# Risk of Cardiovascular Events Associated With Current Exposure to HIV Antiretroviral Therapies in a US Veteran Population

Manisha Desai,[1,2] Vilija Joyce,[3] Eran Bendavid,[4,5] Richard A. Olshen,[2] Mark Hlatky,[6] Adam Chow,[3] Mark Holodniy,[3] Paul Barnett,[3] and Douglas K. Owens[3,4]

[1]Quantitative Sciences Unit, Center for Biomedical Informatics Research, Department of Medicine, [2]Division of Biostatistics, Department of Health Research & Policy, Stanford University, [3]VA Palo Alto Health Care System, [4]Center for Primary Care and Outcomes Research, and Center for Health Policy, [5]Division of General Medical Disciplines, Department of Medicine, and [6]Division of Health Policy, Department of Health Research & Policy, Stanford University, Stanford, California

*Background.* To characterize the association of antiretroviral drug combinations on risk of cardiovascular events.

*Methods.* Certain antiretroviral medications for human immunodeficiency virus (HIV) have been implicated in increasing risk of cardiovascular disease. However, antiretroviral drugs are typically prescribed in combination. We characterized the association of current exposure to antiretroviral drug combinations on risk of cardiovascular events including myocardial infarction, stroke, percutaneous coronary intervention, and coronary artery bypass surgery. We used the Veterans Health Administration Clinical Case Registry to analyze data from 24 510 patients infected with HIV from January 1996 through December 2009. We assessed the association of current exposure to 15 antiretroviral drugs and 23 prespecified combinations of agents on the risk of cardiovascular event by using marginal structural models and Cox models extended to accommodate time-dependent variables.

*Results.* Over 164 059 person-years of follow-up, 934 patients had a cardiovascular event. Current exposure to abacavir, efavirenz, lamivudine, and zidovudine was significantly associated with increased risk of cardiovascular event, with odds ratios ranging from 1.40 to 1.53. Five combinations were significantly associated with increased risk of cardiovascular event, all of which involved lamivudine. One of these—efavirenz, lamivudine, and zidovudine—was the second most commonly used combination and was associated with a risk of cardiovascular event that is 1.60 times that of patients not currently exposed to the combination (odds ratio = 1.60, 95% confidence interval, 1.25–2.04).

*Conclusions.* In the VA cohort, exposure to both individual drugs and drug combinations was associated with modestly increased risk of a cardiovascular event.

*Keywords.* HIV; antiretroviral therapy; cardiovascular event; myocardial infarction.

In recent years, many studies have evaluated whether drugs used in human immunodeficiency virus (HIV) antiretroviral therapy (ART) increase the risk of cardiovascular events [1]. Understanding the relationship between ART and cardiovascular risk is complex; the typical ART regimen contains at least 3 drugs from 2 drug classes, and many patients are exposed to multiple regimens over time. Further, clinicians may in part select ART regimens based on either the patient's risk of cardiovascular disease or on progression of cardiovascular disease. Such selection potentially induces what is referred to as confounding by indication, where associations between ART and cardiovascular outcomes may be distorted as a consequence of drug initiation being related to the risk of cardiovascular disease.

Prior studies suggest that certain ART agents may be associated with increased risk of cardiovascular disease (eg, [2–5]), but findings from these studies have not been consistent. In a systematic review we performed previously [1], observational studies demonstrated an

increased risk of myocardial infarction (MI) for patients recently exposed to abacavir and those recently exposed to protease inhibitors. Additionally, the observational studies in our review indicated an increased risk of cardiovascular disease with each additional year of exposure to indinavir and to lopinavir. In contrast, 4 published meta-analyses based on secondary analyses of randomized controlled trials, found no increased risk of cardiovascular disease [6]. However, the randomized trials had much shorter follow-up and fewer participants than did the observational studies, which limited their power to demonstrate increased risk. Our systematic review highlighted how methodologic choices can influence interpretation greatly and lead to discrepant findings.

In the current study, we evaluate the risk of ART on cardiovascular outcomes in a large cohort of US veterans from the Veterans Health Administration (VHA). This cohort is particularly well suited to assess cardiovascular risk because the patients are older and have more baseline cardiovascular risk factors than many other cohorts. Two prior analyses in this cohort [7, 8] have reached different conclusions about whether abacavir is associated with increased cardiovascular risk. We attempt to reconcile differences among previous studies by addressing methodological issues highlighted in our systematic review [1] and evaluate combinations of antiretroviral medications rather than just single agents.

