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Recent abacavir use increases risk for Types 1 and 2 myocardial infarctions among adults with HIV

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Abstract

Background—There is persistent confusion as to whether abacavir (ABC) increases the risk for myocardial infarction (MI), and whether such risk differs by Type 1 (T1MI) or 2 (T2MI) MI in adults with HIV.

Methods—Incident MIs in NA-ACCORD participants were identified from 2001 to 2013. Discrete time marginal structural models addressed channeling biases and time-dependent confounding to estimate crude (HR) and adjusted hazard ratios (aHR) and 95% confidence intervals; analyses were performed for T1MI and T2MI separately. A sensitivity analysis evaluated whether Framingham Risk Score (FRS) modified the effect of ABC on MI occurrence.

Results—8,265 adults who initiated antiretroviral therapy contributed 29,077 person-years and 123 MI events (65 T1MI, 58 T2MI). Median follow-up time was 2.9 (interquartile range 1.4, 5.1) years. ABC initiators were more likely to have a history of IDU, hepatitis C virus infection, hypertension, diabetes, impaired kidney function, hyperlipidemia, low (<200 cells/mm^3) CD4 counts, and a history of AIDS. The risk of the combined MI outcome was greater for persons who used ABC in the prior 6 months (aHR=1.84 [1.17, 2.91]; and persisted for T1MI (aHR=1.62 [1.01,]) and T2MI (aHR=2.11 [1.08, 4.29]). FRS did not modify the effect of ABC on MI (p=0.14) and inclusion of FRS in the MSM did not diminish the effect of recent ABC use on the combined outcome.

Conclusions—Recent ABC use was associated with MI after adjustment for known risk factors and for FRS. However, screening for T1MI risks may not identify all or even most persons at risk for ABC use-associated MIs.

Keywords

HIV; abacavir; myocardial infarction; causal inference

INTRODUCTION

Aging adults with HIV are at increased risk for myocardial infarction (MI) compared to otherwise similar adults without HIV.[1, 2] This increased risk is likely the result of an amalgam of simultaneously occurring factors, including: 1) increased prevalence of traditional MI risk factors among adults with HIV;[3–6] 2) HIV-associated immune activation and dysregulation, excess inflammation and hypercoagulation[7, 8] that is blunted but not normalized with antiretroviral (ART)-induced virologic suppression and;[7, 9, 10] 3) possibly the use of specific ART drugs.[4, 11, 12]

There have been conflicting reports linking increased risks of MI and use of nucleoside reverse transcriptase inhibitor (NRTI) agents, with considerable attention focused on abacavir (ABC). Initial reports came from the Data Collection on Adverse Events of Anti-

HIV Drugs (D:A:D cohort); D:A:D remains the largest cohort in which this relationship has been examined systematically to date. Their analysis included 25,000 adults with HIV followed prospectively for at least 10 years and demonstrated a nearly two-fold risk of MI incidence associated with recent ABC exposure (with the prior 6 months), though more remote or cumulative ABC exposures were not associated[13]

Other observational studies have corroborated these findings[14–17]. The French Hospital Database on HIV[18] initially reported findings similar to those of D:A:D regarding recent ABC use and MI risk (OR=2.01, 95% CI 1.11–3.64) but this association did not remain significant after accounting for cocaine or intravenous drug use.[18]

Other cohorts have failed to identify such an association[19] The U.S. Food and Drug Administration (FDA) undertook a meta-analysis, including participants in randomized controlled trials, and found no increased risk of cardiovascular disease associated with ABC use.[20] However, of the 26 studies included in this analysis, only 5 reported a mean follow-up time >2 years and none reported a follow-up time of >5 years.[20] Reports from cohorts that have not demonstrated an ABC/MI association have differed widely in analytic methodology and clinical definitions used.

Tenofovir dioproxil fumarate (TDF) has been used more commonly in combination ART regimens than ABC since both became available, and ABC use has been more common among persons for whom TDF use was contraindicated, particularly because of renal impairment (calculated GFR<60 ml/min). Since renal insufficiency is an independent risk for MI, selection of ABC for use among persons with kidney disease may represent a channeling bias enriching the population of ABC users with persons who have higher MI risk compared to non-users; such bias may have influenced ABC use from 2008-onward[13, 21,22] in individuals with known cardiovascular disease (CVD) risk factors. Further, given the links between protease inhibitor use and dyslipidemia (which may increase the risk of MI), as well as the link between delayed antiretroviral therapy initiation and low CD4 counts (which have also been linked with MIs),[23] time-dependent confounding of the ABC and MI relationship is possible.

The objective of the current analysis was to determine the effect of recent ABC use on the risk of MIs overall and stratified as either a type1 MI type (T1MI) or type 2 MI (T2MI). We utilized data from the North American Cohort Collaboration on Research and Design (NA-ACCORD) and analytical methods that attempted to account for potential channeling bias and time-dependent confounding of the ABC and MI relationship.

METHODS

Study Population: The NA-ACCORD

The NA-ACCORD is the largest consortium of HIV cohorts in the US and Canada. It serves as the North American region of the International Epidemiology Databases to Evaluate AIDS project (IeDEA), supported by the National Institutes of Health. Details on this collaboration have been published previously.[24] Briefly, NA-ACCORD consists of single and multi-site clinical and interval cohort studies that accumulate data from adults (≥18

years old) with HIV at ≥200 sites in the US and Canada. Participating cohorts submit comprehensive data on enrolled participants to the Data Management Core (University of Washington, Seattle WA) where data are harmonized across cohorts and transmitted to the Epidemiology/Biostatistics Core (Johns Hopkins University, Baltimore, MD), which conducted the analyses presented here. The human subjects research activities of the NA-ACCORD and each of the participating cohort studies have been reviewed and approved by their respective local institutional review boards (IRB) and by the Johns Hopkins University School of Medicine.

For the present study, seven US clinical cohorts within the NA-ACCORD with complete access to both inpatient and outpatient electronic medical records (EMR) validated the occurrence of MI between 1 January 2001 and 31 December 2013. The study population was restricted to persons observed to initiate ART. A flow chart depicting the selection of NA-ACCORD participants for the current study can be found in Supplement Figure 1.

