JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0b013e31826f993c

Title: No Association of Abacavir Use with Myocardial Infarction: Findings of an FDA Meta-analysis

Authors: Xiao Ding PhD, Eugenio Andraca-Carrera PhD, Charles Cooper MD, Peter Miele MD, Cynthia Kornegay PhD, Mat Soukup, PhD, Kendall Marcus MD

Xiao Ding, Ph.D.
Office of Biostatistics/Center for Drug Evaluation and Research (CDER)/FDA
10903 New Hampshire Ave., Silver Spring, MD 20993
Email: Xiao.Ding@post.harvard.edu
Phone: 301-796-4209

Eugenio Andraca-Carrera, Ph.D.
Office of Biostatistics/CDER/FDA
10903 New Hampshire Ave., Silver Spring MD 20993
Email: Eugenio.AndracaCarrera@fda.hhs.gov
Phone: 301-796-0825

Charles K. Cooper, M.D.
Office of Translational Sciences/CDER/FDA
10903 New Hampshire Ave., Silver Spring, MD 20993
Email: Chuck.Cooper@fda.hhs.gov
Phone: 301-796-0698

Peter S. Miele, M.D.
Office of Anti-Infective Products/CDER/FDA
10903 New Hampshire Ave., Silver Spring, MD 20993
Email: Peter.Miele@fda.hhs.gov
Phone: 301-796-4046

Cynthia J. Kornegay, Ph.D.
Office of Surveillance and Epidemiology /CDER/FDA
10903 New Hampshire Ave., Silver Spring, MD 20993
Email: Cynthia.Kornegay@fda.hhs.gov
Phone: 301-796-0187

Mat Soukup, Ph.D.
Office of Biostatistics/CDER/FDA
10903 New Hampshire Ave., Silver Spring, MD 20993
Email: Mat.Soukup@fda.hhs.gov
Phone: 301-796-1005

Corresponding Author:
Kendall A. Marcus, M.D.
Office of Anti-Infective Products/CDER/FDA
10903 New Hampshire Ave., Silver Spring, MD 20993

Email: Kendall.Marcus@fda.hhs.gov
Phone: 301-796-0755
Fax: 301-796-9883

Meetings at Which Data were Presented in Part:

18th Conference on Retroviruses and Opportunistic Infections, February 27-March 2, 2011, Boston (Abstract #808)

Conflicts of Interest

None of the authors have any conflicts of interest to declare.

Role of Funding Source

No funding source was used to support any part of the planning, conduct, or manuscript preparation for the meta-analysis.

ABSTRACT

Background: Several studies have reported an association between abacavir (ABC) exposure and increased risk of myocardial infarction (MI) among HIV-infected individuals. Randomized controlled trials (RCT) and a pooled analysis by GlaxoSmithKline, however, do not support this association. To better estimate the effect of abacavir use on risk of MI, the U.S. Food and Drug Administration (FDA) conducted a trial-level meta-analysis of RCTs in which abacavir use was randomized as part of a combined antiretroviral regimen.

Methods: From a literature search conducted among four databases, 26 RCTs were selected that met the following criteria: conducted in adults, sample size greater than 50 subjects, status completed, not a pharmacokinetic trial, and not conducted in Africa. The Mantel-Haenszel method, with risk difference and 95% confidence interval, was used for the primary analysis, along with additional alternative analyses, based on FDA-requested adverse event reports of MI provided by each investigator.

Results: The 26 RCTs were conducted from 1996 to 2010, and included 9868 subjects (5028 ABC, 4840 non-ABC). Mean follow-up was 1.43 person-years in the ABC group and 1.49 person-years in the non-ABC group. Forty-six (0.47%) MI events were reported (24 [0.48%] ABC, 22 [0.46%] non-ABC), with no significant difference noted between the two groups (risk difference 0.008% with 95% CI [-0.26%, 0.27%]).

Conclusions: To the best of our knowledge, our study represents the largest trial-level meta-analysis to date of clinical trials in which abacavir use was randomized. Our analysis found no association between ABC use and MI risk.

