Risk of Myocardial Infarction and Abacavir Therapy: No Increased Risk Across 52 GlaxoSmithKline-Sponsored Clinical Trials in Adult Subjects

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Background: Recently, the Data collection of Adverse events of Anti-HIV Drugs Group (D:A:D) described results from their international observational cohort of 33,347 HIV-1–infected individuals, suggesting unexpected increased risk of myocardial infarction (MI) associated with abacavir (ABC) therapy [relative rate 1.9, 95% confidence interval (CI): 1.47 to 2.45; $P = 0.0001$]. To contribute to the scientific question, we summarized GlaxoSmithKline HIV clinical trial data to determine if a similar signal emerged.

Methods: We compiled data from GlaxoSmithKline-sponsored clinical trials with ≥24 weeks of combination antiretroviral therapy comprising 14,174 HIV-infected adults who received ABC (n = 9502; 7641 person-years) or not (n = 4672; 4267 person-years).

Findings: Baseline demographics and HIV disease characteristics, including lipids and glucose values, were similar. MI rates were comparable among subjects exposed [n = 16 (0.168%; CI: 0.096 to 0.273; 2.09 per 1000 person-years)] or not [n = 11 (0.235%; CI: 0.118 to 0.421; 2.57 per 1000 person-years)] to ABC-containing therapy. Results of 12 trials with randomization to ABC or not were consistent (2.15 per 1000 person-years vs. 4.10 per 1000 person-years).

Interpretations: In this pooled summary, we observed few MI events overall and no excess risk of MI with ABC therapy. It is unclear why results from this data set seem discrepant to the Data collection of Adverse events of Anti-HIV Drugs data set, particularly, as the non-ABC MI event rate is similar. Further data are needed to evaluate any association between ABC and increased risk of MI.

Received for publication May 8, 2008; accepted January 7, 2009.

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The results of this summary were published in part as a letter to the editor: Cutrell AG, Brothers CH, Yeo JM, et al. Abacavir and the potential risk of myocardial infarction. *Lancet*. 2008;371:1413.

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Key Words: abacavir, coronary artery disease, myocardial infarction

(*J Acquir Immune Defic Syndr* 2009;51:20–28)

INTRODUCTION

Combination antiretroviral therapy (CART) has led to dramatic improvements in morbidity and mortality due to HIV infection, with mortality declining from 20–30 deaths per 100 person-years before 1995 to 2–5 deaths per 100 person-years in 1998[1,2] and continuing to decline in recent years.[3] HIV has become a manageable chronic disease with continued increased survival and hence aging of the infected population. Consequently, questions related to comorbidities, common with increasing age, and long-term toxicities of CART have emerged.[4,5] In particular, there is increasing interest in the potential association of metabolic disorders, coronary heart disease, and use of antiretroviral therapy (ART). In line with the aging population and the effectiveness of CART, more than 50% of deaths in HIV-infected persons receiving CART are now from causes other than AIDS.[6] In a mortality survey in France, the most frequent non–AIDS-related causes of death included cancer, hepatitis C virus infection, and cardiovascular disease (CVD) in 11%, 9%, and 7% of cases, respectively[7]; in a more recent survey, non–AIDS-related death continued to increase and distribution of causes of non-AIDS death were similar.[8]

Several of the traditional risk factors for coronary heart disease, including elevated low-density lipoprotein cholesterol, elevated triglycerides, central adiposity, hypertension, insulin resistance, and diabetes mellitus, can be impacted by HIV infection itself and by ART.[9,10] The extent to which these CART-induced abnormalities may result in a clinically relevant increased risk of CVD has been investigated with conflicting results. Initial focus was on protease inhibitors (PIs) known to be associated with atherogenic dyslipidemia and increased risk of premature "atherosclerotic events."

To assess the association between exposure to CART and risk of myocardial infarction (MI), the Data collection of Adverse events of Anti-HIV Drugs (D:A:D) study, a large, prospective, observational study, was initiated. After their initial report of a 26% increase in the relative risk of MI per

year of exposure to CART,[11] the D:A:D further reported a 16% increase in the relative risk of MI per year of exposure to PIs.[12] Controlling for exposure to nucleoside reverse transcriptase inhibitors (NRTIs) reduced the association for PIs, suggesting that NRTIs could contribute to the observed effect. In the most recent analysis, which focused on NRTIs with the hypothesis that the risk would be linked to the thymidine analogues due to their known metabolic effects, the D:A:D study reported an unexpected association between the recent use of abacavir (ABC) and didanosine and an increased risk of MI [ABC relative risk 1.9, 95% confidence interval (CI): 1.47 to 2.45; $P = 0.0001$].[13] No association between risk of MI and use of zidovudine, stavudine, or lamivudine was consistently noted. There was insufficient exposure in the cohort to assess tenofovir and emtricitabine.