## METHODS

### Study Design and Participants
Our study is based on a longitudinal cohort of HIV-infected US veterans selected from the VHA Clinical Case Registry (CCR). The CCR contains information on demographic, diagnostic, therapeutic, and health-care utilization data on all HIV-infected patients from all VHA facilities [9]. As of March 2010, the CCR contained data on 62 024 patients. We included patients with evidence of a positive HIV lab test on or after 1 January 1996, who also received subsequent medical care in the VHA. We excluded patients with exposure to antiretroviral drugs prior to 1 January 1996 so that the patients in the cohort would have opportunity for treatment with combination ART. We also excluded patients never exposed to any agents during their observation period, as our study question was whether, among treated patients, some ART regimens lead to increased risk of cardiovascular events. Our final cohort included 24 510 HIV-infected patients from January 1996 through December 2009 (See Supplementary Appendix, Figure 1).

### Outcomes
Our primary outcome is the occurrence of any cardiovascular event including MI, stroke, or cardiovascular procedures such as percutaneous coronary intervention and coronary artery bypass surgery [10, 11]. Details on ascertainment are provided in the Appendix. Subjects were followed from the date of the first positive HIV lab test or first ART prescription (referred to as baseline) until the event of interest, death, or last documented activity in the CCR. Subjects who did not develop the event of interest by the end of the study period or who died during the study period without experiencing the event were censored. Secondary outcomes include time to first cardiovascular event, the occurrence of first MI, and time to first MI.

### Drug Exposure
Our primary exposures were time-varying indicators of current exposure to specific antiretroviral drugs and to prespecified combinations of antiretroviral drugs, where 15 individual antiretroviral drugs and 23 drug combinations with sufficient person-years of exposure were considered (See Supplementary Appendix for specific details).

### Statistical Analysis
We made use of marginal structural models in a pooled logistic regression to reduce confounding by weighting subjects by the probability for treatment initiation [12]. Model selection for weights was performed as suggested by Cole and Hernan [13]. Our secondary analysis involved a Cox model of the hazard of cardiovascular events as a function of time-varying exposure to drugs, with all drugs (or combinations) considered jointly. We used multiple imputation methods to account for missing data. See the Supplementary Appendix for a full description of analytic approaches.

We used Wald tests to assess significance. As we evaluated the association of 38 drugs/combinations on risk of cardiovascular events (CVE), we applied a Bonferroni correction (significance level of 0.0013 = 0.05/38) to control the family-wise error rate at 0.05.

Analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina).

## RESULTS

On average, patients were 46.5 years old at baseline (Table 1). Patients were almost all male (97.6%), with 33.8% identifying as white and 42.4% as black. Almost half (47.1%) of subjects had some evidence of ever being a smoker, and 11.6% had evidence of diabetes. At baseline, fewer than 1% of subjects had a history of any cardiovascular events, and 18% had exposure to statins for at least 1 year. One-third of subjects (33.3%) had a viral load greater than 50 000 copies/mL, and 13.6% had a CD4 count of 50/mm$^3$ or lower. Data were missing on race and ethnicity in about 23% of the cohort, and on baseline viral load and baseline CD4 count in 12.3% and 7.8% of subjects. Whereas 32.3% of subjects were missing data on total cholesterol, a higher percentage of 75% and 88% were missing

**Table 1.   Baseline Characteristics of Eligible US Veterans With Human Immunodeficiency Virus Identified From the Clinical Case Registry, Total Cohort (n = 24 510)**