Keywords: abacavir, myocardial infarction, antiretroviral therapy, meta-analysis

Introduction

Combination antiretroviral therapy (cART) has dramatically decreased the morbidity and mortality associated with HIV infection and has led to prolonged survival overall.[1] As a result of declines in AIDS-related mortality, as well as the increasing age of the HIV-infected population, non-AIDS causes of death such as cardiovascular disease (CVD), viral hepatitis, and malignancy now account for the majority of deaths among HIV-infected persons receiving cART.[2,3] While traditional cardiovascular risk factors contribute to MI risk in HIV-infected persons as in the general population, the risk of myocardial infarction (MI) in HIV-infected persons on cART appears to be significantly higher.[4-6] Both HIV infection itself and cART may contribute independently to this increased cardiovascular risk.[7]

Data collection of Adverse events of Anti-HIV Drugs (D:A:D) study, a large, prospective, observational study with an international cohort of 33,347 HIV-1-infected individuals, was initiated to explore the association between cART and risk of MI. The D:A:D study has reported a 26% increase in the relative risk of MI per year of exposure to cART in general, and a 16% increase with the protease inhibitor drug class.[8,9] Unexpectedly, the D:A:D study also reported an increased risk of MI associated with current or recent (within six months) use of abacavir (ABC) (relative risk 1.9, 95% confidence interval (CI): 1.47 to 2.45, p = 0.0001) and didanosine (relative risk 1.49, 95% CI: 1.14 to 1.95, p=0.003) after a median follow-up of 5.1 years as compared to other antiretroviral drugs.[10]

Because the D:A:D data are observational, other researchers have sought to replicate the ABC association using independent datasets. The findings have been conflicting. Several observational studies appear to support the results of the D:A:D study.[11.,12] Also, the Strategies for Management of Anti-Retroviral Therapy (SMART) trial, a randomized clinical trial (RCT) evaluating treatment strategy, found an association between ABC and increased risk of CVD.[13] On the other hand, analysis of pooled data from 52 GlaxoSmithKline (GSK) sponsored clinical trials with at least 24 weeks of cART found no excess risk of MI with ABC therapy.[14] Among the GSK sponsored trials, 36 were RCTs: 12 randomized with respect to ABC therapy, 14 randomized with respect to other antiretrovirals and used ABC as a background medication, and ten permitted ABC as a background medication or did not include ABC at all. Sixteen GSK trials were single arm trials: 13 included ABC as a component of cART and three allowed ABC as background medication. Similarly, a recent analysis of data from six RCTs of initial cART regimens in the AIDS Clinical Trials Group (ACTG) found no significant association between recent ABC use and risk of MI.[15] Since the pooled analysis of GSK data did not stratify by trial, it cannot be considered a proper meta-analysis. The ACTG pooled analysis has the important limitation that only three of the six trials included in the analysis had a randomized ABC arm.

Given the conflicting results from the observational studies, the SMART trial, and pooled analyses by GSK and ACTG, the U.S. Food and Drug Administration (FDA) set out to conduct a meta-analysis of RCTs in which ABC use was randomized as part of cART to

estimate the effect of ABC use on the risk of MI. The meta-analysis of RCTs was undertaken to reduce potential biases that may not be controlled for in analyses of observational studies and to preserve randomization within a trial which was not accounted for in the GSK and ACTG analyses.

Methods

The FDA conducted a literature search in March of 2009 for all clinical trials that included a randomized abacavir treatment arm. In the literature search, the term "abacavir" was queried in either the Subject or Title for articles about human studies utilizing three data bases: IPA, Inteleos, and Embase. GSK conducted a similar search on the Scopus database. Based upon the queries by both FDA and GSK, the literature search produced 544 non-unique references. The FDA removed duplicate articles and screened articles meeting the following pre-specified inclusion and exclusion criteria:

1. Include parallel-arm, randomized trials where abacavir treatment was randomized.
2. Exclude pharmacokinetic trials.
3. Exclude pediatric trials.
4. Exclude trials with fewer than 50 subjects.
5. Exclude prematurely terminated or unfinished trials.
6. Exclude trials conducted in Africa.

Trials with fewer than 50 subjects randomized to abacavir were generally pharmacokinetic, Phase 1 or Phase 2 studies. Terminated or unfinished trials were excluded from the meta-analysis due to the difficulty of obtaining data and possible poor or incomplete adverse event records. Trials conducted in Africa were excluded because of differing cardiovascular risks, comorbidities, and access to care in that subject population.

After removing duplicates, 47 unique articles met the inclusion and exclusion criteria for trial selection. Thirty-four of the 47 articles referenced at least one of the five ACTG trials or 16 GSK trials. The remaining 13 articles referenced 11 trials conducted by academic centers. The FDA review team contacted GSK and the investigators responsible for these trials to assess their relevance to this meta-analysis and to request subject level data. A standardized data request was sent to the owners of these datasets.

MI was the pre-specified endpoint of interest. While all available subject level data was obtained for the majority of clinical trials, the FDA was able to obtain only subject level data for adverse event reports of MI for five trials. For trials in which the FDA was not able to obtain additional subject level data, summary level data, such as treatment arm, demographics and baseline characteristics, were requested from each sponsor/investigator in order to obtain consistent trial level information.