Because the D:A:D data are observational, the authors acknowledge the potential limitations of the analysis, including the inability to entirely rule out bias. Furthermore, there are difficulties in measuring the impact of one therapeutic agent when used in complex treatment patterns and in disentangling the impact of multiple variables that potentially impact the risk of an outcome. Because of limitations inherent in all observational databases studying treatment effects, replication of observational results in other independent data sets is desirable.

In view of the latest D:A:D findings and to contribute to the scientific discussion, we analyzed data from the GlaxoSmithKline (GSK) Clinical Trial Data repository to assess whether a similar signal was seen from pooled clinical trial data.

METHODS

We used the HIV Data Repository, an aggregated clinical trials database maintained by GSK. This Repository includes prospectively collected data from GSK-sponsored trials and contains clinical studies from all phases of drug development (with emphasis on phases II–IV). All studies in the Repository were considered for this investigation and were included if they had an authorized clinical database to allow analysis in 4Q 2007 and were of at least 24-week combination treatment duration. Data from 54 clinical trials were initially summarized to evaluate the number of coronary artery disorders (CAD). Because the expected and observed number of coronary artery events in pediatric subjects is low, we focused our analyses on the adult subjects (n = 14,174) from the remaining 52 trials. The number of CADs and related variables reported in subjects who had or had not taken ABC as part of CART are presented. In all studies, data were collected prospectively in standardized case report forms, monitored against source documentation, and had close follow-up for reported adverse events (AEs) and serious adverse events (SAEs). It is important to note that these studies were generally designed as efficacy studies, and the primary end point was not cardiovascular (CV) outcomes.

For trials in CART-experienced subjects, antiretroviral drugs taken by subjects before entering a study were not utilized as data on prestudy CART were not collected consistently. CART taken while in the studies was categorized as ABC containing or non-ABC containing.

AEs of interest were tabulated separately for 2 analysis periods: "as treated" and intent-to-treat (ITT) "switch included." The as treated period was defined as the time between a subject entering a study and changing his/her treatment group or leaving the study. The ITT switch included treatment period was defined as the time between a subject entering and leaving the study; treatment groups stated are those for the first treatment period. Percentages are based on the frequency of AEs reported by patients; 95% CIs are based on exact binomial 2-sided CIs. Total drug exposure in person-years was calculated until time to event or end of study, whichever occurred first. Incidence rates per 1000 person-years were calculated, and Poisson regression models were used to calculate unadjusted relative rates; 95% CIs were calculated for rates and relative rates. Exposure categories were constructed according to exposure to ABC or not in the CART. The cumulative duration for each subject within each of these classifications during the clinical trial was calculated. A single subject might contribute to only 1 or both of these exposure categories until the time of first event or study end. An event was associated with the exposure category at the time of the event's occurrence, even with prior exposure to the other category. For all statistical methods, summaries were produced separately for adult naive, adult experienced, and for all subjects combined. All analyses were performed using SAS version 8.

AE terms reported in the MedDRA (Medical Dictionary for Regulatory Activities) High-Level Terms of *coronary artery disorders NEC* (not elsewhere classified) and *ischemic coronary artery disorders* (hereafter referred to as "CADs") were used to select the events of interest, that is, myocardial ischemia or infarction. The following specific preferred terms were included in the 2 High-Level Terms: coronary artery atherosclerosis, coronary artery disease, coronary artery occlusion, acute MI, angina pectoris, angina unstable, MI, and myocardial ischemia. In addition, MI and acute MI (hereafter referred to as "MI") were further evaluated separately from the other terms in the summary tables. All reported cases of MI were reported as SAEs and were therefore subject at the time of reporting to stringent follow-up and verification including source document review to ensure accuracy and completeness of diagnosis.

To be comprehensive in our retrospective identification of MIs, we reviewed all fatal AEs from any cause. The purpose of this additional step was to consider if for any fatality, despite MedDRA coding otherwise, potential attributability to an MI could not be reasonably ruled out. This review was conducted by listing all subject fatalities, blinded to treatment, as coded by MedDRA terminology at the time of the report. Upon inspection of this subject listing, selected SAE case narratives were further reviewed for additional details. Of 70 fatalities by any cause, 10 fatalities were further inspected for reasons such as arrhythmia, hypertensive CVD, atherosclerotic heart disease, cardiac arrest/failure, sudden death, and death due to natural causes. Recognizing the subjective element to this review, we conducted the review independently by 2 GSK physicians and separately by a blinded external expert cardiologist.