Outcome: MI

The primary outcome for this study was incident MI. The protocol for ascertainment, validation, and classification of MIs within the NA-ACCORD has been previously published.[25] Briefly, potential MI events were centrally ascertained within the NA-ACCORD data repository using a standard protocol based on primary screening for MI that included the presence of an inpatient or outpatient MI diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] diagnoses including 410 codes, 411.0, 412 and 429.7), or serum cardiac enzyme levels above the laboratory-specific upper limit of normal for troponin-I, troponin-T, or creatine kinase MB. Comprehensive medical records regarding each potential MI identified by this screening were abstracted from electronic medical records, de-identified and uploaded to the central NA-ACCORD data repository via a secure website. Information regarding specific antiretroviral (ART) drug use was redacted to avoid possible reviewer bias. Each potential MI event was adjudicated by at least two physician reviewers with extensive expertise in MI adjudication. A third review was conducted if discrepancies occurred. Events were classified as either T1MI, which is caused by atherosclerotic plaque rupture or erosion with intraluminal thrombus, or T2MI, which is caused by ischemic imbalance between myocardial oxygen supply and demand often found in the settings of hypotension and sepsis according to the universal definition of myocardial infarction.[26] Reviewers also identified persons who screened positive for an MI and then underwent a cardiac intervention indicating severe underlying coronary artery disease (usually coronary artery bypass graft or percutaneous coronary intervention with stent placement); these events were considered validated MIs and classified as T1MIs. For this study, only incident MI events were included as an outcome. A patient with an MI identified at or prior to ART exposure (baseline) was excluded from subsequent analysis.

Exposure: Recent abacavir use

Exposure to ABC was measured from prescription and medical records. Recent ABC use was updated as a time-varying variable in the analysis and defined as any reported use within the prior 6 months.

Confounders

Sex, race and ethnicity, year of birth, and HIV transmission risk (including injection drug use) were self-reported at enrollment. Cigarette smoking was defined as ever having smoked cigarettes based on clinician-recorded diagnoses and/or patient-reported responses to questionnaires administered by individual cohorts. Hepatitis C virus (HCV) infection was defined as having a positive serum HCV antibody test, detectable plasma HCV RNA, or evidence of an HCV genotype test as reported in medical records while under observation in the NA-ACCORD.

Treated hypertension was defined as a clinical diagnosis of hypertension and a prescription of antihypertensive medication. Diabetes mellitus was defined as a diagnosis of diabetes and prescription of diabetes-related medication, or a diabetes-specific medication, or a glycosylated hemoglobin (HbA1c) level ≥6.5%. Statin use was defined as prescription of an HMG-CoA reductase inhibitor medication. Low HDL cholesterol was defined as ≤40 mg/dL for men and ≤50 mg/dL for women. High LDL was defined as ≥130 mg/dL. Elevated total cholesterol was defined as ≥240 mg/dL. These were considered dichotomous variables. Due to the effect of statins, only LDL and total cholesterol measurements prior to statin initiation were considered. Elevated triglycerides were defined as ≥300 mg/dL. We calculated estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and[27] dichotomized eGFR to represent renal function (eGFR ≥60 and <60 mL/min).

History of an AIDS-defining illness was based on clinical diagnoses defined according to the 1993 CDC case definition[28]; a CD4 count <200 cells/ μL was not included in this definition. CD4 cell count was categorized in 3 strata (<200, 200–349, and ≥350 cells/μL.) HIV virologic suppression was defined as a plasma HIV-1 RNA level ≤400 copies/mL. ART was defined as three ARV agents from at least two classes or a triple nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) regimen containing ABC or TDF. Due to previous studies[29] suggesting a link between use of ART combinations that included a protease inhibitor (PI-based) with MI[29,30], HIV treatment regimens were classified as PI-based and non-PI based.

Statistical Analysis

We utilized marginal structural models (MSM)[30] to determine the risk of MI with ABC use as a time-varying exposure in the presence of time-varying confounders that are affected by previous treatment. This approach accounts for channeling bias that may have existed among individuals with renal function impairment (and potentially higher prevalence of other known MI risk factors) receiving ABC because of the contraindication for TDF use by such persons.[31] The use of MSM also accounts for time-dependent confounding of the ABC and MI relationship occurring after ART initiation. Individuals began contributing person-time to the analysis from the time of ART initiation until the earliest date of: 1) incident MI; 2) death; 3) 6 months after discontinuation of ABC use (because our measure of interest was current or recent ABC use, within the prior 6 months); 4) loss to follow-up (defined as one year after last CD4 or HIV RNA measurement) or; 5) administrative censoring at the last date of the cohort full MI observation, or December 31, 2013. As noted above, participants

with a validated MI at, or prior to, study entry were excluded as they were no longer at risk for their first MI event.

Individuals who initiated a non-ABC-containing ART regimen but subsequently received abacavir were included and contributed person time to the appropriate group. For the MSM analysis, we constructed the necessary stabilized weights as the product of probabilities from three models: initiating ABC, discontinuing ABC once initiated, and censoring (see Supplement Figure 2 for box plots of the stabilized weights). Our primary analysis estimated the relationship of recent ABC use with the combined T1 and T2MI outcome. Two sub-group analyses were performed. First, the outcome was re-defined as T1MI only; individuals who had a T2MI were excluded altogether from the T1MI analysis. For the second sub-group analysis, the outcome was re-defined as T2MI; persons with a T1MI were altogether excluded from the T2MI analysis. Due to the decreased number of events when stratified by MI type, we employed a bootstrapped approach using the bootstrap-*t* approach (1,000 first iterations and 25 second iterations) to estimate 95% confidence intervals for the sub-group analyses.

Two sensitivity analyses were performed. First, to test the *a priori* hypothesis that Framingham Risk Score (FRS) modified the effect of ABC use on MI occurrence, we used a global test of heterogeneity with a nested models approach to determine if the MSM model with an interaction term for ABC and FRS was a better fit, providing statistical evidence of interaction. Second, we estimated a *naïve model* that did *not* account for the channeling bias or time-dependent confounding by removing the weights. Although all the variables in the MSM were retained in the naïve model, we measured all confounders at study entry; only recent ABC use and age were time-varying.

