

# Abacavir Use and Risk of Acute Myocardial Infarction and Cerebrovascular Events in the Highly Active Antiretroviral Therapy Era

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(See the editorial commentary by Bozzette on pages 92–93.)

**Background.** Some studies have suggested that exposure to antiretroviral therapy (ART) with abacavir is associated with an increased risk of acute myocardial infarction (AMI).

**Methods.** Using the Veterans Health Administration's Clinical Case Registry we calculated the risk of AMI and cerebrovascular events (CVA) associated with the cumulative use of abacavir and other nucleoside combinations. We also evaluated the impact of pre-existing chronic kidney disease on the selection of abacavir versus tenofovir in the last recorded ART regimen, and on highly active antiretroviral therapy-associated AMI and CVA risks.

**Results.** A total of 19,424 human immunodeficiency virus–infected patients contributed 76,376 patient-years of follow. After adjusting for age, hypercholesterolemia, hypertension, type 2 diabetes, and smoking, the hazard ratio (HR) for each year of abacavir use was 1.18 (95% confidence interval [CI], .92–1.50;  $P = .191$ ) for AMI and 1.16 (95% CI, .98–1.37;  $P = .096$ ) for CVA. Abacavir use was more common among patients with prior chronic kidney disease than was tenofovir use (12.46% versus 7.15%;  $P = .0001$ ), and chronic kidney disease was associated with a significantly higher risk of AMI (HR, 2.41; 95% CI, 1.73–3.36), and CVA (HR, 1.80; 95% CI, 1.44–2.24). Compared with patients who received neither tenofovir nor abacavir, patients who received tenofovir had lower risk of AMI (HR, 0.16; 95% CI, .08–.33;  $P = .0001$ ) and CVA (HR, 0.22; 95% CI, .15–.32;  $P = .001$ ). Use of abacavir was associated with lower risk of CVA (HR, 0.60; 95% CI, .45–.79).

**Conclusions.** We observed no association between cumulative or current abacavir use and AMI or CVA. Abacavir use was more common than was tenofovir use among patients with prior chronic kidney disease, and chronic kidney disease independently predicted higher rates of AMI and CVA.

In the potent antiretroviral therapy (ART) era, the overall increase in survival of human immunodeficiency virus (HIV)–infected patients has been associated with a shift in the underlying causes of death among such patients to fewer AIDS-related deaths and more deaths that are not

AIDS-related. Several database analyses and observational cohort studies have reported a higher incidence of cardiovascular disease (CVD) among HIV-infected patients than among HIV-negative controls [1–5]. CVD now account for 8%–22% of deaths among HIV-infected patients, and this percentage appears to be increasing [6–9] in the aging HIV-infected population [10].

Potential causes of increased CVD risk among HIV-infected patients include a greater prevalence of known CVD risk factors, such as smoking, among HIV-infected patients [11]; ART; or a direct effect of HIV infection itself. Cumulative use of protease inhibitors [12, 13] and, recently, both cumulative and recent use of abacavir and didanosine [14, 15] have been shown to be associated with increased cardiovascular risk among HIV-infected patients.

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Although this cardiovascular risk associated with antiretroviral use has been much debated, cohort analyses have shown no absolute increase over time in the incidence of or mortality from acute myocardial infarctions (AMIs) among HIV-infected patients [5, 7, 16], despite the reported increase in the proportion of patients receiving highly active antiretroviral therapy (HAART) [17].

Furthermore, the HAART-associated increased cardiovascular risk among HIV-infected patients has not been consistently observed by other cohorts or clinical trials [1–5, 18]. In one study, the impact of HIV infection and HAART on cardiovascular risk was seen only in the group of patients younger than 33 years of age [18].

Other factors not controlled for in the above-mentioned cohort analyses could account for at least part of the increased cardiovascular risk attributed to ART. In some studies, hepatitis C virus coinfection has already been shown to be an independent predictor of CVD both in the general population [19] and among HIV-infected patients [20–22]. Also, chronic kidney disease (CKD) is a known CVD risk factor in the general population [23–25] and in the HIV-infected population [26]. Renal dysfunction is also a known driver for the selection of abacavir versus tenofovir (tenofovir) in the treatment of HIV-infected patients but has not been evaluated systematically as a potential covariate in the evaluation of abacavir-associated cardiovascular risk. We used the Department of Veterans Health Administration (VHA) HIV Clinical Case Registry (CCR) [27] to elucidate the impact of abacavir use on incident CVD, adjusting for traditional cardiac risk factors and renal dysfunction.