Our initial intention was to supplement the descriptive data summaries presented in this article with a more

sophisticated multivariate analysis, adjusting for available baseline CV risk factors. However, given the relatively small number of CAD and MI events observed and missing baseline CAD risk factor data for many individuals, this additional work was not viable. Instead, further investigations were conducted with 12 studies that randomized adult subjects to ABC or control. This supporting assessment removed one potential source of bias; that the allocation of subjects to ABC-containing CART or not is random and thus both treatment regimens have the balance for CV risk factors that one would expect from randomization.

RESULTS

Description of Studies

Fifty-four studies were initially summarized; data from 52 adult trials are presented here (the remaining 2 studies being in pediatrics). Thirty-six were randomized studies; 12 were randomized with respect to ABC therapy (ie, had an experimental control for ABC), 14 were randomized with respect to other ARTs and prescribed ABC as a background medication, and 10 either allowed ABC as a possible background medication or did not include ABC at all. Sixteen studies were single arm in design; 13 of these included ABC as a component of CART and 3 allowed ABC as background medication, and 23 were conducted in therapy-experienced subjects. Most studies were initiated between 1997 and 2004.

Of the 12 adult studies randomized with respect to ABC, 8 included a comparison with PI-based therapy (primarily unboosted indinavir or nelfinavir), 1 was a comparison with zidovudine, and 3 included ABC placebo as the control. Three of these 12 studies were conducted in therapy-experienced subjects.

Subject Characteristics

Data from 14,174 adult subjects who received CART were categorized at baseline: 9502 received ABC-containing regimen, whereas 4672 received non–ABC-containing regimen. Eighty-two percent were male, and the median age was 37 years at the time of enrollment into the source studies. Where ethnicity data were available (n = 13,898), 58% were white, 24% black, and 14% of American Hispanic origin. Ten percent had a prior AIDS diagnosis. Baseline demographics and HIV disease characteristics of subjects exposed to ABC- and non–ABC-containing CART were similar. Ten-year CVD risk at baseline as measured by Framingham risk score was not calculated because not all components of the Framingham equation were collected. However, available baseline lipid profiles and glucose were comparable between the 2 groups and did not change substantially during follow-up (Table 1).

Subject Exposure to CART

The median number of days on study drugs without switching (ie, as treated) and on study drugs including switching (ie, subjects categorized at baseline to an ABC-containing CART potentially switching to a non–ABC-containing regimen and vice versa) is displayed in Table 2. Overall, the study duration of treatment-experienced trials is shorter compared with treatment-naive trials. However, for the subset of 12 trials randomized with respect to ABC, the duration of study drug exposure is 1 year on average for both the treatment-naive population and the treatment-experienced population (data not shown).

Incidence of CADs and MI

For the as treated summary, 23 CAD events were reported in the 9502 adult subjects receiving an ABC-containing CART [0.242%; 95% CI: 0.154 to 0.363] compared with 20 events in the 4672 subjects receiving a non–ABC-containing CART (0.428%; 95% CI: 0.262 to 0.660). There were 11 MIs in subjects receiving an ABC-containing CART (0.116%; 95% CI: 0.058 to 0.207) compared with 7 events in subjects receiving a non–ABC-containing CART (0.150%; 95% CI: 0.060 to 0.308) (Table 3). One CAD event (specifically angina pectoris) was reported in each pediatric group (n = 509; data not shown). The frequency of these events was comparable in all categories analyzed, and no higher risk for coronary or myocardial events was identified in any of the ABC-treated subgroups.

Of all CAD events, 3 were fatal (all in the ABC-exposed group). Two of these fatal events were MI and the other was coronary artery atherosclerosis.

Because the ITT switch included period comprises a longer period of follow-up, the numbers of events in this analysis are nominally higher, as would be expected, but still similar (Table 4). The most commonly reported non-MI events were angina pectoris [26 reports total (adult ITT switch included)], followed by coronary artery disease[8] and single reports of unstable angina, coronary artery occlusion (angiographic finding in patients being investigated for chest pain), myocardial ischemia, and coronary artery atherosclerosis.

Relationship Between Exposure to ABC and Development of Outcome

The rates per 1000 person-years of CAD and MI events were similar across ABC-exposed and non–ABC-exposed groups (Table 5). The CIs around the relative rate include one supporting a conclusion of no observed difference between the groups.

Close follow-up of all cases of MI was conducted. Of the 16 ABC-associated MIs, 13 were confirmed hospital diagnoses of which 7 also reported angiographic findings. Two of the remaining 3 subjects died before confirmation of the diagnosis but had subsequent autopsy proof of MI. The last subject was diagnosed with "possible" MI, but definitive proof was not provided. Of the 11 non–ABC-associated MIs, 9 were hospital-confirmed diagnoses, 5 of which included angiographic findings. Of the remaining 2, 1 had multiple episodes of unstable angina with angiographically proven coronary artery disease treated with stent placement; this person eventually died of sudden cardiac death attributed to probable MI. The final subject had advanced HIV disease and eventually died during hospitalization with a diagnosis of MI as the terminal event.