Finally, we replicated the analysis published by the original D:A:D report of the relationship of ABC and MI.[22] By replicating the D:A:D approach, we sought to evaluate whether similar findings could be ascertained among these two distinct study populations using similar methods. See Supplement Figure 1, Table 1, and Table 4 for details on the D:A:D replication analysis.

All analyses were performed using SAS version 9.3 (SAS Institute) and a p-value <0.05 guided statistical interpretations.

RESULTS

A total of 8,265 adults contributed 29,077 person years and 123 events (65 T1MI, 58 T2MI). Median follow-up time was 2.9 (interquartile range [IQR] 1.4, 5.1) years. Median follow up time was similar in ABC initiators (3.0 [IQR 1.4, 5.5] years) compared with persons who initiated other ART regimens (median= 2.9 [1.5, 5.1], p=0.27). Compared to persons who did not initiate ABC, ABC initiators were more likely to be older, female, Black, have a history of IDU and heterosexual HIV transmission risk, have HCV infection, treated hypertension, diabetes, impaired kidney function, elevated total cholesterol, elevated triglycerides, low (<200 cells/mm^3) CD4 count, and a history of clinical AIDS diagnosis at

study entry (Table 1). There was a decrease in ABC use (defined as ≥1 month of ABC use) from a peak of 39% of participants in 2002 to a low of 9% in 2013 (Supplement Figure 3).

The primary analysis of the combined MI outcome showed an increased risk among persons who had used ABC in the prior 6 months ($p<0.0001$); this difference persisted when stratifying the outcome by MI type (T1MI $p<0.0001$, T2MI $p<0.0001$, Figure 1). The proportion of MI events that were type 1 or type 2 did not vary significantly by calendar period.

After accounting for potential channeling biases and time-varying confounding in the MSM approach, persons with recent ABC exposure had an 84% increase in MI risk compared to those without recent ABC exposure (aHR=1.84 [1.17, 2.91], Table 2). Stratifying by MI type (T1MI or T2MI),[22] there was a 62% increase in the risk of T1MI with recent ABC (aHR=1.62 [1.01, 2.94]); the risk of T2MI was 2-fold with recent ABC use (aHR=2.11 [1.08, 4.29]).

To address the *a priori* hypothesis that cardiovascular disease risk modified the effect of ABC on MI occurrence, FRS at study entry were estimated for participants. Cumulative incidence of combined MI was highest among persons with the highest FRS (Figure 2). Stratification by MI type demonstrated that the ABC use/MI relationship persisted with T1MI, as expected, and also with T2MI. There was no statistical evidence that FRS modified the effect of ABC on the risk of combined MI (p-value of interaction=0.14). To further adjust for any differences by cardiovascular disease risk, we included FRS in the MSM approach after excluding those variables already included in the FRS; the effect of recent ABC use on combined MI remained similar (aHR=1.88 [1.20, 2.95], Supplement Table 2).

In the analysis restricted to ART naïve persons who were observed to initiate ART, channeling biases that may have existed among persons with greater risk factors for T1MI were not taken into account; in this analysis, there was a 75% increase in the risk of combined MI with recent ABC use (aHR=1.76 [1.15, 2.68], Supplementary Table 3).

The results of the replicated D:A:D approach in the NA-ACCORD (aHR=1.63 [1.21, 2.18]) were remarkably similar to the D:A:D's findings (aHR=1.70 [1.17, 2.47], Supplementary Table 4).

The point estimates for the relationship of ABC and MI from the main analysis, sub-group analyses, sensitivity analyses, and the D:A:D replication and original studies can be visually compared in Figure 3.

DISCUSSION

In this large, demographically diverse cohort of adults with HIV in care, we identified an increased risk of MI associated with recent use of ABC (vs. use of ART not including ABC). This association was apparent regardless of MI type, both T1MI and T2MI. While ABC recipients were enriched for traditional risk factors for T1MI (compared to non-ABC recipients) including kidney disease, our methods accounting for channeling biases and time-dependent confounding adjusted for this potential bias. In models that included *a priori*

stratification for FRS or specific adjustment for FRS, we observed no attenuation of the magnitude of the association between recent ABC use with MI occurrence.

Further, we were able to evaluate whether differential associations between ABC use by MI type existed. This is particularly relevant because recent work from our group has demonstrated that 45% of MIs occurring among adults with HIV are T2MI.[1] While we found that recent ABC use was associated with MI occurrence regardless of type, the magnitude of the association may be higher in T2MI. In several studies, increased MI risk has been associated with recent ABC use (within approximately 6 months of last use), implying that the pro-MI effects diminish within 6 months of ABC discontinuation. Our study purposely focused on recent and early (part of first ART regimen received) ABC exposure, with the advantage of using adjudicated MIs, a design that mimicked a clinical trial of ART initiation and included both T1 and T2MI. However, some studies have also suggested that cumulative exposure to ABC beyond 6 months may further increase MI risk,[32,33] possibly out to 24–36 months of exposure. Precise mechanisms by which ABC exposure increases the risk of MI are not currently clear. Our current understanding of potential pathophysiologic mechanisms by which ABC use may contribute to MI risk include promotion of enhanced platelet activation, aggregation and increased adhesion to vascular endothelial cells (and consequent promotion of thrombus formation) via interference with processing of purinergic mediators, resulting in an overall ABC effect that appears to involve endothelial activation.[34] While prothrombotic states probably exist for both T1MI and T2MI, ABC's effect feasibly could create an enhanced vulnerability to MI that is distinct from, but possibly additive to, MI risk from pre-existing coronary atherosclerosis or systemic inflammation or immune dysregulation. Such an effect could manifest early during ABC exposure but feasibly could also be an ongoing effect that is cumulative in nature.