All reported MI events were included in this analysis. Events were reported by trial investigators, but were not adjudicated by FDA due to lack of access to additional subject level data for laboratory values, electrocardiograms, patient narratives, and medical

records. As such, we were not able to independently determine the number of MI events for each trial.

Statistical analysis methods were specified in advance and documented in a statistical analysis plan (SAP). The primary analysis method was Mantel-Haenszel (M-H) risk difference and the associated 95% confidence interval. This method used all trials, including trials with no MI events. For trials with more than two arms, arms that were part of the same comparison group (abacavir versus non-abacavir) were combined. Calculation of the Mantel-Haenszel odds ratio and associated 95% confidence interval was also planned; this method only used trials with at least one event of interest. Additional alternative analysis were planned to assess the robustness of the results, including a random effects model and exact approaches.

Results

As shown in Figure 1, a total of 26 randomized controlled clinical trials were included in the meta-analysis. These trials are listed in Table 2. The FDA procured subject level data from all 16 GSK trials and five academic trials, but was unable to get any data for six other academic trials, as shown in Table 1. The five ACTG trials provided trial level data following the FDA data request. Within this 26 trial data base, 5028 subjects were randomized to ABC-containing cART regimens and 4840 subjects were randomized to non-ABC cART regimens. The mean follow-up for the 26 trials was 719 person-years with a minimum of 42.2 person-years and a maximum of 1257.3 person-years. This resulted in an average duration of follow-up of 1.62 person-years for each subject with a minimum of 0.49 person-years per subject (COL30305) and a maximum of 4.72 person-years per subject (ACTG 372A).

Baseline subject characteristics were not provided to the FDA for any of the 26 trials. If available, these data were obtained from publications. Table 3 depicts a summary of baseline subject characteristics grouped by trial sponsor (GSK, ACTG, other academic). As shown in the table, important baseline covariates including gender, age, body mass index (BMI), CD4 count, and HIV viral load are comparable between the ABC group and the non-ABC group.

Of the 9868 subjects included in the analysis, a total of 46 (0.47%) MI events were reported, including 24 (0.48%) MI events from subjects randomized to an ABC-containing regimen and 22 (0.46%) MI events from subjects randomized to a non-ABC regimen. Table 4 depicts a summary of overall results as well as results by trial sponsor (GSK, ACTG, other academic). Overall, no statistically significant difference in MI events was detected between subjects receiving ABC-containing regimens and non-ABC regimens: risk difference=0.008% with a 95% CI of (-0.26%, 0.27%) and a corresponding odds ratio of 1.02 with 95% CI (0.56, 1.84). Separate analyses by the trial sponsors (GSK, ACTG, and other academic) also did not show statistically significant difference in the MI risk between the ABC-treated subjects and the non-ABC treated subjects. Figure 2 depicts a forest plot of the 26 trials sorted by average duration of follow-up (longest duration at the top to shortest duration at the bottom). No trends regarding total person-years of follow-up were seen in the meta-analysis. No single trial

showed a statistically significant increased risk of developing MI between subjects treated with ABC and subjects treated with non-ABC regimens.

Alternative Analyses

In the previous section, results based on Mantel-Haenszel (M-H) risk difference and Mantel-Haenszel odds ratio are presented. The M-H risk difference method uses information from all the trials, including those with zero events; in contrast, the M-H odds ratio method excludes trials without events.

Based on the exact and efficient inference procedure, the risk difference between ABC-containing regimen and non-ABC regimen is 0.03%, with a 95% CI of (-0.44%, 0.50%).[27] This result is consistent with the primary result based on the M-H risk difference. This method also utilizes data from trials with zero events. Similar to many exact approaches, this exact risk difference tends to provide conservative confidence intervals.

In the pre-specified statistical analysis plan, fixed effect models were chosen over a random effect model because of the small number of events expected. In order to evaluate the heterogeneity in the data, the Cochran's Q statistic and the I^2 statistic were calculated based on all the trials with at least one event. The Q statistic was 20.51 and the corresponding p-value for test of heterogeneity was 0.75, suggesting that no statistically significant heterogeneity was found. Similarly, the I^2 statistic was 0.17, suggesting that only 17% of the between-trial variation was due to heterogeneity rather than to random chance. Therefore, the choice of fixed effects model is appropriate in this meta-analysis. However, a random effects model that incorporates trials with zero events, the modified D-L method, yielded a risk difference of 0.0003% with a 95% CI of (-0.26%, 0.26%).[28, 29] The result is very similar to the primary results based on a fixed effect model (the M-H risk difference).