Because not all 52 studies in these summaries were randomized with respect to ABC, the potential for channeling bias by factors related to ABC and other drug exposures may be of concern; therefore, further analyses were conducted with

TABLE 1. Summary of Demographic and HIV Disease Characteristics at Baseline; Adult Subjects

	Adult Naive		Adult Experienced	
	ABC Exposed n = 5859	**No ABC n = 2406**	**ABC Exposed n = 3643**	**No ABC n = 2266**
Age at screening, n (yrs)	5858	2406	3639	2263
Median (range)	36 (17–78)	35 (18–74)	40 (18–78)	39 (18–74)
Median (IQ range)	36 (30–42)	35 (30–41)	40 (35–46)	39 (34–45)
Race, n (%)	5728	2314	3591	2265
Asian	278 (5)	85 (4)	29 (<1)	18 (<1)
Black	1677 (29)	515 (22)	764 (21)	357 (16)
American Hispanic	878 (15)	414 (18)	463 (13)	215 (9)
White	2812 (49)	1250 (54)	2305 (64)	1657 (73)
Other	83 (1)	50 (2)	30 (<1)	18 (<1)
Sex, n (%)	5858	2406	3643	2266
Male	4579 (78)	1892 (79)	3147 (86)	1933 (85)
Viral load (log_{10} copies/mL), n	5793	2397	3626	2247
Median (range)	4.8 (1.3–7.6)	4.7 (1.3–6.6)	4.2 (0.8–6.7)	4.2 (1.4–7.1)
Median (IQ range)	4.8 (4.4–5.3)	4.7 (4.2–5.1)	4.2 (3.0–5.0)	4.2 (3.9–4.9)
CD4 count (cells/mm^3), n	5819	2393	3629	2250
Median (range)	273 (0–1883)	337 (0–1729)	265 (0–2089)	295 (0–1799)
Median (IQ range)	273 (156–410)	337 (226–478)	265 (112–462)	295 (142–464)
CDC class, n (%)	5859	2406	3643	2266
A	4091 (70)	1852 (77)	1127 (31)	742 (33)
B	985 (17)	439 (18)	398 (11)	377 (17)
C	483 (8)	97 (4)	523 (14)	311 (14)
Missing	300 (5)	18 (<1)	1595 (44)	836 (37)
Cholesterol (mmol/L), n	5484	2272	2249	1808
Median (range)	4.1 (1.0–10.1)	4.2 (1.6–10.1)	4.8 (0.05–15.0)	4.6 (1.8–15.0)
Median (IQ range)	4.1 (3.5–4.8)	4.2 (3.6–4.9)	4.8 (4.0–5.6)	4.6 (3.9–5.5)
HDL (mmol/L), n	2215	172	48	24
Median (range)	0.9 (0.1–3.1)	0.9 (0.9–2.5)	1.0 (0.3–2.6)	1.1 (0.5–1.5)
Median (IQ range)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	1.0 (0.8–1.1)	1.1 (0.9–1.2)
LDL (mmol/L), n	2143	166	39	23
Median (range)	2.5 (0.1–6.3)	2.7 (0.8–6.4)	3.2 (1.0–5.5)	3.7 (1.3–5.2)
Median (IQ range)	2.5 (2.0–3.0)	2.7 (2.1–3.4)	3.2 (2.3–4.1)	3.7 (2.8–4.1)
Triglycerides (mmol/L), n	5482	2272	2234	1803
Median (range)	1.4 (0.3–28.9)	1.4 (0.2–15.5)	2.1 (0.1–38.1)	1.9 (0.4–35.3)
Median (IQ range)	1.4 (1.0–2.0)	1.4 (1.0–2.0)	2.1 (1.3–3.5)	1.9 (1.2–3.2)
Glucose (mmol/L), n	4999	2353	2201	1662
Median (range)	5.0 (1.3–27.2)	5.0 (0.9–24.1)	5.2 (2.2–26.0)	5.2 (2.1–26.2)
Median (IQ range)	5.0 (4.6–5.5)	5.0 (4.6–5.6)	5.2 (4.7–5.8)	5.2 (4.6–5.8)

Baseline laboratory parameters were reported irrespective of fasting state. High-density lipoprotein and low-density lipoprotein were not collected routinely in these clinical studies.
CDC, Centers for Disease Control and Prevention; HDL, high-density lipoprotein; IQ, interquartile; LDL, low-density lipoprotein.

12 studies of adults that randomized to ABC or control. This supporting analysis (repeating the corresponding analysis of the full data set) has fewer subjects (n = 3262 subjects) and events (n = 11 MI events) but removes one potential source of bias; the allocation of subjects to ABC-containing CART or not is random and thus both treatment regimens have the balance for CV risk factors that one would expect from randomization. As in the full analysis, these results do not show an increased incidence (rate per 1000 person-years) of MI events; rates were similar in ABC-containing vs. non–ABC-containing CART (2.1 vs. 4.1, respectively; relative risk 0.52, 95% CI: 0.2 to 1.8).