While exact mechanism(s) by which ABC exerts pro-MI effects remain speculative, our results suggest that clinical screening practices for MI risk among adults with HIV focused only on more traditional T1MI risks may be insufficient. As many as 50% of the T2MIs in NA-ACCORD are related to sepsis, cocaine use or "other illicit drug-induced vasospasm[26,31], and in the current analysis we found an adjusted HR of 1.76 among IDU for T2MI. Such findings are consistent with observations from the French Hospital Database on HIV, which reported that, after adjustment for cocaine or recreational intravenous drug use, an association between recent ABC use and MI was not apparent[18]. In addition, recent work[35] demonstrated a prominent association of cocaine use with the development of MIs among adults with HIV, prompting the suggestion that treating cocaine addiction may comprise an important adjunctive measure in MI prevention for this patient group.

Our analysis identified other risk factors for T2MI, including Black race, hypertension and diabetes, traditional risk factors for T1MI, as well as a CD4 < 200 cells/mm^3. It is important to note that our analysis was not focused on describing the mechanism of any ART-related causations of MI, but rather isolating the effect of recent ABC use on MI risk in the context of channeling bias and time-dependent confounding. After adjusting for other factors in the model, these variables continued to be independently associated with T2MI. The identification of the prominence of T2MIs among persons living with HIV, as described by

Drozd et al. (1), and our current finding of an independent association between recent ABC use and MI (both T2MI and T1MI) broaden our understanding the spectrum of potential etiologies of MIs in this population. Potential interactions between lifestyle-related factors, genetics, inflammation, various causes of hypoxemia, as well as exposures to specific ARV drugs, may help to expand our understanding of the diverse etiologic factors contributing to MI among persons living with HIV

The NA-ACCORD differs from randomized interventional ART trials from which some ABC and MI data have been analyzed previously (such as those included in the FDA meta-analysis)[20] because the NA-ACCORD analysis reflects data involving ABC utilization in clinical practice, including among adults at diverse stages of HIV disease with various types of MI risk factor profiles, and involved much longer follow-up. Our present study also represents an important improvement in verification of clinical MI events. Classification of MIs included source medical record review, standardized MI criteria and central adjudication by experts, included assignation into T1MI or T2MI categories. No MIs were included that were based only on participant self-report or on clinical ICD codes alone. Uniquely, there were a sufficient number of adults with available data from the time of ART initiation while observed in the NA-ACCORD, analysis of whom not only avoided potential analytic biases associated with prevalent ART use[36] but also enabled the use of MSM approaches that seek to overcome analytic challenges involving time-dependent confounding. The D:A:D investigators were conscientious of excluding potential mediators from the analysis[22],but in doing so, questions were raised as to whether the findings would be corroborated with alternative approaches. We note that an earlier analysis from the NA-ACCORD showed a weaker, though qualitatively similar, adjusted association between ABC exposure and MI.[37] Unlike the prior analysis, the current analysis limited the study sample to patients who were observed to initiate ART to better mimic a clinical trial. We were also able to add more recently adjudicated MIs to the sample, although the selection criteria necessary for the our approach restricted the sample and associated number of MI events in comparison with another previous NA-ACCORD study (Supplement Figure 1).[1]

We acknowledge that as an observational study lacking a randomized assignment of ABC, confounding is still possible and many variables exist that could potentially be predictive not only of MI occurrence but also of the prescribing of ABC. Our methods adjusted for kidney function, which is associated with ABC and TDF prescription, and also for T1MI risk factors such as diabetes, pro-atherogenic hyperlipidemia, hypertension and smoking which may also impact the prescribing of ABC. To date, we are not aware of evidence that risk factors for T2MI (sepsis, cardiac arrhythmia, recreational drug use, anemia, an impaired functional level, female sex) are associated with ABC and TDF prescribing and there is no apparent reason to suspect that ABC recipients would be enriched in T2MI risks compared to non-ABC (largely TDF) users. It should also be noted that it is possible that reverse channeling bias (i.e. the avoidance of ABC use among persons with traditional CAD risk factors) may have existed in the prescription of ABC after initial reports of its association with increased MI risk. If such a phenomenon existed it may or may not have attenuated apparent associations between recent ABC use and MI occurrence.[1] We further acknowledge that even with the large overall sample size, the number of MIs was limited

and power to detect statistical evidence that FRS modified the effect of ABC on MI was limited.

In summary, in this large, diverse, North American cohort of adults with HIV in clinical care, we found that recent (within six months) ABC use significantly increased the risk of MI, both for T1 and T2 MI events. These associations persisted after adjusting for known MI risks, including kidney disease and for FRS. Our MI ascertainment and adjudication procedures were detailed, precise and involved central standardized adjudication by experts. Despite limitations, we believe that we have undertaken the most rigorous analysis possible within the limitations of our dataset, using a study population and analytic methods that better address concerns raised from previous reports evaluating ABC use and MI risk. Our findings imply that analyses seeking to ascertain factors associated with MI among adults with HIV should include routine stratification by MI type. Clinicians may struggle to identify appropriate patients for ABC therapy, integrating known risk factors for T1 MI and the less well-defined risks for T2 MI. Our evolving understanding of the prominence of T2MI among adults with HIV makes patient selection for ABC use more challenging. Future work may focus on identifying the best subset of patients who can benefit from ABC with the least amount of risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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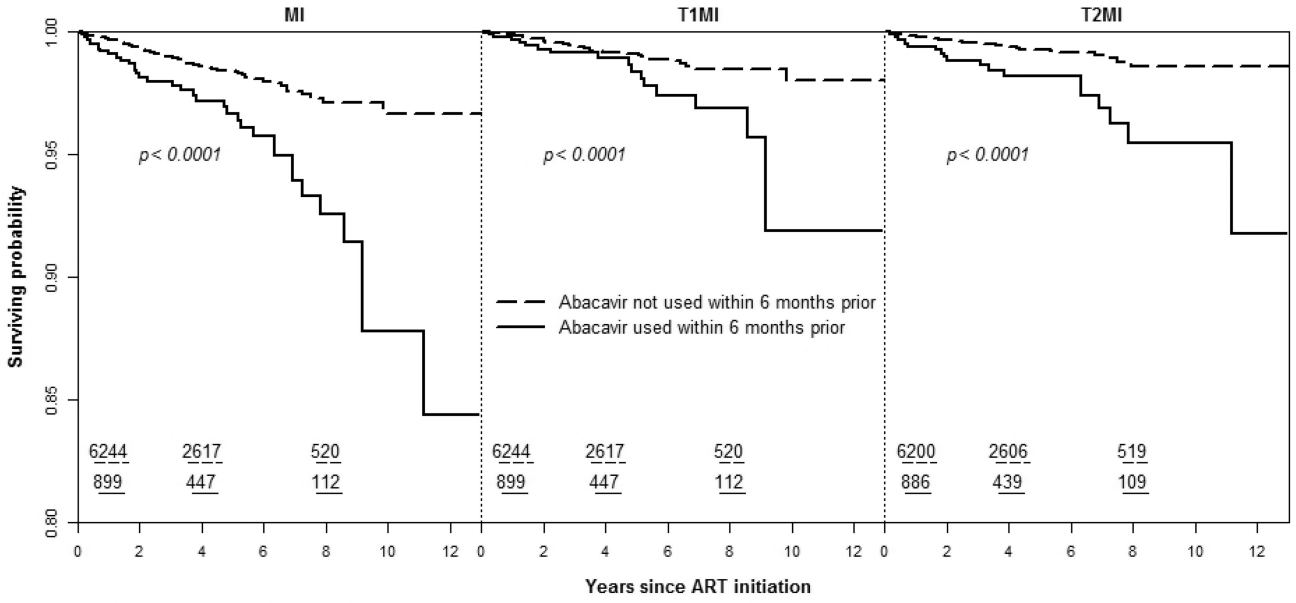