Stratified odds ratios based on the exact method and the Peto method were also conducted as alternative analyses. The stratified odds ratio based on the exact method was 1.02 with 95% CI (0.54, 1.92), and the Peto stratified odds ratio was 1.02 with 95% CI (0.56, 1.83). These results are consistent with the primary analysis based on the Mantel-Haenszel odds ratio. Note that trials with zero events do not contribute to any of the analyses based on odds ratios.

Duration of Follow-up

If a differential duration of follow-up were to exist between the ABC and non-ABC groups (for example, ABC subjects might have tended to drop out of a trial earlier than non-ABC subjects), the results of this meta-analysis might be biased. As shown in Table 5, for all 21 trials with available information, the average duration of follow-up was similar between the ABC and the non-ABC groups. Overall, the average duration of follow-up was 1.43 years for the ABC group and 1.49 years for the non-ABC group.

As shown in Table 5, the duration of follow-up was well balanced between the ABC and non-ABC groups within each trial. The duration, however, varied noticeably across the different trials. The interpretation of the risk difference in a trial-level meta-analysis is challenging when trials have different durations. In our meta-analysis, though, results were consistent regardless of the measure of risk; i.e., the risk difference or odds ratio.

Discussion

Recent observational studies have suggested increase in risk of MI for patients with current or recent exposure to abacavir. Because residual confounding is not completely controllable in observational studies and because of concerns of multiple testing, we conducted a meta-analysis with a pre-specified primary endpoint and statistical analysis plan of prospective, controlled trials in which abacavir use was randomized and in which MI risk was moderate (0.45%).

Through a process of literature search, trial identification, and data acquisition, the FDA conducted a meta-analysis based on 26 RCTs in which ABC was randomized as part of cART to estimate the effect of ABC use on MI risk. We originally intended to obtain subject level data for each trial in order to conduct a subject level meta-analysis that utilized a consistent definition of MI, as this would provide a greater level of evidence than a trial-level meta-analysis. However, subject level data were not procured for the five ACTG trials, thereby not allowing a subject level meta-analysis. Realizing that a trial level meta-analysis has some limitations as discussed below, we felt that obtaining key trial characteristics, such as a pre-specification of the primary safety endpoint, MI, and a statistical analysis plan, would provide meaningful information for the research question of interest.

Based upon our trial-level meta-analysis, no statistically significant association between the use of ABC and increased risk of developing MI was found. The Mantel-Haenszel risk difference between ABC-containing cART regimens and non-ABC cART regimens was 0.008% with a 95% CI of (-0.26%, 0.27%). The Mantel-Haenszel odds ratio of ABC compared with non-ABC was 1.02 with a 95% CI of (0.56, 1.84). These results were robust to various alternative analyses.

The major strengths of our meta-analysis are the minimization or elimination of confounding and selection bias through maintaining the abacavir randomization within each trial and preserving the study level randomization. In addition, our analysis was based upon the pre-specification of a single hypothesis that does not have the weakness of multiple testing associated with it.

One weakness in our analysis is that MI events were not adjudicated and were reported as part of adverse event reporting in clinical trials. In our analysis, MI was based upon an FDA request to the trial sponsor/investigator and not on events reported in the literature. In addition, protocols were provided for the majority of studies to confirm event ascertainment similarities. While such steps were meant to limit errors in event

ascertainment, absent a consistent and thorough adjudication process from all trials we were left to rely on event ascertainment as reported by trial investigators.

Another weakness of our meta-analysis is that it is based upon trial level information and not subject level information because we were not able to procure the subject level data for all trials included in our meta-analysis. A subject level analysis with adjudicated event ascertainment would be considered the highest standard in the assessment of MI risk with abacavir use. This would allow, for example, an assessment of the timing of events, assessments of data quality, application of consistent methods for event determination, and assessments of informative censoring. Given these limitations, it is still worth noting that discontinuation rates were low overall in these HIV trials, minimizing the possible effects of informative censoring.

One potential limitation associated with the use of clinical trial data relates to the possibility that subjects enrolled in these clinical trials may be at decreased risk of MI relative to the general population due to various exclusion criteria. This could lessen the likelihood of finding a positive association with MI. However, recent observational studies involving French and Kaiser-Permanente health record databases demonstrate a risk of MI amongst HIV-infected patients that is similar to that seen in our study.[30, 31] Furthermore, in the D:A:D study, the relative risk for MI was constant within all risk groups with current use of abacavir. If this is true, our study's ability to identify a risk difference observed between abacavir and non-abacavir randomized subjects should not have been impacted by the particular magnitude of MI risk inherent to the subjects in our study. While several limitations are noted with our trial-level meta-analysis, to our knowledge this represents the largest trial-level meta-analysis to date of clinical trials in which abacavir use was randomized. When taken together with the results from other publications, our meta-analysis raises questions about an association between MI and ABC use, re-affirming that a clear determination of MI risk remains uncertain. For a more certain understanding of the cardiovascular safety profile of abacavir use, an appropriately powered randomized clinical trial with a pre-specified analysis plan and adjudicated primary CVD endpoints would need to be conducted.