To be comprehensive in our adjudication of cases, we reviewed all fatal AEs. Based on this further review, we identified 2 deaths in which MI could not be ruled out despite an alternative diagnosis and coding otherwise. A 62-year-old male receiving fosamprenavir, ABC, and lamivudine experienced fatal cardiac failure and status asthmaticus approximately 11 months after starting study medication. A 43-year-old white male received ABC, lamivudine, and efavirenz and experienced fatal cardiac arrest with a history of atherosclerotic heart disease and methamphetamine use. The cardiac arrest occurred 120 days after starting treatment and 28 days after the last dose of ABC. This review of all fatal cases was

TABLE 2. Summary of Study Duration; Adult Subjects

	Adult Naive		Adult Experienced	
	ABC Exposed n = 5859	No ABC n = 2406	ABC Exposed n = 3642*	No ABC n = 2266
Exposure to first study regimen, as treated, in days: median (minimum, maximum)	337 (1, 1431)	339 (1, 926)	116 (1, 854)	141 (1, 915)
Duration of study, switch included, in days: median (minimum, maximum)	365 (1, 1431)	372 (1, 959)	134 (1, 1041)	186 (1, 1459)

*A complete record unavailable for 1 subject.

also undertaken independently by an external expert, and no further cases of possible MI were identified. In a sensitivity analysis of the 16 MI events plus these 2 fatal events, the resulting incidence rate in the ABC-containing arm is 2.29 per 1000 person-years (18 events of 7845 person-years). The corresponding relative rate is 0.97 (95% CI: 0.5 to 2.1), consistent with the interpretation of no increased risk observed in ABC-containing CART.

The cumulative distributions of time to onset of MI between the ABC- and non–ABC-containing CART groups by treatment group are shown (Fig. 1). There were no obvious differences between groups, nor was there any apparent higher incidence of MI for ABC during any one time period of observation. However, caution should be applied when drawing firm conclusions from this graph due to the relatively limited number of events and the study durations (usually 48 weeks).

Ongoing pharmacovigilance at GSK requires routine proactive processes for identifying safety signals and includes ongoing awareness and review of important individual cases: systematic, regular, and proactive review of aggregate safety data (including disproportionality analysis of spontaneously reported cases to detect increased frequency of reporting)[14] and systematic regular review of the literature. All relevant data sources are interrogated when evaluating safety signals, for example, external sources such as the Food and Drug Administration Adverse Events Reporting System database, clinical studies, epidemiological studies, and preclinical information. A cumulative evaluation of ischemic cardiac disorders and ABC-containing products was performed in 2006, which included an analysis of data reported from the World Health Organization Monitoring Centre in Uppsala, Sweden.[15] This was updated in 2008. Results from these reviews did not suggest that ABC was more frequently associated with ischemic cardiac disorders than other drugs in the class.

DISCUSSION

In summary, we were unable to demonstrate increased risk of MI or coronary artery disease with ABC therapy in our data set. Event rates in subjects exposed to ABC or not were similar. Our data summary was prompted by the recent finding from the D:A:D cohort that not only PIs were associated with increased risk of MI[12] but also individual NRTIs were associated with risk of MI. The D:A:D cohort is one of the largest sources of observational study data in HIV-infected patients, with 33,347 patients followed for 157,912 person-years. The study was initiated, at the request of the European Medicines Evaluation Agency, to prospectively address the role of CART in risk of MI in HIV-infected patients. Systematic adjudication

TABLE 3. CAD and MI by Subgroup and ABC Exposure

	As Treated Population Subgroup					
	Adult Naive		Adult Experienced		Total	
	ABC	No ABC	ABC	No ABC	ABC	No ABC
CAD						
As treated, n	5859	2406	3643	2266	9502	4672
Any CAD, n (%)	19 (0.324)	9 (0.374)	4 (0.110)	11 (0.485)	23 (0.242)	20 (0.428)
					95% CI: 0.154 to 0.363	95% CI: 0.262 to 0.660
Grade 3 or grade 4 or severe events, n (%)*	11 (0.188)	2 (0.083)	3 (0.082)	4 (0.177)	14 (0.147)	6 (0.128)
					95% CI: 0.081 to 0.247	95% CI: 0.047 to 0.279
Any serious events, n (%)†	13 (0.222)	4 (0.166)	1 (0.027)	5 (0.221)	14 (0.147)	9 (0.193)
					95% CI: 0.081 to 0.247	95% CI: 0.088 to 0.365
MI						
As treated, n	5859	2406	3643	2266	9502	4672
Any MI, n (%)	11 (0.188)	3 (0.125)	0	4 (0.177)	11 (0.116)	7 (0.150)
					95% CI: 0.058 to 0.207	95% CI: 0.060 to 0.308
Grade 3 or grade 4 or severe events, n (%)	9 (0.154)	0	0	3 (0.132)	9 (0.095)	3 (0.064)
					95% CI: 0.043 to 0.180	95% CI: 0.013 to 0.188

*Events graded according to the 1994 Division of AIDS Toxicity Grading Scale where grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = life threatening.
†The standard regulatory definition of SAEs, as outlined in the International Conference on Harmonisation (ICH) E2A, was used independent of severity.