## METHODS

### Data Source

Our source of data was the Veterans Health Administration (VHA)'s Clinical Case Registry (CCR) in the HAART era for the period 1996–2004. The CCR database aggregates detailed demographic, diagnostic, therapeutic, and health care utilization data on all HIV-infected patients from all VHA facilities to the unique patient level. It comprises Veterans Administration (VA)-specific codes for health care utilization (hospitalizations and clinic visits), National Pharmacy Benefits Management codes for drug utilization, as well as current procedural terminology and *International Classification of Diseases, 9th Revision*, (ICD-9) codes for procedures and diagnoses, respectively.

### Exposure Ascertainment

Each patient's follow-up time was defined as time from his or her inclusion into the CCR database to (1) the first episode of an AMI or a CVA, (2) the last recorded patient encounter, or (3) 31 December 2004 (the date of censoring of the dataset), whichever came first. For cumulative exposure, patient-days of antiretroviral (ARV) use prior to the AMI or CVA event were calculated, and survival analyses were done to predict new AMI or CVA. ARV supply data were extracted from pharmacy records. Continuous

use of a given ARV was inferred when drug refill records reflected continuous supply without interruption of at least 30 days. We defined the following 4 exposure categories using cumulative ARV exposure as a time-dependent variable: (1) HAART (receiving  $\geq 3$  ARV drugs) containing abacavir; (2) HAART with another nucleoside reverse-transcriptase inhibitor (NRTI); (3) receipt of ART that was not HAART; and (4) no receipt of ART.

The following demographic variables were extracted: age, race (black, white or other), and sex. For other cardiovascular risk factors, patient records were reviewed for the presence of the ICD-9 codes (Table 1) when they appeared as one of the listed discharge diagnoses.

Serum creatinine measurements were extracted from the laboratory records during the whole observation period. Patients were identified as having CKD if the most recent estimated glomerular filtration rate (eGFR) was 60 by the modification of diet in renal disease method:  $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times (S_{Cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$ .

Lipid profiles were extracted from each patient record, including total cholesterol. For patients with 1 measurement of the lipid profile during the study period, the measurement with the highest level of total cholesterol was used, regardless of a history of lipid-lowering therapy. These laboratory measures were used to classify patients as having or not having hypercholesterolemia (defined as total cholesterol 240 mg/dL).

Patients were considered to be hepatitis C virus (HCV) positive when they either had a recorded positive HCV antibody test result or a documented diagnostic code for HCV infection.

AMI and CVA analyses were performed separately. The impact of CKD on the effect of ARV exposure on AMI and CVA was then evaluated.

In a second analysis, we segregated patients into 4 groups by the NRTI used at the time of event occurrence or at the last observation: (1) abacavir, but no tenofovir; (2) tenofovir, but no abacavir; (3) both abacavir and tenofovir; or (4) neither abacavir nor tenofovir. Unlike the previous analysis, discrete patient groups—not exposure categories—are examined. However, similar to the previous analysis, abacavir or tenofovir use at the censor date was inferred only when drug refill records reflected a continuous supply without interruption of at least 30 days. If not, patients were classified as “neither abacavir nor tenofovir,” even if their last recorded regimen contained either of these drugs. We then evaluated the impact of preexisting CKD (defined as eGFR 60 between 360 and 30 days prior to regimen initiation) both on the selection of abacavir or tenofovir in the last regimen and on the effect of tenofovir or abacavir on AMI and CVA.

### Outcome Ascertainment

We report on 2 outcomes: incident AMI and incident CVA. These were identified using the ICD-9 codes presented

**Table 1. International Classification of Diseases, 9th Revision Codes Used to Identify Hepatitis C Virus (HCV) Infection, Diabetes Mellitus, Tobacco Use, and Cardiovascular Events**

Exposure and outcome measures	ICD-9-CM codes used
HCV infection	070.41 "acute hepatitis C with hepatic coma"; 070.44 "chronic hepatitis C with hepatic coma"; 070.51 "acute hepatitis C without mention of hepatic coma"; 070.54 "chronic hepatitis C without mention of hepatic coma"; V02.62 "hepatitis C carrier".
Hypertension	401 "essential hypertension"
Diabetes mellitus	250.0 "diabetes mellitus without mention of complication"; 250.1 through 250.9 "diabetes mellitus with complications"
Smoking	305.1 "tobacco use disorder", or V15.82 "history of tobacco use"
Acute myocardial infarction	410 "acute myocardial infarction" except with a fifth digit of 2 (indicating a subsequent instead of initial episode of care);
Cerebrovascular events, including stroke or transient ischemic attack	433, "occlusion and stenosis of precerebral arteries"; 434, "occlusion of cerebral arteries"; 436, "acute but ill-defined cerebrovascular disease"; 437.0, "cerebral atherosclerosis"; 437.1, "other generalized ischemic cerebrovascular disease"; 431, "intracerebral hemorrhage"; and 435, "transient cerebral ischemia."

in Table 1. The use of ICD-9 codes within the CCR database for exposures and AMI and CVA outcomes has been validated in previous studies [28–31].