Figure 1.

Kaplan Meier survival estimates for time from ART initiation to first myocardial infarction, by recent (within the last 6 months) abacavir use, NA-ACCORD

Numbers above the x-axis denote the number of participants at risk at 1, 4, and 8 years after ART initiation (top: no ABC; bottom: recent ABC use).

MI = T1MI and T2MI

Primary = T1MI

Secondary = T2MI

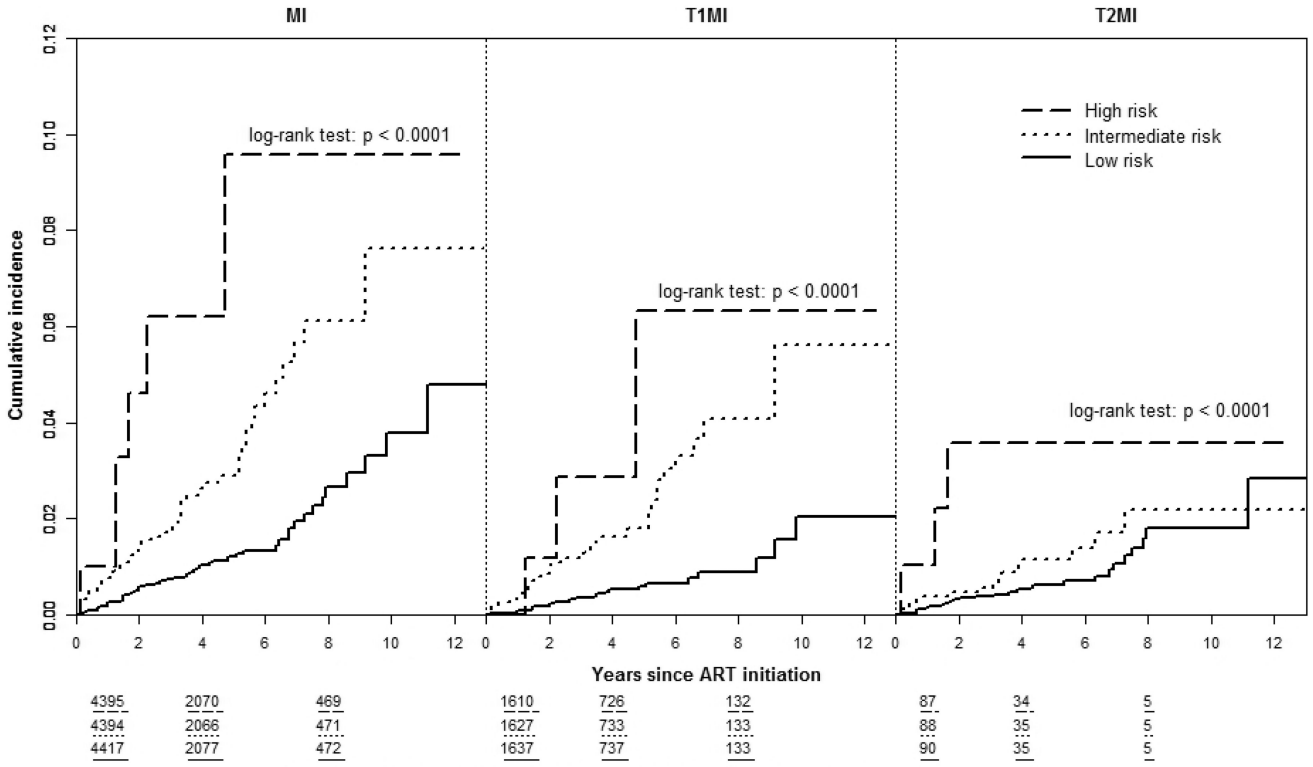

Figure 2.

Cumulative incidence of myocardial infarction, by Framingham risk score, NA-ACCORD

Numbers below the x-axis denote the number of participants at risk at 1, 4, and 8 years after ART initiation (top: high risk; middle: intermediate risk; bottom: low risk).