| Demographics | |
|---|---|
| Age, mean (SD) | 46.5 (10.1) |
| Male, % | 97.6 |
| Race, % | |
| White | 33.8 |
| Black | 42.4 |
| Other | 1.2 |
| Missing | 22.6 |
| Ethnicity, % | |
| Hispanic | 5.5 |
| Missing | 22.5 |
| Ever smokers, % | 47.1 |
| Diabetes, % | 11.6 |
| CKD, % | 8.7 |
| History of stroke, % | 0.36 |
| History of myocardial infarction, % | 0.42 |
| History of percutaneous coronary intervention, % | 0.13 |
| History of coronary artery bypass surgery, % | 0.09 |
| History of any cardiovascular event, % | 0.87 |
| Era in which subject entered cohort | |
| 1996–2000 | 53 |
| 2001–2005 | 32.1 |
| 2006–2009 | 14.9 |
| HIV Severity | |
| Viral load, % | |
| ≤400 | 12.1 |
| 401–3500 | 17 |
| 3501–10 000 | 7.7 |
| 10 001–50 000 | 17.7 |
| >50 000 | 33.3 |
| Missing | 12.3 |
| CD4 count (categories), % | |
| ≤50 | 13.6 |
| 51–100 | 8 |
| 101–200 | 14.5 |
| 201–350 | 20.8 |
| 351–500 | 16.5 |
| >500 | 18.9 |
| Missing | 7.8 |
| Cardiovascular risk factors | |
| Ever statin use, >1 Y, % | 18.3 |
| Blood pressure, median (SD) | |
| Systolic | 126.2 (14.9) |
| Missing, % | 33.7 |
| Diastolic | 76.2 (9.5) |
| Missing, % | 33.7 |
| Total cholesterol, mean (SD) | 174.9 (45.6) |
| Missing, % | 32.3 |
| HDL, mean (SD) | 40.5 (15.2) |
| Missing, % | 75.4 |

*Table 1   continued.*

| LDL, mean (SD) | 104 (36.6) |
|---|---|
| Missing, % | 88.1 |
| BMI, mean (SD) | 25 (4.5) |
| Missing, % | 36.3 |

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; SD, standard deviation.

baseline values of high-density lipoprotein and low-density lipoprotein, respectively.

Of the 24 510 subjects included in the cohort with over 164 059 person-years of follow-up, 934 experienced a cardiovascular event during the study period (Table 2). The most commonly used individual agents were lamivudine (used by 19 633 patients), zidovudine (15 524), and tenofovir (15 005). Of the 23 combinations considered, the most common were efavirenz/emtricitabine/tenofovir (6800 patients) and efavirenz/lamivudine/zidovudine (6229 patients).

Current exposure to 4 drugs was statistically significantly associated with cardiovascular events (Figure 1) – lamivudine (odds ratio [OR] = 1.53; 95% confidence interval [CI], 1.34–1.75), abacavir (OR = 1.50; 95% CI, 1.26–1.79), efavirenz (OR = 1.40; 95% CI, 1.19–1.66), and zidovudine (OR = 1.41; 1.22–1.63) at the Bonferroni-corrected level of 0.0013 (Figure 1 and Supplementary Appendix Table 1). Current exposure to 5 combinations was statistically associated with cardiovascular events (Figure 2). These included abacavir/lamivudine/atazanavir (OR, 2.08; 95% CI, 1.41–3.06); zidovudine/lamivudine/atazanavir (OR, 2.04; 95% CI, 1.37–3.02); abacavir/lamivudine/efavirenz (OR, 1.94; 95% CI, 1.34–2.79); zidovudine/lamivudine/efavirenz (OR, 1.60; 95% CI, 1.25–2.04); and zidovudine/abacavir/lamivudine (OR, 1.60; 95% CI, 1.21–2.11).

We found similar results in a secondary analysis that utilized the extended Cox model and implicated 4 drugs and 2 combinations (Supplementary Tables 1 and 2 in Appendix), with 2 of the drugs the same as those identified by the marginal structural models (abacavir and zidovudine) and 2 others (emtricitabine and ritonavir) that were elevated but did not reach the Bonferroni-corrected level of statistical significance in the marginal structural model analysis. One of the combinations identified (efavirenz/lamivudine/zidovudine) was also identified by the marginal structural model; four combinations identified by the marginal structural models were not implicated by the Cox model.

Findings for MI based on the marginal structural models demonstrated associations that were in the same direction and of similar magnitude but with lower levels of statistical significance (Supplementary Tables 3 and 4 in Appendix).

**Table 2.** Events and Exposures at Last Follow-up for Eligible US Veterans With Human Immunodeficiency Virus Identified From the Clinical Case Registry (n = 24 510)