### Statistical Analysis

We calculated rates of AMI and CVA, and we performed survival analyses (Cox Proportional Hazard model) to evaluate

time until incident AMI and CVA events. Hazard ratios (HRs) for AMI and CVA associated with each antiretroviral exposure category (HAART with abacavir, HAART with other NRTIs, and monotherapy or dual-therapy ART) were calculated. Cumulative use of ART was treated as time-varying covariate. Two survival analyses were then performed with models adjusting for CKD and for traditional CVD risk factors (age, diabetes, hypertension, hypercholesterolemia, and smoking), respectively. In a second survival analysis, ART use was treated as a fixed covariate based on the composition of the patient's last regimen, and HRs for AMI and CVA associated with the receipt of either abacavir, tenofovir, or both in the last antiretroviral regimen on record was calculated. All statistical analyses were performed using SAS, version 9.2 (SAS Institute).

## RESULTS

### Study Population, Follow-up Time, and AMI and CVA Rates

We included 19,424 patients who enrolled at VA facilities for HIV care and were entered into the CCR registry. A total of 14,063 patients (75.0%) received any ART for at least 30 days during the follow-up period. The mean duration of treatment episodes ( $\pm$  standard deviation [SD]) was  $1.93 \pm 2.07$  years.

During the observation period, representing 76,376 person-years (PY) of follow-up (median duration, 3.93 years), a total of 278 AMIs and 868 CVAs were diagnosed. Rates of AMI and CVA were 3.69 (95% CI, 3.28–4.15) and 11.68 (95% CI, 10.93–12.48) per 1000 PY of observation, respectively. Rates of AMI remained relatively constant from 1996 through 2004 (data not shown). Table 2 shows the prevalence of CVD risk factors, CKD, and HCV infection among patients with or without AMI or CVA.

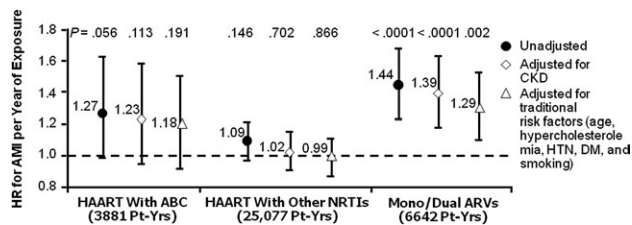
### Cumulative Abacavir Use and Risk of AMI and CVA

Among patients receiving ART, unadjusted HRs for AMI were 1.27 (95% CI, .99–1.62;  $P = .056$ ) for those who received

**Table 2. Traditional Cardiovascular Disease (CVD) Risk Factors for Patients With and Patients Without Acute Myocardial Infarction (AMI) or Cerebrovascular Event (CVA)**

Variable	Total (n = 19,424)	AMI (n = 278)	No AMI (n = 19,146)	P	CVA (n = 868)	No CVA (n = 18,556)	P
Age, median years	46	51	46	.001	50	45	.001
Male sex, %	98	99	97	.255	98	97	.09
Smoking, %	29	33	28	.116	22	28	.001
Diabetes, %	13	22	13	.001	20	12	.001
Hypertension, %	38	68	38	.001	57	37	.001
Hypercholesterolemia, %	26	41	26	.001	26	26	.97
Chronic kidney disease, % <sup>a</sup>	8	18	7	.001	15	7	.001
HCV infection, %	32	38	31	.013	36	31	.004

<sup>a</sup> Defined as estimated glomerular filtration rate 60, as determined by modification of diet in renal disease method.



**Figure 1.** Cumulative exposure to abacavir (ABC) or other nucleoside reverse-transcriptase inhibitors (NRTIs) and the risk of acute myocardial infarction (AMI). CKD, chronic kidney disease, defined as an estimated glomerular filtration rate 60 by Modification of Diet in Renal Disease method; DM, diabetes mellitus; HAART, highly active antiretroviral therapy; HR, hazard ratio; HTN, hypertension.

HAART with abacavir, 1.09 (95% CI, .97–1.21;  $P = .146$ ) for those who received HAART with other NRTIs, and 1.44 (95% CI, 1.23–1.67;  $P = .001$ ) for monotherapy and dual-therapy ART regimens (Figure 1).

eGFR was found to have a significant impact on AMI and CVA risk. Rates of AMI and CVA by eGFR category (60, 60–89, and  $\geq 90$ ) are presented in Table 3, as well as unadjusted HRs for AMI and CVA associated with eGFR 60 and 60–89, compared with eGFR  $\geq 90$ .