MI = T1MI and T2MI

Primary = T1MI

Secondary = T2MI

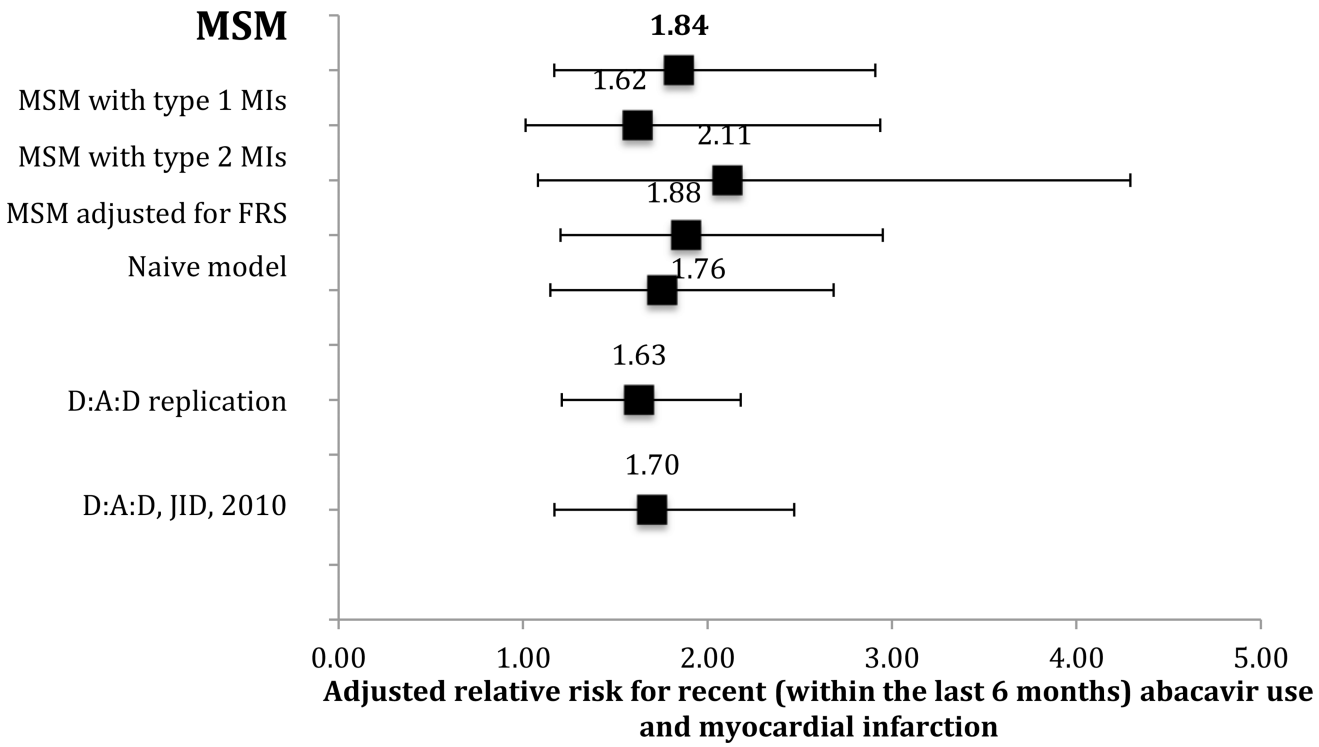

Figure 3.

Estimated risk of MI with recent (within the last 6 months) abacavir use under different approach and model scenarios

The "MSM" is the marginal structural model approach; the main analysis.

The "MSM restricted to type 1 MIs" excluded individuals with a type 2 MI. 95% confidence intervals were bootstrapped.

The "MSM restricted to type 2 MIs" excluded individuals with a type 1 MI. 95% confidence intervals were bootstrapped.

The "MSM adjusted for FRS" model included both type 1 and type 2 MIs in the outcome as well as participants' Framingham Risk Score (FRS) at baseline (intermediate/high vs. low risk).

The "Naïve analysis" removed the weights from the MSM model. The model estimated the risk of the combined T1 and T2MI outcome among those with and without recent ABC exposure, not accounting for potential channeling bias or time-dependent confounding.

The "MSM", "MSM restricted to type 1 MIs," "MSM restricted to type 2 MIs," MSM adjusted for FRS," and "Naïve analysis" models were adjusted for age, sex, race and ethnicity, HIV transmission risk group, year of ART initiation, cigarette smoking, hepatitis C infection, treated hypertension, diabetes mellitus, renal function, high LDL, TC:HDL ratio, high triglycerides, statin use, CD4 count, HIV viral load, and a history of clinical AIDS diagnosis.

The "D:A:D replication" estimate was made using the NA-ACCORD data following the D:A:D, JID, 210 approach. This effect of abacavir was adjusted for cumulative exposure to abacavir, age, sex, race and ethnicity, HIV transmission risk group, cigarette smoking, years since ART initiation, calendar year, and cohort. Unlike the D:A:D approach, measures of

family history of CVD, previous CVD disease, and BMI were not available or included in the model.

The “D:A:D, JID, 2010” point estimate is from Worm et al., JID, 2010.

Table 1

Characteristics of participants at antiretroviral therapy initiation, NA-ACCORD

	ABC initiators (n=1,462)		Did not initiate ABC (n=6,803)	
	N	%	N	%
Age (years)				
<40	545	37	3,174	47
40–49	556	38	2,293	34
50–59	294	20	1,095	16
60–69	67	5	241	4
Male	1,083	74	5,519	81
Race and ethnicity				
White	570	39	3,135	46
Black	673	46	2,289	34
Hispanic	130	9	889	13
Other/unknown	89	6	490	7
HIV transmission risk				
MSM	635	43	3,920	58
IDU	251	17	628	9
Heterosexual	465	32	1,769	26
Other	111	8	486	7
Year of ART initiation				
2001–2004	651	45	1,105	16
2005–2007	399	27	1,728	25
2008–2013	412	28	3,870	58
Ever cigarette smoker	1,083	74	4,995	73
Hepatitis C infection	364	25	1,047	15
Treated hypertension	422	29	1,166	17
Diabetes mellitus	107	7	288	4
Renal function (eGFR ≥60)	1,328	91	6,691	98
High LDL (≥130 mg/dL)	270	18	1,278	19
Low HDL (≤40 mg/dL men, (≤50 mg/dL women	699	48	3,739	55
High total cholesterol (≥240 mg/dL)	202	14	668	10
Total cholesterol : HDL ratio ≥5.0	425	29	2,207	32
High triglycerides (≥300 mg/dL)	488	33	1,975	29
Statin use	108	7	364	5
CD4 count (cells/mm^3)				
≥350	348	24	2,207	32
200–349	476	33	2,204	32
<200	638	44	2,392	35
Detectable HIV viral load (>400 copies/mL)	1,294	89	6,133	90
History of clinical AIDS diagnosis	433	30	1,358	20
HIV treatment regimen				

	ABC initiators (n=1,462)		Did not initiate ABC (n=6,803)	
	N	%	N	%
Non-PI ART	788	54	4,034	59
PI based	674	46	2,769	41
	No. of events	Person years	No. of Events	Person Years
MI Outcomes	36	5,333	87	23,745
T1MI outcomes	17	5,268	48	23,650
T2MI outcomes	19	5,263	39	23,615

Footnotes:

Age, sex, race/ethnicity, and HIV transmission risk group were measured at enrollment into the NA-ACCORD.