| Type of Event | Number of Events |
|---|---|
| Cardiovascular events[a] | 934 |
| Myocardial infarction | 467 |
| Antiretroviral agent/combination | N (mean years of exposure) |
| Abacavir | 7834 (2.2) |
| Atazanavir | 6325 (1.85) |
| Didanosine | 5638 (1.8) |
| Efavirenz | 14 268 (2.24) |
| Emtricitabine | 11 768 (1.77) |
| Indinavir | 5880 (1.8) |
| Lamivudine | 19 633 (3.37) |
| Lopinavir | 7207 (1.95) |
| Nelfinavir | 6839 (1.98) |
| Nevirapine | 5246 (2.19) |
| Ritonavir | 5124 (0.67) |
| Saquinavir | 2930 (1.43) |
| Stavudine | 9474 (2.33) |
| Tenofovir | 15 005 (2.30) |
| Zidovudine | 15 524 (2.64) |
| Efavirenz/Emtricitabine/Tenofovir | 6800 (1.47) |
| Atazanavir/Emtricitabine/Tenofovir | 3660 (1.30) |
| Efavirenz/Lamivudine/Zidovudine | 6229 (1.67) |
| Emtricitabine/Lopinavir/Tenofovir | 2562 (1.07) |
| Abacavir/Atazanavir/Lamivudine | 1695 (1.27) |
| Lamivudine/Lopinavir/Zidovudine | 2953 (1.16) |
| Emtricitabine/Nevirapine/Tenofovir | 804 (1.27) |
| Abacavir/Efavirenz/Lamivudine | 2481 (1.15) |
| Atazanavir/Lamivudine/Zidovudine | 1795 (1.14) |
| Lamivudine/Nevirapine/Zidovudine | 2583 (1.56) |
| Lamivudine/Nelfinavir/Zidovudine | 3920 (1.48) |
| Abacavir/Lamivudine/Zidovudine | 3890 (1.54) |
| Emtricitabine/Fosamprenavir/Tenofovir | 570 (1.05) |
| Abacavir/Lamivudine/Lopinavir | 1763 (1) |
| Efavirenz/Lamivudine/Tenofovir | 3433 (0.64) |
| Lamivudine/Lopinavir/Tenofovir | 2374 (0.93) |
| Efavirenz/Lamivudine/Stavudine | 2735 (1) |
| Indinavir/Lamivudine/Zidovudine | 3663 (1.39) |
| Emtricitabine/Nelfinavir/Tenofovir | 422 (0.76) |
| Abacavir/Lamivudine/Nevirapine | 1002 (1.16) |
| Darunavir/Emtricitabine/Tenofovir | 675 (0.78) |
| Atazanavir/Didanosine/Tenofovir | 523 (0.91) |
| Atazanavir/Lamivudine/Tenofovir | 1893 (0.67) |

[a] Cardiovascular events include stroke, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery.

## DISCUSSION

Ours is the first study to our knowledge to evaluate the association between combinations of antiretroviral medications and risk of cardiovascular events. Five combinations were implicated by our primary analysis. All combination therapies identified contained lamivudine; 3 contained abacavir; 3 contained zidovudine, 2 contained efavirenz, and 2 contained atazanavir.

We chose to evaluate combinations of ART drugs because the drugs are always used in combination. It is possible that combinations of drugs may elevate cardiovascular risk in a way that would not be discoverable by assessing only individual drugs or by assessing classes of drugs, as prior studies have done. For example, an interaction between 2 drugs might create a level of cardiovascular risk that neither drug alone would produce. In this study, 2 combinations associated with risk of cardiovascular events contained atazanavir, although atazanavir alone was not associated with increased risk. As atazanavir has no known atherogenic properties, this may be a reflection of these particular combinations, and it may be that in combination with other agents, atazanavir does not increase risk. Indeed, evidence from our study on other combinations containing atazanavir (eg, with emtricitabine and tenofovir, and with didanosine and tenofovir) does not support concerning associations.

A key concern in our analysis was the possibility of confounding by indication. Many prior studies have used Cox models. Although this approach attempts to adjust for confounding by incorporating time-varying confounders, previous literature suggests it can be particularly problematic when confounding by indication is likely [12]. To address this, we used marginal structural models, a relatively new class of models designed to minimize such confounding. Subject-specific weights are incorporated into the analysis and estimated by the inverse of a subject's probability of having his own observed treatment history. Weights for a subject are updated at each time interval. Assuming all relevant confounders have been measured and are incorporated into estimating the probabilities, this weighting effectively creates for a risk set at each time interval, a pseudo-population in which the time-dependent confounders no longer predict choice of ART therapy at that time. The weighted estimator of the effect of ART therapy on cardiovascular event can then take on a causal interpretation. In secondary analyses, we used a Cox model to assess the sensitivity of our results to model specification. For individual drugs, odds ratios and hazard ratios were relatively similar, although statistical significance varied. For combinations of drugs, the marginal structural model identified four combinations not identified by the Cox model. Given the nature of our observational data and potential for confounding, we believe the analysis with marginal structural models is the most appropriate.