In a multivariate model adjusting for CKD (defined as eGFR 60), the HR of AMI for HAART with abacavir was 1.23 (95% CI, .95–1.58;  $P = .113$ ). HAART with other NRTIs and monotherapy and dual-therapy ART had HRs of 1.02 (95% CI, .91–1.15;  $P = .702$ ) and 1.39 (95% CI, 1.18–1.63;  $P = .001$ ), respectively. Adjustment for age, hypercholesterolemia, hypertension, type 2 diabetes, and tobacco use resulted in an HR of 1.18 (95% CI, .92–1.50;  $P = .191$ ) per year for HAART with abacavir; an HR of 0.99 (95% CI, .87–1.11;  $P = .866$ ) for HAART with other NRTIs; and an HR of 1.29 (95% CI, 1.10–1.52;  $P = .002$ ) for monotherapy and dual-therapy ART (Figure 1).

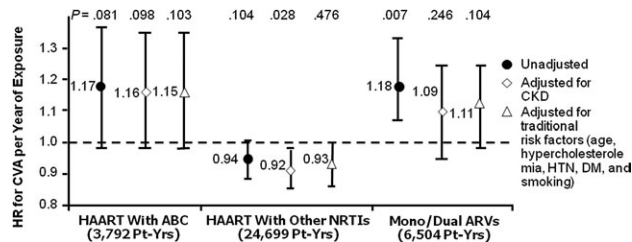
Other factors associated with AMI in the multivariable model included older age (HR, 1.79 for each 10 year increment; 95%

**Table 3. Impact of Chronic Kidney Disease on Risk of Acute Myocardial Infarction (AMI) and Cerebrovascular Event (CVA)**

eGFR <sup>a</sup>	AMI rate	Hazard ratio <sup>b</sup> for AMI (95% confidence interval)	$P$	CVA rate	Hazard ratio <sup>b</sup> for CVA (95% confidence interval)	$P$
60	11.33	3.85 (2.74–5.42)	.001	30.58	2.95 (2.40–3.62)	.002
60–89	3.89	1.33 (1.00–1.76)	.048	12.57	1.28 (1.09–1.50)	.001
$\geq 90$	2.92	1		9.74	1	

<sup>a</sup> Initial estimated glomerular filtration rate, by modification of diet in renal disease method.

<sup>b</sup> Unadjusted hazard ratio of AMI or CVA, compared with glomerular filtration rate  $\geq 90$ .



**Figure 2.** Cumulative exposure to abacavir (ABC) or other nucleoside reverse-transcriptase inhibitors (NRTIs) and the risk of cerebrovascular event (CVA). CKD, chronic kidney disease, defined as an estimated glomerular filtration rate 60 by Modification of Diet in Renal Disease method; DM, diabetes mellitus; HAART, highly active antiretroviral therapy; HR, hazard ratio; HTN, hypertension.

CI, 1.60–2.01;  $P = .001$ ), hypertension (HR, 2.05; 95% CI, 1.57–2.67;  $P = .001$ ), duration of ARV (HR, 1.12 for each year of use of any ARV; 95% CI, 1.01–1.25;  $P = .0411$ ).

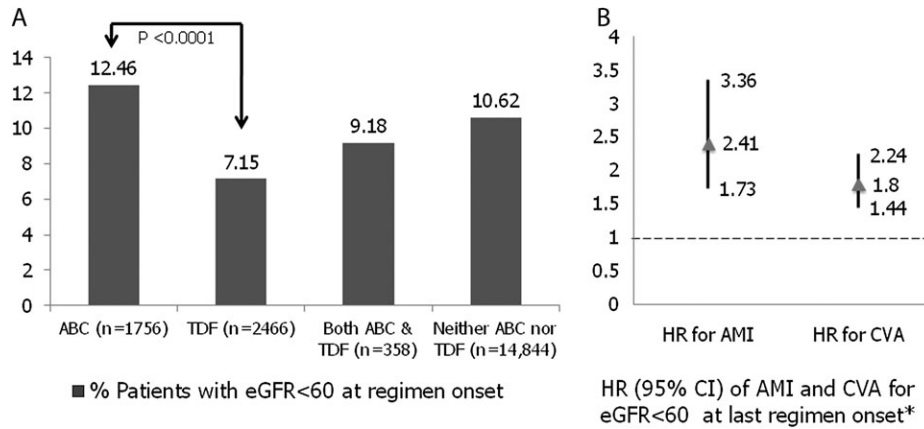
Unadjusted HRs of CVA were 1.17 (95% CI, .98–1.39;  $P = .081$ ) for HAART with abacavir, 0.94 (95% CI, .87–1.01;  $P = .104$ ) for HAART with other NRTIs, and 1.18 (95% CI, 1.05–1.34;  $P = .007$ ) for monotherapy and dual-therapy ART (Figure 2).