Cigarette smoking status was determined as ever having medical record information or substance survey information that denoted cigarette smoking.

Hepatitis C infection was defined as 1) a positive antibody test, or 2) a detectable HCV RNA, or 3) the presence of a genotype result. If an individual ever met this definition, they were considered HCV infected at all times under observation (a time-fixed variable).

Hypertension was defined as 1) a hypertension diagnosis, and 2) prescription for an antihypertensive medication.

Diabetes was defined as 1) a diabetes diagnosis and prescription for diabetes-related medications, or 2) prescription for a diabetes-specific medication, or 3) hemoglobin A1C ≥6.5%.

Renal function was estimated as estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI study equation.

The “study entry” window used for measurement of hypertension, diabetes and renal function was as close to study entry as possible, within the window of prior to study entry through 9 months after study entry.

High low-density lipoprotein (LDL) was defined as LDL ≥130 mg/dL. If there was an LDL measurement ≥130 mg/dL within the window of prior to study entry through 9 months after study entry, then the individual was classified as having high LDL for the entire time they were under observation; otherwise they were classified as having LDL <130 mg/dL.

Low high-density lipoprotein (HDL) was defined as ≤40 mg/dL for men and ≤50 mg/dL for women. If there was an HDL measure ≤40 mg/dl for men or ≤50 mg/dL for women within the window of prior to study entry through 9 months after study entry, then the individual was classified as having low HDL for the entire time they were under observation; otherwise they were classified as having HDL >40 mg/dL.

High total cholesterol was defined as total cholesterol ≥240 mg/dL. If there was a total cholesterol measurement ≥240 mg/dL within the window of prior to study entry through 9 months after study entry, then the individual was classified as having high cholesterol for the entire time they were under observation; otherwise they were classified as having total cholesterol <240 mg/dL.

High triglycerides was defined as triglycerides ≥300 mg/dL. If there was a triglyceride measure >=300 mg/dl within the window of prior to study entry through 9 months after study entry, then the individual was classified as having high triglycerides for the entire time they were under observation; otherwise they were classified as having triglycerides <300 mg/dL.

Statin use included prescription of cerivastatin, fluvastatin, lovastatin, prvastatin, rosuvastatin, simvastatin, pravastatin & aspirin, atorvastatin & amlodipine, ezetimibe & simvastatin, pitavastatin, lovastatin & niacin. Statin prescription was measured within the window of prior to study entry through 9 months after study entry.

CD4 count and HIV RNA were measured at measured as close to study entry as possible, within the window of 9 months prior to study entry through 3 months after study entry.

History of clinical AIDS diagnosis was defined as those who had a first clinical AIDS diagnosis at, or prior to, study entry.

HIV treatment regimen used was measured as close to study entry as possible, within the window of 6 months prior to study entry through study entry.

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Table 2

Estimated crude (HR) and adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI) from marginal structural models for the risk of myocardial infarction (MI) after ART initiation, overall and by MI type, N=8,265 and n=123 MIs (n=65 type 1, n=58 type 2) (the *italic* point estimates are plotted in Figure 3)

	Outcome: Type 1 and Type 2 MI				**Outcome: Type 1 MI**		**Outcome: Type 2 MI**	
	HR	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
Prescription of ABC in the last 6 months								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	**2.66**	**1.81, 3.90**	***1.84***	***1.17, 2.91***	***1.62***	***1.01, 2.94***	***2.11***	***1.08, 4.29***
Age (years)								
<40	**0.19**	**0.12, 0.32**	**0.31**	**0.17, 0.57**	**0.16**	**0.05, 0.43**	0.54	0.24, 1.36
40–49	**0.48**	**0.31, 0.72**	**0.57**	**0.36, 0.89**	**0.50**	**0.27, 0.90**	0.70	0.37, 1.32
50–59	1.00	--	1.00	--	1.00	--	1.00	--
≥60	1.66	0.87, 3.14	1.01	0.49, 2.11	1.34	0.50, 2.94	1.05	0.15, 2.22
Sex								
Male	1.00	--	1.00	--	1.00	--	1.00	--
Female	1.17	0.78, 1.77	1.43	0.86, 2.37	1.81	0.82, 4.09	1.26	0.58, 2.48
Race and ethnicity								
White	1.00	--	1.00	--	1.00	--	1.00	--
Black	1.37	0.94, 1.77	1.08	0.70, 1.66	**0.53**	**0.27, 0.97**	**2.47**	**1.25, 5.88**
Hispanic	0.57	0.27, 2.00	0.76	0.35, 1.65	0.87	0.34, 3.40	0.81	0.23, 4.00
Other/unknown	0.93	0.42, 1.22	1.03	0.46, 2.31	0.70	0.20, 3.12	2.00	0.68, 14.52
HIV transmission risk								
MSM	1.00	--	1.00	--	1.00	--	1.00	--
IDU	**1.79**	**1.08, 2.97**	0.71	0.34, 1.48	0.47	0.14, 1.37	1.06	0.28, 3.72
Heterosexual	1.09	0.71, 1.67	0.58	0.34, 1.00	0.52	0.24, 1.07	0.63	0.28, 1.41
Other	**2.06**	**1.12, 3.76**	1.40	0.68, 2.88	1.90	0.79, 4.66	0.85	0.20, 5.30
Year of ART initiation								
2001–2004	**1.65**	**1.04, 2.62**	1.60	0.97, 2.63	**2.20**	**1.17, 4.16**	1.05	0.48, 2.42
2005–2007	1.00	--	1.00	--	1.00	--	1.00	--
2008–2013	1.14	0.71, 1.84	1.40	0.84, 2.31	1.19	0.61, 2.37	1.70	0.89, 3.89