We also evaluated how using MI alone affected our findings. Findings were comparable in direction and magnitude to those in our primary analysis. However, fewer associations reached statistical significance, likely due to the reduction in events by approximately half. Notably, a recent analysis by the D:A:D
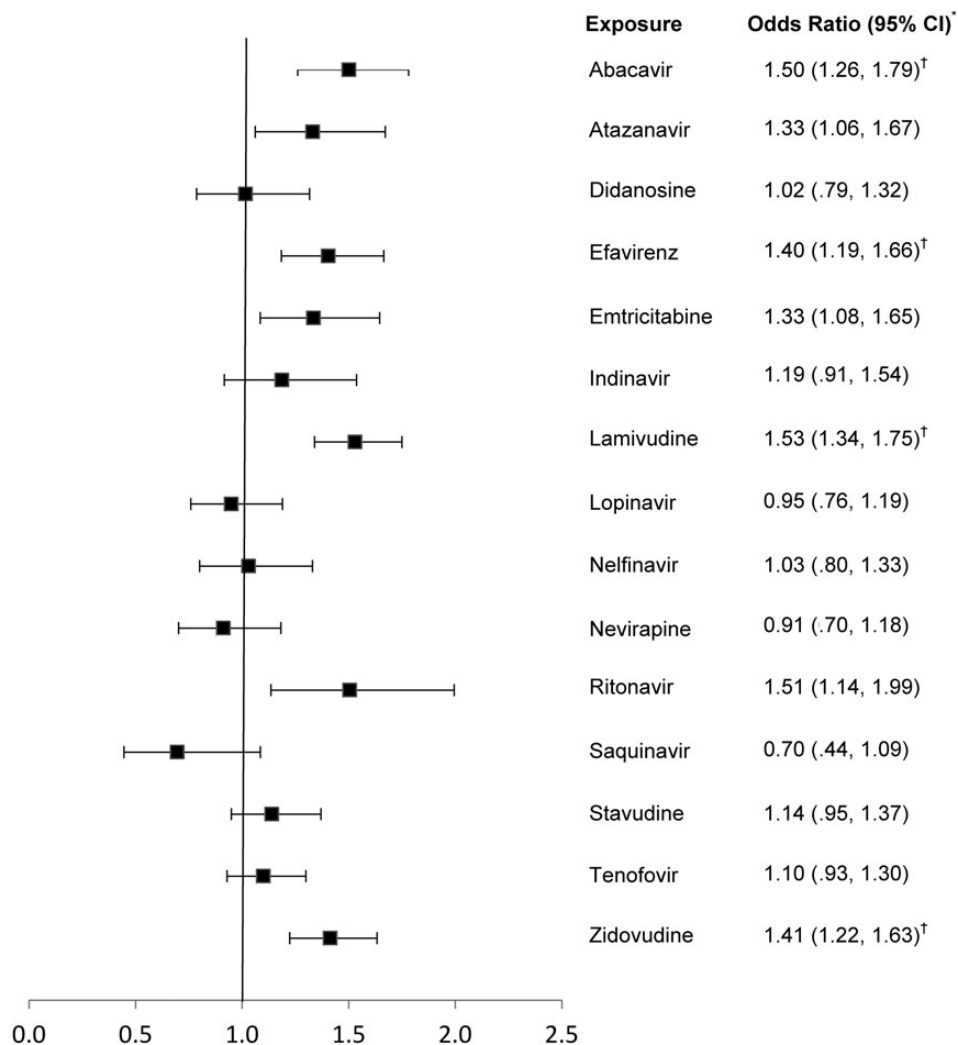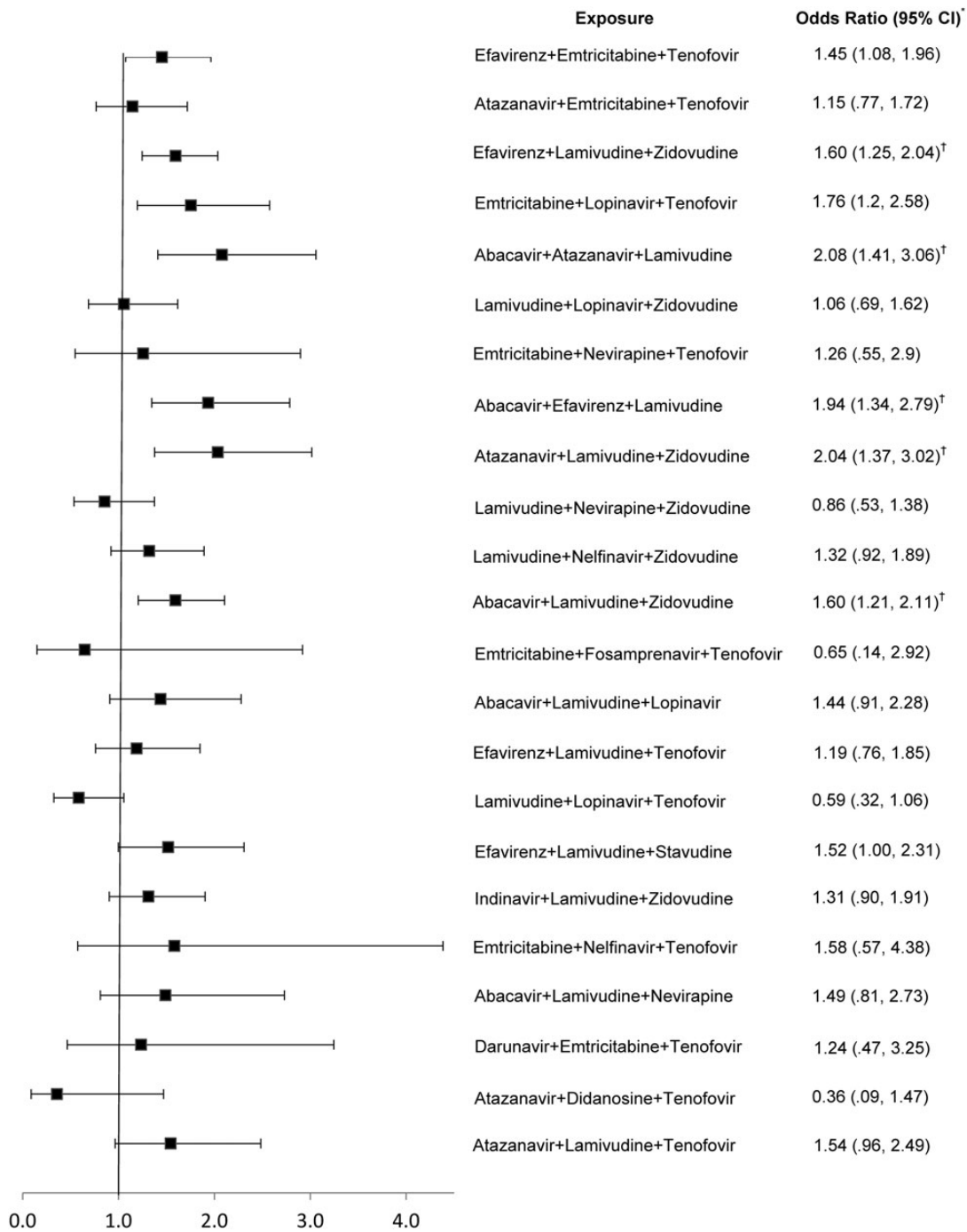
**Figure 1.** Estimated effect of antiretroviral drug exposure on cardiovascular event. *Point estimates are interpreted as increase/decrease in odds of cardiovascular events given current exposure to therapy relative to not currently exposed to therapy. †Statistically significant according to the Bonferroni adjusted *P* value. Abbreviation: CI, confidence interval.