In a multivariate model adjusting for CKD (defined as eGFR 60), the HR of CVA for HAART with abacavir was 1.16 (95% CI, .97–1.38;  $P = .098$ ). HAART with other NRTIs had an HR of 0.92 (95% CI, .85–.99;  $P = .028$ ), and monotherapy and dual-therapy ART had an HR of 1.09 (95% CI, .95–1.24;  $P = .246$ ). Adjustment for age, hypercholesterolemia, hypertension, type 2 diabetes, and tobacco use resulted in an HR of 1.15 (95% CI, .97–1.37;  $P = .103$ ) per year of HAART with abacavir; 0.93 (95% CI, .86–1.00;  $P = .476$ ) for HAART with other NRTIs, and 1.11 (95% CI, .98–1.25;  $P = .104$ ) for monotherapy and dual-therapy ART. Other factors associated with CVA in multivariate analysis were older age (HR, 1.65; 95% CI, 1.54–1.76;  $P = .001$ ) and hypertension (HR, 1.48; 95% CI, 1.28–1.75;  $P = .001$ ).

### Current Abacavir and Tenofovir Use and Risk of AMI and CVA

A total of 1760 patients had abacavir (but no tenofovir) in their last recorded regimen (contributing 7815 PY); 2440 were receiving a regimen containing tenofovir but not abacavir (11,822 PY); 356 were receiving both abacavir and tenofovir (1811 PY); and 14,868 were receiving a regimen containing neither abacavir nor tenofovir or were not receiving ARVs at event occurrence or end of follow-up (54,909 PY). There was no significant difference between the median duration of prior antiretroviral exposure between the abacavir and the tenofovir groups, which were 1.7 years (interquartile range [IQR], 0.6–3.5) and 2.1 years (IQR, 0.7–4.0), respectively.

A significantly greater proportion of patients who initiated an abacavir regimen had CKD at baseline (defined as eGFR 60), compared with those who initiated a tenofovir-containing



**Figure 3.** Impact of preexisting chronic kidney disease (CKD; defined as an estimated glomerular filtration rate 60 by Modification of Diet in Renal Disease method) on nucleoside reverse-transcriptase inhibitor (NRTI) use in last regimen in the database (A); and on acute myocardial infarction (AMI) and cerebrovascular event (CVA) rate during last regimen (B). Patients not receiving HAART at censor date were included in the "neither ABC nor TDF" group. \*eGFR 60, compared with eGFR  $\geq$ 60 (adjusted for last antiretroviral regimen). ABC, abacavir; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HAART, highly active antiretroviral therapy; TDF, tenofovir.

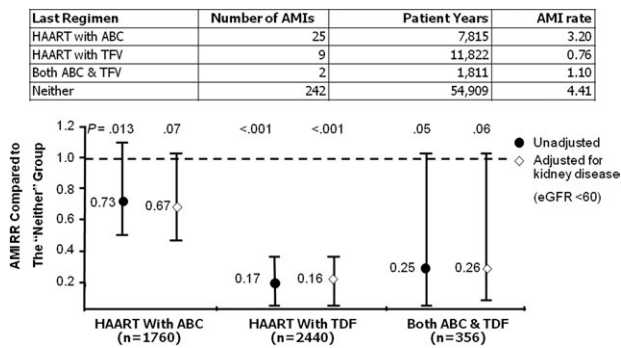
regimen (12.46% versus 7.15%;  $P = .001$ ; Figure 3A). CKD prior to regimen initiation was associated with an HR for AMI and CVA during that regimen of 2.41 (95% CI, 1.73–3.36) and 1.80 (95% CI, 1.44–2.24), respectively (Figure 3B).

Figures 4 and 5 present the PY of exposure measurement, AMI and CVA event rates, and HRs associated with abacavir and/or tenofovir exposure. Rates of AMI were 4.41 events per 1000 PY for patients currently receiving no ARV or a regimen containing neither abacavir nor tenofovir (the reference group), 3.20 events per 1000 PY during abacavir therapy, 0.76 events per 1000 PY during tenofovir therapy, and 1.10 events per 1000 PY during therapy containing both abacavir and tenofovir. After adjusting for CKD, compared with the reference group, patients given abacavir had an HR for AMI of 0.67 (95% CI, .43–1.03;  $P = .07$ ); those given tenofovir had an HR of 0.16 (95% CI, .08–.33;  $P = .001$ ), and those given both abacavir and tenofovir had an HR of 0.25 (95% CI, .06–1.02;  $P = .06$ ).