TABLE 4. CADs and MI by 2 Assessment Periods

	Population Subgroup					
	Adult Naive		Adult Experienced		Total	
n	ABC 5859	No ABC 2406	ABC 3643	No ABC 2266	ABC 9502	No ABC 4672
CAD						
As treated, n (%)	19 (0.324)	9 (0.374)	4 (0.110)	11 (0.485)	23 (0.242) 95% CI: 0.154 to 0.363	20 (0.428) 95% CI: 0.262 to 0.660
ITT switch included, n (%)	27 (0.461)	11 (0.457)	5 (0.137)	15 (0.662)	32 (0.337) 95% CI: 0.230 to 0.475	26 (0.557) 95% CI: 0.364 to 0.814
MI						
As treated, n (%)	11 (0.188)	3 (0.125)	0	4 (0.177)	11 (0.116) 95% CI: 0.058 to 0.207	7 (0.150) 95% CI: 0.060 to 0.308
ITT switch included, n (%)	15 (0.256)	5 (0.208)	1 (0.027)	6 (0.265)	16 (0.168) 95% CI: 0.096 to 0.273	11 (0.235) 95% CI: 0.118 to 0.421

of MI events was conducted independent of knowledge of antiretroviral treatment history.

The finding that NRTIs may be associated with increased risk of MI was unexpected and in contrast to the original D:A:D hypothesis that thymidine analogues would contribute to the risk of MI, due to their known effects on dyslipidemia, increased risk of diabetes mellitus, increased insulin resistance, and greater intima–media thickness.[13,16–20] The previous PI finding was expected based on established effects on metabolic parameters. It is noteworthy that within the NRTI class, the effect was not observed with agents for which a plausible biologic mechanism exists. HIV infection itself and episodes of uncontrolled viral replication have been shown to be associated with CV events in the Strategies for Management of Antiretroviral Therapy (SMART) study[21]; these results were similar to those of the Staccato trial in which CD4-guided intermittent administration of CART was also associated with increased overall mortality and CV risk[22] and correlated with increased markers of inflammation, impaired thrombolysis, or endothelial dysfunction.[23] Because it is well accepted[24] that a particular care is needed when interpreting observational study data because the effect of temporal factors, channeling bias, missing data, and other potential confounders such as carry over effects of prior ART can influence findings, consistency of findings from multiple independent data sources is important for quality risk–benefit assessments.

Strengths of the data set described here include its high and consistent quality, collected from studies designed to investigate the safety and efficacy of various antiretroviral agents, including ABC. Data were collected prospectively in standardized case report forms. These studies were not designed specifically to investigate differences in CADs, nor did the protocols include a diagnostic algorithm for coronary events, and so we cannot rule out the potential for differential reporting of CAD across investigative centers. However, standard and thorough collection, monitoring against source documentation, and follow-up of all SAEs were consistently undertaken. To try to standardize case ascertainment, many observational cohorts employ a formal adjudication process to review cases. Formal adjudication was not required within these clinical trials where real-time follow-up and case ascertainment were conducted. Of the 27 cases of MI reported here, 22 had a hospital-confirmed diagnosis, 2 were supported with autopsy proof, 1 included coronary artery disease with stent placement, 1 died in hospital with MI listed as a fatal event, and 1 had a possible diagnosis.

TABLE 5. Relationship Between Exposure to ABC and CAD and MI

	Overall Exposure to ABC (Adult Naive and Adult Experienced Populations)			
	Person-Years	No. Events	Rate Per 1000 Person-Years (95% CI)	Relative Rate (95% CI)
CAD				
ABC exposed	7641	26	3.40 (2.317 to 4.997)	0.559 (0.32 to 0.96)
No ABC	4267	26	6.09 (4.148 to 8.948)	—
MI				
ABC exposed	7654	16*	2.09 (1.281 to 3.412)	0.813 (0.38 to 1.75)
No ABC	4278	11	2.57 (1.424 to 4.643)	—
MI in 12 adult trials randomized with respect to ABC				
ABC exposed	1863	4†	2.15 (0.806 to 5.720)	0.523 (0.15 to 1.79)
No ABC	1706	7	4.10 (1.957 to 8.609)	—

*Includes 3 (†2) subjects who discontinued ABC before the MI event but without treatment switch information available. Otherwise, events are categorized on concurrent treatment information.