study group presented at the 21st Conference on Retroviruses and Opportunistic Infections in 2014 with approximately twice the number of MIs than those in our cohort (941 vs 467) yielded findings that suggested the association between abacavir and risk of MI persists as of 2013 and since their first publication of the relationship in 2008 [14].

Previous studies have used cumulative exposure to antiretroviral medications as the definition for the exposure variable [2, 3, 4, 7]. Cumulative exposure has intuitive appeal: more drug exposure seems likely to lead to more risk. However, the relationship between cumulative exposure and risk may be complex and nonlinear. For example, a threshold amount of exposure may be required for risk, or risk may level off after a certain amount of exposure. Some investigators have included both cumulative and current (or recent and past) exposure together in the same model [2, 4],

altering the interpretability of relevant parameters [1]. Our choice of current exposure did not require sophisticated modeling and allowed the interpretation of parameters to be simple and unconditional on exposure to a particular antiretroviral agent. We did, however, explore models with cumulative exposure to gauge general consistency (data not shown). These findings were not contradictory to our primary analyses, and also indicated that investigators considering cumulative exposure should allow for nonlinear relationships such as an inverted "U" shape, as a linearity constraint could lead to misleading results.

Our findings agree with some prior studies but also show some differences. Our finding regarding abacavir is consistent with other studies in the literature. Choi et al [8], Martin et al [15], and Belloso [16] all observed a significant association between abacavir exposure and increased risk of cardiovascular

**Figure 2.** Estimated effect of combination antiretroviral exposure on cardiovascular event. *Point estimates are interpreted as increase/decrease in odds of cardiovascular events given current exposure to therapy relative to not currently exposed to therapy. †Statistically significant according to the Bonferroni adjusted P value. Abbreviation: CI, confidence interval.

event. The D:A:D Study Group [2] and Lang et al [4] examined the association between recent exposure of zidovudine and risk of MI and found no association, whereas we found a significant association with MI. Similarly both D:A:D and Lang evaluated recent exposure of lamivudine on MI and found estimates that

suggested an increased risk, but not one that was statistically significant, as we did.

Of particular note are 2 studies based on the same population as our study, the VHA CCR. Bedimo and colleagues [7] found no association between cumulative use of abacavir and MI; no

**Table 3. Key Differences in Study Design and Analysis for Two Studies of US Veterans Infected With Human Immunodeficiency Virus Identified in the Clinical Case Registry**

| Author (Year) | N (Number of Events) | Person-Years Follow up | Period of Study | Include Subjects Never Exposed to ART | Primary Outcome | Start Time | Statistical Model | Primary Parameter | Conclusions |
|---|---|---|---|---|---|---|---|---|---|
| Bedimo et al [7] | 19 424 (278) | 76 376 | 1996–2004 | Yes | Time to first MI | Activity in CCR | Extended Cox | 1-year increase in abacavir exposure | Abacavir not associated with increased risk |
| Choi et al [8] | 10 931 (501) | 60 588 | 1997–2007 | No | Time to first CVD | ART initiation | Extended Cox | Recent exposure to abacavir and not tenofovir relative to neither abacavir nor tenofovir among abacavir users | Abacavir associated with increased risk |

Abbreviations: ART, antiretroviral therapy; CCR, Clinical Case Registry; CVD, cardiovascular disease; MI, myocardial infarction.

association between cumulative use of abacavir and cerebrovascular events; decreased risk of MI and cerebrovascular events with use of tenofovir relative to neither use of tenofovir and abacavir (hazard ratio [HR] = 0.16, 95% CI, from .08 to .33 and HR = 0.22, 95% CI, from .15 to .32, respectively) and decreased risk of cerebrovascular events with use of abacavir relative to neither use of abacavir and tenofovir (HR = 0.60, 95% CI, from .45 to .79). The authors concluded that abacavir was not significantly associated with MI or cerebrovascular events in contrast to the D:A:D study [2] and speculated that the discrepancy may lie in controlling for chronic kidney disease (CKD)—although nonsignificant findings were observed even without adjustment for CKD. In contrast, Choi and colleagues [8] found recent exposure to abacavir was associated with an increased risk of cardiovascular events, and recent tenofovir exposure was associated with increased risk of heart failure.

Although there are several differences in the design of the 2 studies (Table 3), we suggest that the discrepancy arose because the questions addressed differ fundamentally. Although both studies evaluated abacavir and tenofovir, the reference group for comparisons differed. Bedimo et al [7] reported on risk associated with a 1-year increase in exposure of abacavir among abacavir users, which can also be interpreted as the risk of 1-year abacavir exposure relative to no ART exposure, whereas Choi et al [8] reported on recent exposure to abacavir and not tenofovir relative to neither abacavir nor tenofovir among abacavir users. It is therefore not surprising that the results were discrepant. Our analysis, as discussed, implicates current use of abacavir as increasing risk for cardiovascular events.

Our study has several strengths. We made use of marginal structural models, developed to address selection bias, particularly where confounding by indication is known to be an issue [12]. We applied a flexible missing data tool to handle the missing data and

accounted for multiple testing to control false discoveries. Finally, we employed sensitivity analyses to provide insight into how our findings were affected by modeling choices.