	Outcome: Type 1 and Type 2 MI				Outcome: Type 1 MI		Outcome: Type 2 MI	
	HR	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
Cigarette smoking								
Never	1.00	--	1.00	--	1.00	--	1.00	--
Ever	**1.73**	**1.07, 2.80**	1.39	0.83, 2.34	1.69	0.81, 4.24	1.12	0.55, 2.36
Hepatitis C infection								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	**1.77**	**1.20, 2.62**	1.15	0.66, 2.00	1.51	0.81, 3.03	0.82	0.29, 2.12
Hypertension								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	**4.14**	**2.90, 5.90**	**2.39**	**152, 3.77**	**2.45**	**1.46, 4.26**	**2.29**	**1.14, 4.54**
Diabetes mellitus								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	**3.89**	**2.35, 6.43**	1.59	0.86, 2.95	1.15	0.42, 2.57	**2.75**	**1.12, 6.29**
Renal function								
eGFR ≥60	1.00	--	1.00	--	1.00	--	1.00	--
eGFR <60	**5.74**	**3.33, 9.88**	1.60	0.81, 3.16	1.69	0.60, 4.35	1.71	0.62, 4.94
High LDL								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	1.16	0.69, 1.97	0.83	0.46, 1.50	0.94	0.45, 1.83	0.60	0.17, 3.39
TC:HDL ratio								
<5.0	1.00	--	1.00	--	1.00	--	1.00	--
≥5.0	1.37	0.89, 2.10	1.24	0.77, 2.00	1.49	0.81, 2.90	0.95	0.46, 1.99
High triglycerides								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	1.37	0.89, 2.10	0.82	0.49, 1.36	0.82	0.42, 1.49	0.77	0.33, 1.46
Statin use								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	**3.12**	**1.89, 5.15**	1.62	0.84, 3.14	2.17	0.94, 4.74	0.76	0.19, 5.13
CD4 count (cells/mm^3)								
≥350	1.00	--	1.00	--	1.00	--	1.00	--
200–349	0.93	0.53, 1.64	0.97	0.54, 1.75	0.78	0.40, 1.74	1.56	0.52, 4.45

	Outcome: Type 1 and Type 2 MI				Outcome: Type 1 MI		Outcome: Type 2 MI	
	HR	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
<200	**1.89**	**1.15, 3.10**	1.66	0.97, 2.81	1.21	,	**3.23**	**1.28, 9.14**
HIV viral load (copies/mL)								
≤400	0.92	0.48, 1.78	0.84	0.42, 1.66	0.78	0.28, 2.00	0.76	0.22, 3.53
>400	1.00	--	1.00	--	1.00	--	1.00	--
History of clinical AIDS diagnosis								
No	1.00	--	1.00	--	1.00	--	1.00	--
Yes	**2.33**	**1.62, 3.34**	**1.54**	**1.03, 2.29**	1.06	0.61, 1.86	**2.14**	**1.30, 4.11**

Footnotes:
The T1MI and T2MI models used a bootstrap-*t* approach to estimating the 95% confidence intervals due to the decrease in power in these sub-groups, that approximately divided the number of events into the two groups.
The models were adjusted for all the covariates seen here and cohort (time fixed).
Prescription of abacavir in the last 6 months is time-varying,
Age was a time-varying variable.
Sex, race/ethnicity, and HIV transmission risk group were measured at enrollment into the NA-ACCORD.
Year of ART initiation was a time-fixed variable.
Cigarette smoking status was determined as ever having medical record information or substance survey information that denoted cigarette smoking.
Hepatitis C infection was defined as 1) a positive antibody test, or 2) a detectable HCV RNA, or 3) the presence of a genotype result. If an individual ever met this definition, they were considered HCV infected at all times under observation (a time-fixed variable).
Treated hypertension was defined as 1) a hypertension diagnosis, and 2) prescription for an antihypertensive medication. Treated hypertension was measured as close to study entry as possible, within the window of prior to study entry through 9 months after study entry and was time-fixed.
Diabetes was defined as 1) a diabetes diagnosis and prescription for diabetes-related medications, or 2) prescription for a diabetes-specific medication, or 3) hemoglobin A1C ≥6.5%. Diabetes was measured as close to study entry as possible, within the window of prior to study entry through 9 months after study entry and was time-fixed.
Renal function was estimated as estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI study equation. Renal function was measured as close to study entry as possible, within the window of prior to study entry through 9 months after study entry and was time-fixed.
High low-density lipoprotein (LDL) was defined as LDL ≥130 mg/dL. If there was an LDL measurement ≥130 mg/dL within the window of prior to study entry through 9 months after study entry, then the individual was classified as having high LDL for the entire time they were under observation; otherwise they were classified as having LDL <130 mg/dL.
High triglycerides was defined as triglycerides ≥300 mg/dL. If there was a triglyceride measure >=300 mg/dl within the window of prior to study entry through 9 months after study entry, then the individual was classified as having high triglycerides for the entire time they were under observation; otherwise they were classified as having triglycerides <300 mg/dL.
Statin use included prescription of cerivastatin, fluvastatin, lovastatin, prvastatin, rosuvastatin, simvastatin, pravastatin & aspirin, atorvastatin & amlodipine, ezetimibe & simvastatin, pitavastatin, lovastatin & niacin. Statin prescription was measured within the window of prior to study entry through 9 months after study entry.
CD4 count and HIV RNA were measured at measured as close to study entry as possible, within the window of 9 months prior to study entry through 3 months after study entry.
History of clinical AIDS diagnosis was defined as those who had a first clinical AIDS diagnosis at, or prior to, study entry.