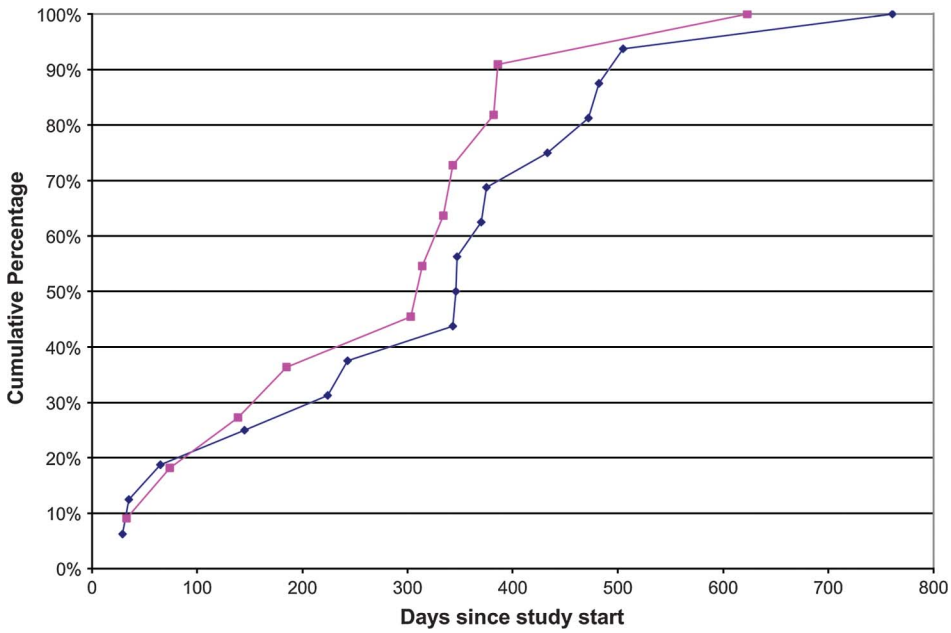

FIGURE 1. Cumulative distribution of MIs (n = 27) by days since study start. ♦ABC-containing HAART; ■non–ABC-containing HAART.

We note weaknesses of our analyses. Some but not all our studies were randomized for an ABC vs. a control. However, across all studies, baseline demographics and HIV disease characteristics including available lipid and glucose values were similar between ABC and non-ABC groups. Importantly, only total cholesterol levels were collected in the majority of these studies as shown in Table 1. The studies did not routinely collect baseline information on all CV risk factors and thus, unlike D:A:D, did not adjust for the confounding effects of these variables in the analysis. We also did not adjust for other concurrent ARTs as a covariate. Due to the relatively small number of events, a full statistical analysis exploring the impact of other covariates was not performed, and this represents a limitation to our analysis. However, the analysis repeated with the 12 adult studies that were randomized with respect to ABC showed results consistent with the overall analysis. The control agents in these trials included placebo with background therapy (n = 439, 13%), zidovudine (not shown to be associated with MI in D:A:D, n = 649, 20%), atazanavir (generally accepted as having a favorable lipid profile and a low CV risk, n = 278, 9%), nelfinavir (associated with a more favorable lipid profile than ritonavir-boosted PIs, n = 438, 13%), and unboosted indinavir (associated with a more favorable lipid profile than ritonavir-boosted PIs but also with altered glucose tolerance and therefore may increase CV risk in the long term, n = 855, 26%); 1 trial compared ABC + amprenavir with nelfinavir (n = 301, 9%), and 2 trials in patients stable on PI therapy compared a randomized continuation of the PI or a switch to ABC (n = 302, 9%). These last 2 trials resulted in improvements in lipid profiles and may have reduced CV risk for patients switching to ABC. Of 3262 subjects from the 12 randomized clinical trials (RCTs), 57% came from studies with a control group containing a PI, 25% came from studies in which neither treatment contained a PI, and 18% came from studies in which both treatments contained (or could have contained in the background) a PI. The control agents in these trials would therefore be unlikely to underestimate the relative risk of ABC vs. control. We cannot rule out, however, a confounding effect of PI therapy in the control arms of these studies.

Even with >14,000 subjects in the integrated trial data, the power to detect a doubling of risk is low because of the low frequency of MIs. A 2-group χ^2 test with a 0.05 2-sided significance level will have approximately 50% power to detect a doubling of risk from the control group. This assumes an event rate of 2 per 1000 compared with 4 per 1000 (odds ratio of 1.908) when the sample sizes are 5000 (control group) and 9600 (ABC group), respectively. The sample size of a randomized, controlled, clinical trial adequately powered at 80% comparing incidence of MIs as assumed above would be prohibitive.