There are also limitations to our study. First, cardiovascular events were ascertained exclusively through ICD-9 and CPT codes, borrowing methods suggested by previous authors [10, 11]. Thus, the events are not adjudicated. Such methods are known to be highly specific with good sensitivity. Consequently, although we are confident that those events we identify are true positives, there may be a small proportion we do not ascertain, and it is difficult to know the affect this would have on the point estimates. Because the number of events not identified is relatively small, however, we believe the impact on describing the associations is negligible. Marginal structural models can be effective only if variables involved in predicting treatment initiation are observed. Another limitation is that we have not accounted for potential competing risks. For example, those treated with abacavir may be less likely to die of their disease if abacavir is more effective in managing their HIV disease than other ARTs, thereby allowing these patients to live longer putting them at greater risk for cardiovascular events simply as a consequence of living longer lives. Finally, we did not consider newer agents such as integrase inhibitors or second generation non-nucleoside reverse transcriptase inhibitors that are currently available, and several of the drugs and combinations we considered are rarely or no longer used in current practice. In particular, didanosine, indinavir, nelfinavir, and ritonavir (as a standalone protease inhibitor) have been replaced by more efficacious and better-tolerated antiretroviral drugs. We considered them here, however, as they were used by our study population during the study period and in that sense contributed to the relevant exposures. Thus, associations of antiretroviral drugs and ART combinations that are in clinical use now were

considered alongside therapies to which subjects were being exposed at the time.

Observational studies like ours have well-known inherent challenges when characterizing associations between drug exposures and disease. The systematic review our team performed on this topic demonstrated discrepancies in findings across observational studies—even when using the same cohort. The findings provided us with an opportunity to select analytic and design approaches to address these methodological issues but also highlighted difficulties in conducting such studies that are specific to the observational design [1]. We thought carefully about our study design and to whom we should generalize our findings including the window of exposure time, exclusion of those never exposed to ART, and how to model exposure over time. Our use of marginal structural models was an attempt to address the specific issue of confounding by indication. Further, the publication of our well-annotated code is an attempt to provide full transparency of our methods and to allow for replication in other populations.

In summary, we found that 4 individual ART drugs and 5 ART combinations were associated with modestly increased risk of cardiovascular events in a veteran population. To provide some context for our findings, we note that the absolute risk of cardiovascular events for our cohort is twice that of a population with similar cardiovascular risk factors (approximately 4% vs 1.8%). The absolute risk, however, is still low. We suggest clinicians interpret our findings in light of the relatively low absolute risk of cardiovascular events. In our view, the primary consideration in choice of ART regimen should be its efficacy for HIV and tolerability. In situations in which equally effective regimens are available, clinicians may want to consider the potential elevation in risk of cardiovascular events, particularly in patients who are older or who have cardiovascular risk factors. Because our population was essentially all men, our findings should not be generalized to women. Although we used statistical models designed to mitigate confounding, our findings are based on observational data with significant inherent limitations. Replication of our findings in other populations would strengthen the evidence for elevated risk from ART and provide further guidance about the selection of ART regimens in patients at risk for cardiovascular disease.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

## References

1. Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One **2013**; 8:e59551.
2. 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.
3. 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.
4. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. Arch Intern Med **2010**; 170:1228–38.
5. 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.
6. Ding X, Andraca-Carrera E, Cooper C, et al. No association of myocardial infarction with abacavir use: findings of an FDA meta-analysis. J Acquir Immune Defic Syndr **2012**; 61:441–7.
7. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. Clin Infect Dis **2011**; 53:84–91.
8. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS **2011**; 25:1289–98.
9. Backus LI, Gavrilov S, Loomis TP, et al. Clinical Case Registries: simultaneous local and national disease registries for population quality management. J Am Med Inform Assoc **2009**; 16:775–83.
10. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. Stroke **2002**; 33:2465–70.
11. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using *international classification of diseases*, revisions 9 and 10. Stroke **2005**; 36:1776–81.
12. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiol **2000**; 11:550–60.
13. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol **2008**; 168:656–64.
14. Sabin CA, Reiss P, Ryom L, et al; for the D:A:D study group. Is there continued evidence for an association between abacavir and myocardial infarction risk? [abstract 747LB] In: 21st Conference on Retroviruses and Opportunistic Infections, Boston, **2014**.
15. 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.
16. Belloso WH, Orellana LC, Grinsztejn B, et al. Analysis of serious non-AIDS events among HIV-infected adults at Latin American sites. HIV Med **2010**; 11:554–64.