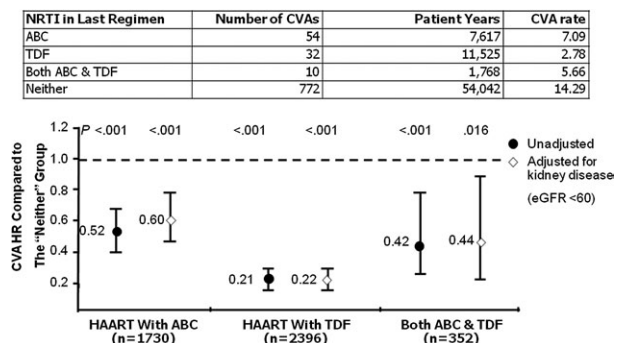
Compared with those receiving neither abacavir nor tenofovir in their last regimen, patients given abacavir had an HR for CVA of 0.60 (95% CI, .45–.79;  $P = .0001$ ); those given tenofovir had an HR for CVA of 0.22 (95% CI, .15–.32;  $P = .001$ ), and those given both abacavir and tenofovir had an HR of 0.44 (95% CI, .23–.86;  $P = .02$ ).

## DISCUSSION

In the univariate analyses, we observed a marginal association between cumulative abacavir use and AMIs or CVAs. This nonsignificant association was further reduced by controlling for either CKD or traditional cardiovascular risk factors. Our findings contrast with those of the data collection on adverse events of anti-HIV drugs (D:A:D) cohort and the strategies for management of anti-retroviral therapy (SMART) study, which observed a significant association between recent and cumulative use of abacavir and cardiovascular disease [15, 32]. They



**Figure 4.** Impact of abacavir (ABC) or tenofovir (TDF) use in the last regimen on the rates and relative risk of acute myocardial infarctions (AMI). eGFR, estimated glomerular filtration rate (by modification of diet in renal disease method); HAART, highly active antiretroviral therapy; HR, hazard ratio.



**Figure 5.** Impact of abacavir (ANC) or tenofovir (TDF) use in the last regimen on the rates and relative risk of cerebrovascular events (CVA). HAART, highly active antiretroviral therapy; HR, hazard ratio.

also differ from the findings of the Danish cohort, which showed an association between cumulative use of abacavir and increased risk of hospitalization for AMI [33].

In multivariate analysis controlling for traditional CVD risk factors, cumulative exposure to any ARV was associated with a modest but statistically significant increased risk of AMI. The HR (1.12) is close to the one reported by the D:A:D analysis [12, 13]. This was driven by the group of patients receiving a non-HAART regimen (monotherapy or dual-therapy ART), which had the highest HR for AMI (1.44).

CKD was associated with a significant increase in risk for AMI and CVA. HRs for AMI and CVA associated with CKD were greater than those associated with the traditional cardiovascular risk factors that were analyzed, and controlling for CKD further reduced the HR for AMI and CVA associated with abacavir use. The D:A:D investigators reported that adjusting for low eGFR value did not modify their findings relating to recent abacavir exposure and AMI risk [34]. Unfortunately, in the subsequent analysis of their data [32], there was no inclusion of CKD in the models that analyzed the cardiovascular risk associated with antiretroviral drugs.

Separating patients according to the receipt of abacavir, tenofovir, both, or neither in their last ART regimen during the period of observation allowed us to evaluate the impact of CKD on the selection of ART regimen and the impact of renal dysfunction immediately prior to a regimen initiation on the cardiovascular risk associated with that regimen. Not surprisingly, abacavir use was significantly more common than was tenofovir use among patients with an eGFR 60. The presence of CKD prior to initiation of the last regimen also predicted a higher likelihood of developing AMI or CVA during that regimen.

Tenofovir use in the last regimen was associated with a significantly lower rate of AMI, and both abacavir and tenofovir were associated with significantly lower rates of CVA during that regimen. Together with the findings that cumulative exposure to monotherapy and dual-therapy ART was associated with the highest HR for AMI, these findings, if confirmed, suggest a beneficial effect of HAART on HIV-associated cardiovascular risk, as was suggested by Bozzette et al [28] and the SMART study [35]. This beneficial effect appears to be more pronounced for tenofovir than for abacavir and may be secondary to its direct effect in lipids, which was recently demonstrated in the AIDS clinical trials group study 5206 (an 18% decrease in total cholesterol after 12 weeks of “add on” therapy) [36]. Our results show that CKD is an even greater cardiovascular risk factor among HIV-infected patients than it is among the general population [24, 29]. Considering the apparent beneficial effect of HAART on cardiovascular events outlined above, it might be inferred that initiating ART in patients with CKD is likely to avert more events than would be the case among patients with normal kidney function.

It is, of course, impossible to conclusively reconcile the discordant findings from our study and previous cohorts and trials analyzing the impact of abacavir use on cardiovascular risk, given the large number of potential confounders. However, it is noteworthy that the studies showing a significant association between abacavir or other antiretroviral drugs and cardiovascular risk have included exclusively or predominantly ARV-experienced patients who initiated ART outside of a randomized trial and did not exclude patients with or control for CKD [14, 15, 32, 37], whereas all prospective studies enrolling exclusively ARV-naive patients, most with healthy renal function, showed no drug impact [38–40].

Our study was observational, as were most of the above-mentioned studies; therefore, it is difficult to control for all biases and to assess causality.