Nonetheless, we found a relative rate for MI of 0.81 with a 95% CI of 0.38 to 1.75 (and 0.52 with 0.15 to 1.75 95% CI for the 12 trials randomized with respect to ABC), whereas D:A:D found a relative rate of 1.90 with a 95% CI of 1.47 to 2.45. The CIs from the 2 data sets have very little overlap and thus are suggestive of inconsistent findings. The reasons for this inconsistency are not clear, particularly, as the MI rates observed in the non–ABC-containing groups in each data set were similar. It is also not clear which result more accurately reflects the true influence of ABC on the risk of MI. Clinical trial patients may differ from subjects in observational cohorts. Furthermore, GSK clinical trials were generally performed with 24- and 48-week follow-up, whereas follow-up in the D:A:D cohort was typically longer. At this point in time, the interpretation is inconclusive and would benefit from further study.

Identification of risk factors in observational databases can be an important hypothesis-generating research but cannot establish causality, which typically includes proof of

a plausible biologic mechanism. The D:A:D finding was unexpected, and the nature of the observed association between ABC and the risk of MI is unknown. In GSK's preclinical pharmacology studies, there was no evidence that ABC caused significant effects on the CV system in mouse, rat, or dog. There were no off-target effects in receptor binding studies, including cholinergic, adrenergic, histaminergic, and serotonergic receptors. Furthermore, no effect was seen in tissue responsiveness to arachidonic acid, bradykinin, or angiotensin II. In rat and mouse carcinogenicity studies, there were increases in the severity and incidence of myocardial degeneration, attributed to slight exacerbation of high background incidence in a progressive age-related degenerative effect normally seen in aging animals. In repeat dose studies in rats, myocardial changes were of low severity and incidence, making their relationship to treatment questionable. Mild focal lesions of myocardial degeneration, necrosis, inflammation, and fibrosis are a common finding in the hearts of aging rats. There were no vascular changes and associated ischemia observed in repeat dose studies in either rodent or nonrodent species. In studies designed to determine the level of biotransformation of ABC to carbovir in rats and monkeys, there were no signs of cardiac toxicity at doses of ABC up to 500 $mg \cdot kg^{-1} \cdot d^{-1}$ for 30 days. The active metabolite of ABC, carbovir, has been associated with cardiac fibrosis in short-term studies in rodents,[25] and this metabolite is formed at very low concentrations (0.4%–1.2% of the ABC levels in rats and monkeys). For comparison, after a 600-mg single dose of ABC in humans (n = 8), the mean area under the curve ratio of carbovir to ABC was 5.3%. Myocardial degeneration or fibrosis would more likely lead to progressive congestive heart failure rather than myocardial ischemia and MI that is associated with coronary artery disease. The preclinical profile of ABC therefore does not suggest any direct mechanism by which ABC would increase the incidence of ischemic heart disease and MI in humans.

Clinical data, moreover, indicate that an increase in CV risk due to ABC-induced effects on established risk factors for coronary heart disease such as cholesterol (both total and low-density lipoprotein fraction), triglycerides, glucose, or insulin resistance is unlikely. The results from several clinical studies prospectively comparing an ABC-containing regimen with other non–ABC-containing regimens in antiretroviral-naive subjects indicate that ABC has at most minimal effect on serum lipids, blood glucose, circulating insulin levels, or insulin resistance.[26–31] Furthermore, in studies where ABC was substituted for PIs in subjects with PI-associated hyperlipidemia, significant improvement in lipid profiles was observed.[32,33] Overall, the limited metabolic impact of ABC led to it being specifically cited as a replacement option in treatment guidelines when ART modification was required for prevention of CVD.[34]

In summary, NRTIs currently constitute the cornerstone of CART with ABC recognized as a key component and recommended in a number of treatment guidelines.[34,35] The recent D:A:D data suggest that recent ABC use may be associated with an increased risk of MI; this finding was not replicated in the GSK trials' aggregate data set. Whether ABC has a role in coronary heart disease risk needs further clarification and understanding; however, it is clear that CART overwhelmingly provides substantial survival benefit to patients with HIV. As with all medications, physicians and patients must weigh the risks of HIV disease against the overall benefits and risks of the antiretroviral medicines available.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the statistical programming team at SRG Interesource Satellite Operations, in particular Harry Staines, Suki Pabla, Dupe Bassey, Lee Tombs, and Pinal Patel. We thank Dr. Gary Koch for his expert review of and comments on this article and Dr. Peter Kowey for his expert review of this article and independent adjudication of fatal AEs. Finally, we gratefully acknowledge the thousands of subjects who participated in the 52 clinical trials described here and the investigators involved.

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