of vigilance in the HIV community, continued 'comparative effectiveness' studies to characterize the cardiovascular risk of specific ART agents, and studies to identify mechanisms underlying these relationships.

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Fig. 1. Cardiovascular disease event rates among users of abacavir, tenofovir, or other antiretroviral therapy (ART)

**P* values were less than 0.01, significant compared to use of other antiretroviral therapy.

Fig. 2. Association between recent abacavir exposure and risk of cardiovascular events in subgroups defined by baseline characteristics

CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate. CV risk category based on Framingham risk score (<10% = low, 10–20% = moderate, >20% = high). All estimates based on multivariate adjusted analyses. *P* value for test of interaction between recent abacavir use and characteristic reported. **Total of 501 events. In three comparisons above (race, CD4 cell count, BMI), there were fewer than 501 events as some participants were categorized under 'other race,' or were missing information on CD4 cell count and/or BMI.

Fig. 3. Association between recent tenofovir exposure and risk of heart failure in subgroups defined by baseline characteristics

CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate. CV risk category based on Framingham risk score (<10% = low, 10–20% = moderate, > 20% = high). All estimates of *P* value for test interaction between recent tenofovir use and characteristic reported. **Total of 194 events. In three comparisons above (Race, CD4 cell count, BMI), there were fewer than 194 events as some participants were categorized under 'other race', or were missing information on CD4 cell count and/or BMI.

Table 1

Clinical characteristics of HIV-infected persons at the time of initiation of abacavir, tenofovir, or other antiretroviral therapy^a.

	Abacavir (n = 3235)	Tenofovir (n = 4314)	Other ART (n = 9122)
Age, years	46 (10)	49 (9)	46 (10)
Race (%)			
White	44	46	41
Black	49	47	50
Other	7	8	9
Female (%)	2	3	2
Antiretroviral naive (%)	29	22	100
Duration of exposure (years)	1.6 (1.6)	1.3 (1.1)	
Comorbid conditions (ever) (%)			
Hypertension	43	39	41
Diabetes	19	16	17
Dyslipidemia	57	55	52
Smoking	51	50	49
Cardiovascular disease	21	18	21
Heart failure	9	6	8
Cancer ^b	18	16	17
Hepatitis B virus ^c	7	8	7
Hepatitis C virus	38	34	38
Measurements at baseline			
CD4 cell count (cells/ μ l)	302 (267)	301 (273)	269 (252)
Viral load (1000 copies/ml)	69 (153)	74 (158)	161 (199)
SBP (mmHg)	129 (18)	128 (17)	128 (19)
DBP (mmHg)	78 (12)	77 (11)	77 (12)
BMI (kg/m ²)	25 (5)	25 (5)	25 (5)
Total cholesterol (mg/dl)	182 (51)	179 (50)	171 (47)
Triglycerides (mg/dl)	218 (224)	209 (279)	184 (217)
Low-density lipoprotein (mg/dl)	105 (39)	103 (37)	102 (37)
High-density lipoprotein (mg/dl)	40 (15)	40 (15)	40 (16)
Glucose (mg/dl)	105 (44)	104 (42)	103 (43)
Albumin (g/dl)	4 (1)	4 (1)	4 (1)
eGFR (ml/min per 1.73m ²)	93 (29)	95 (28)	98 (30)
eGFR <60 ml/min per 1.73m ² (%)	10	6	6
Proteinuria (%)	26	26	21

ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate.

^a Continuous variables reported as mean (standard deviation). Some individuals received abacavir and tenofovir at different points during the period of observation and therefore contributed to both categories. Proteinuria defined by urinalysis protein 30 mg/dl or greater.

^b Defined as gastrointestinal, lung, urogenital, hematological, skin (melanoma, kaposi and nonepithelial skin cancer), other (including history of cancer, eye cancer, brain cancer, soft tissue cancer, thyroid cancer, endocrine cancer, ill-defined cancer).

^cDefined as Ag+ or viral load detectable.

Table 2

Associations of recent exposure to abacavir and tenofovir with risk of cardiovascular events and heart failure.

	Abacavir		Tenofovir	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Atherosclerotic cardiovascular events ^a (<i>n</i> = 501)				
1) Demographic adjusted Cox model ^b	1.40 (1.11–1.77)	0.005	0.96 (0.73–1.27)	0.78
2) Multivariable Cox model ^c	1.48 (1.08–2.04)	0.015	0.78 (0.52–1.16)	0.22
Heart failure (<i>n</i> = 194)				
1) Demographic adjusted Cox model ^b	1.20 (0.80–1.81)	0.37	1.44 (0.94–2.21)	0.09
2) Multivariable Cox model ^c	1.45 (0.85–2.47)	0.17	1.82 (1.02–3.24)	0.04
Individual outcomes				
Coronary disease (<i>n</i> = 316)				
1) Demographic adjusted Cox model ^a	1.46 (1.09–1.95)	0.01	1.02 (0.72–1.45)	0.91
2) Multivariable Cox model ^b	1.43 (0.96–2.13)	0.08	0.87 (0.53–1.42)	0.57
Cerebrovascular disease (<i>n</i> = 147)				
1) Demographic adjusted Cox model ^b	1.62 (1.07–2.47)	0.02	0.85 (0.50–1.45)	0.56
2) Multivariable Cox model ^c	2.10 (1.20–3.66)	0.01	0.67 (0.31–1.42)	0.29
Peripheral arterial disease (<i>n</i> = 79)				
1) Demographic adjusted Cox model ^b	0.83 (0.42–1.61)	0.57	0.69 (0.33–1.41)	0.33
2) Multivariable Cox model ^c	1.00 (0.41–2.46)	0.99	0.70 (0.25–1.98)	0.50

CI, confidence interval; eGFR, estimated glomerular filtration rate.

^a Atherosclerotic cardiovascular event: composite outcome of coronary, cerebrovascular, or peripheral arterial disease.^b Demographic adjusted Cox model includes recent drug exposure, age, sex, and race.^c Multivariable Cox model includes cumulative, recent and past exposure to abacavir and tenofovir, cumulative exposure to all other antiretroviral drugs, age, sex, race, baseline comorbid conditions (diabetes, hypertension, dyslipidemia, prevalent cardiovascular disease, smoking, drug abuse, hepatitis C virus infection, hepatitis B virus infection, and cancer), baseline measurements (eGFR category, proteinuria, BMI category, CD4 cell count, and viral load), calendar year, and current CD4 cell count, viral load, lipids, eGFR, proteinuria, diabetes, hypertension, hepatitis B virus infection, and cancer.