Beyond the high prevalence of traditional cardiovascular risk factors and HAART use among patients with HIV infection, untreated HIV infection itself might be associated with an increased risk of cardiovascular events [18, 41]. Enhanced endothelial activation, inflammation, and increased carotid intima-media thickness occur in HIV-infected patients, compared with uninfected controls, supporting a potential role of inflammation in endothelial activation and cardiovascular disease in HIV infection [42]. Although inflammatory markers tend to significantly improve after HAART initiation or reinitiation in some studies, they might not return to levels comparable to those found in patients without HIV infection, even during long-term suppressive antiretroviral therapy [43–46]. It is conceivable that antiretroviral drugs differ in their propensity to alter markers of immune activation. The SMART study reported higher levels of C-reactive protein and interleukin-6 among patients receiving abacavir than among those receiving other NRTIs and hypothesized that abacavir may have proinflammatory properties and could promote CVD through increased vascular inflammation [14]. Other studies among previously antiretroviral-naive [47] or antiretroviral-experienced [46, 48–50] patients did not observe a difference in inflammatory markers between those who received abacavir and those who received tenofovir. On the other hand, abacavir therapy has recently been shown to be associated with a lower arterial flow-mediated vasodilation than that associated with tenofovir therapy [51].

Limitations of our study include a relatively early stop date (2004) and the fact that AMI and CVA events were not ascertained; only ICD-9 codes were used. However, their accuracy has been validated by other VA studies [28, 30, 31]. Furthermore, because the population is quasi-exclusively male, it is unclear whether the findings will apply to female patients.

Strengths of our study include the large sample size (19,000 patients and 278 AMIs) from a well-defined cohort that includes uniform data collection. The completeness of the data from CCR, including laboratory values, drug dispensation, and diagnoses, allows a very thorough investigation of HIV-related

outcomes. AMI and CVA events and ART data were recorded for the whole period of observation. Also, because all laboratory data were available, it was possible for us to look specifically at renal dysfunction preceding the onset of any antiretroviral regimen.

In conclusion, we could not confirm the association of abacavir therapy and cardiovascular events. The use of HAART has a protective effect on cardiovascular events. Furthermore, kidney disease is a significant cardiovascular risk factor in patients with HIV infection and might account for at least some of the reported associations of some ARVs with CVDs. On the other hand, tenofovir appears to be associated with a lower rate of CVD, which is a finding that may be related to its lipid lowering properties.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

## References

1. Klein D, Hurley L, Quesenberry C, Silverberg M, Horberg M, Sidney S. Hospitalizations for CHD and MI among Northern California HIV+ and HIV- men: changes in practice and Framingham risk scores. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections. Denver, CO, **2006**.
2. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr* **2002**; 30:471-7.
3. Currier JS, Lundgren JD, Carr A, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation* **2008**; 118:e29-35.
4. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* **2007**; 92:2506-12.
5. Obel N, Thomsen HF, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *Clin Infect Dis* **2007**; 44:1625-31.
6. Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol* **2005**; 34:121-30.
7. Lewden C, May T, Rosenthal E, et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalite 2000 and 2005" surveys (ANRS EN19 and Mortavic). *J Acquir Immune Defic Syndr* **2008**; 48:590-8.
8. Crum NF, Riffenburgh RH, Wegner S, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* **2006**; 41:194-200.
9. Smith C, Group DADS. Association between modifiable and non-modifiable risk factors and specific causes of death in the HAART Era:

- the data collection on adverse events of anti-HIV drugs study [abstract 145]. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada, **2009**.
10. Luther VP, Wilkin AM. HIV infection in older adults. *Clin Geriatr Med* **2007**; 23:567-83, vii.
11. Glass TR, Ungsedhapand C, Wolbers M, et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study. *HIV Med* **2006**; 7:404-10.
12. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* **2007**; 356:1723-35.
13. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* **2003**; 349:1993-2003.
14. Strategies for Management of Anti-Retroviral Therapy/INSIGHT and the D:A:D study groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* **2008**; 22:F17-24.
15. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* **2008**; 371:1417-26.
16. Hurley LB, Leyden W, Xu L, et al. Updated Surveillance of Cardiovascular Event Rates among HIV-infected and HIV-uninfected Californians, 1996 to 2008 [abstract 710]. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada. **2009**.
17. Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* **2006**; 43:27-34.
18. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* **2003**; 33:506-12.
19. Lee MH, Yang HI, Wang CH, et al. Hepatitis C virus infection and increased risk of cerebrovascular disease. *Stroke* **2010**; 41:2894-900.
20. Butt A, Xiaoqiang W, Budoff M. Hepatitis C virus infection and the risk of coronary disease [abstract V-4219]. In: Program and abstracts of the 48th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2008). Washington, DC: American Society for Microbiology and the Infectious Diseases Society of America, **2008**.
21. Bedimo R, Westfall AO, Mugavero M, Drechsler H, Khanna N, Saag M. Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. *HIV Med* **2010**; 11:462-8.
22. Freiberg MS, Cheng DM, Kraemer KL, Saitz R, Kuller LH, Samet JH. The association between hepatitis C infection and prevalent cardiovascular disease among HIV-infected individuals. *AIDS* **2007**; 21:193-7.
23. Hostetter TH. Chronic kidney disease predicts cardiovascular disease. *N Engl J Med* **2004**; 351:1344-6.
24. Di Angelantonio E, Danesh J, Eiriksdottir G, Gudnason V. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. *PLoS Med* **2007**; 4:e270.
25. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* **2004**; 351:1296-305.
26. George E, Lucas GM, Nadkarni GN, Fine DM, Moore R, Atta MG. Kidney function and the risk of cardiovascular events in HIV-1-infected patients. *AIDS*; **2010**; 24:387-94.
27. Backus L, Mole L, Chang S, Deyton L. The Immunology Case Registry. *J Clin Epidemiol* **2001**; 54(Suppl 1):S12-15.
28. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* **2003**; 348:702-10.
29. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. *Circulation* **2010**; 121:651-8.
30. Fultz SL, Skanderson M, Mole LA, et al. Development and verification of a "virtual" cohort using the National VA Health Information System. *Med Care* **2006**; 44:S25-30.

31. Giordano TP, Kramer JR, Soucek J, Richardson P, El-Serag HB. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992–2001. *Arch Intern Med* **2004**; 164:2349–54.
32. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis* **2010**; 201:318–30.
33. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med* **2010**; 11:130–6.
34. Post FA, Campbell LJ. Abacavir and increased risk of myocardial infarction. *Lancet* **2008**; 372:803; author reply 804–805.
35. Phillips AN, Carr A, Neuhaus J, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antivir Ther* **2008**; 13:177–87.
36. Tungsiripat M, Kitch D, Glesby MJ, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *AIDS* **2010**; 24:1781–4.
37. Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. *Clin Infect Dis* **2009**; 49:1591–601.
38. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr* **2009**; 51:20–8.
39. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med* **2009**; 361:2230–40.
40. Benson C, Ribaud H, Zheng E, et al. No association of abacavir use with risk of myocardial infarction or severe cardiovascular disease events: results from ACTG A5001. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada, **2009**.
41. Grunfeld C, Delaney JA, Wanke C, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. *AIDS* **2009**; 23:1841–9.
42. Ross AC, Rizk N, O’Riordan MA, et al. Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis* **2009**; 49:1119–27.
43. Ross AC, Armentrout R, O’Riordan MA, et al. Endothelial activation markers are linked to HIV status and are independent of antiretroviral therapy and lipotrophy. *J Acquir Immune Defic Syndr* **2008**; 49:499–506.
44. de Larranaga GF, Bocassi AR, Puga LM, Alonso BS, Benetucci JA. Endothelial markers and HIV infection in the era of highly active antiretroviral treatment. *Thromb Res* **2003**; 110:93–8.
45. de Larranaga GF, Wingeyer SD, Puga LM, Alonso BS, Benetucci JA. Relationship between hepatitis C virus (HCV) and insulin resistance, endothelial perturbation, and platelet activation in HIV-HCV-coinfected patients under highly active antiretroviral treatment. *Eur J Clin Microbiol Infect Dis* **2006**; 25:98–103.
46. Martin A, Amin J, Cooper DA, et al. Abacavir does not affect circulating levels of inflammatory or coagulopathic biomarkers in suppressed HIV: a randomized clinical trial. *AIDS* **2010**; 24:2657–63.
47. McComsey GA, Smith KY, Patel P, et al. Similar reductions in markers of inflammation and endothelial activation after initiation of abacavir/lamivudine or tenofovir/emtricitabine: the HEAT Study [abstract 732]. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada, **2009**.
48. Palella F, Grange S, Elion R, et al. Inflammatory markers among abacavir and non-abacavir recipients in the Womens’ Interagency HIV Study and the Multicenter AIDS Cohort Study [abstract 150B]. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada, **2009**.
49. Martinez E, Larrousse M, Podzamczar D, et al. Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction. *AIDS* **2010**; 24:F1–9.
50. Jong E, Meijers JC, van Gorp EC, Spek CA, Mulder JW. Markers of inflammation and coagulation indicate a prothrombotic state in HIV-infected patients with long-term use of antiretroviral therapy with or without abacavir. *AIDS Res Ther* **2010**; 7:9.
51. Hsue PY, Hunt PW, Wu Y, et al. Association of abacavir and impaired endothelial function in treated and suppressed HIV-infected patients. *AIDS* **2009**; 23:2021–7.