References

1 The CASCADE Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. *Lancet.* 2000; 355: 1158–9.

2 Mocroft A, Brettle R, Kirk O, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. *AIDS.* 2002; 16:1663–71.

3 Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol.* 2005; 34:121–30.

4 D:A:D Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med.* 2003;349:1993–2003.

5 Triant V, Lee H, Hadigan C, et al. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab.* 2007; 92:2506–12.

6 Currier J, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2003; 33:506–12.

7 Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. Results from the DAD Study. *AIDS.* 2003; 17: 1179–93.

8 Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med.* 2003; 349: 1993–2003.

9 The D:A:D Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med.* 2007; 356:1723–35.

10 Sabin C, Worm S, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the DAD Study: a multi-cohort collaboration. *Lancet.* 2008; 371: 1417–26.

11 Obel N, Farkas D, 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.

12 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.

13 Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS.* 2008; 22:F17-24.

14 Brothers C, Hernandez J, Cutrell A, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr.* 2009; 51:20–8.

15 Ribaudo H, Benson C, Zheng Y, Koletar S,et al, ACTG A5001/ALLRT Protocol Team. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis.* 2011; 52:929-40.

16 Podzamczer D, Ferrer E, Sanchez P, et al, ABCDE (Abacavir vs. d4T (stavudine) plus efavirenz) Study Team. Less lipoatrophy and better lipid profile with abacavir as compared to stavudine: 96-week results of a randomized study. *J Acquir Immune Defic Syndr.* 2007; 44:139-47.

17 Martinez E, Arnaiz JA, Podzamczer D, et al, Nevirapine, Efavirenz, and Abacavir (NEFA) Study Team. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med.* 2003; 349: 1036-46.

18 Martin A, Bloch M, Amin J, et al, STEAL Study Group. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96 week trial. *Clin Infect Dis.* 2009; 49:1591-1601.

19 MacArthur R, Novak R, Peng G, et al, Community Programs for Clinical Research on AIDS (CPCRA) 058 Study Team. A comparison of three highly active antiretroviral treatment strategies consisting of non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or both in the presence of nucleoside reverse transcriptase inhibitors as initial therapy (CPCRA 058 First Study): a long-term randomized trial. *Lancet.* 2006; 368: 2125-35.

20 Martinez E, Arranz JA, Podzamczer D, et al, BICOMBO Study Team. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. *J Acquir Immune Defic Syndr.* 2009; 51: 290-7.

21 García-Benayas T, Blanco F, Alcolea A, et al. Short communication: benefits in the lipid profile after substitution of abacavir for stavudine: a 48-week prospective study. *AIDS Res Hum Retroviruses.* 2004; 20: 1289-92.

22 Moyle G, Sabin C, Cartledge J, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. *AIDS.* 2006; 20: 2043-50.

23 clinicaltrials.gov

24 Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection. *J Infect Dis.* 2002; 185: 1251-60.

25 Carr A, Workman C, Smith D, et al. Abacavir substitution for nucleoside analogs in patient with HIV lipoatrophy: a randomized trial. *JAMA.* 2002; 288: 207-15.

26 Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003; 17:2045-52.

27 Tain L, Cai T, Pfeffer M, et al. Exact and efficient inference procedure for meta-analysis and its application to the analysis of independent 2x2 tables

with all available data but without artificial continuity correction. *Biostatistics.* 2009; 10: 275–81.

28 Emerson J, Hoaglin D, Mosteller F. Simple robust procedures for combining risk differences in sets of 2×2 tables. *Stat Med.* 1997; 15: 1465-88.

29 Laird N, Fitzmaurice G, Ding X. Comments on 'Empirical vs natural weighting in random effects meta-analysis'. *Stat Med.* 2010; 29: 1266-7.

30 Klein D, Leyden W, Xu L, et al. Contribution of immunodeficiency to CHD: Cohort study of HIV+ and HIV- Kaiser Permanente members. Presented at: 18th Conference on Retroviruses and Opportunistic Infections; 2011; Boston.

31 Lang, S, Mary-Krause, M, et al. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. AIDS: 15 May 2010 – Volume 24 – Issue 8, pp 1228-1230.

Figure Legends

Figure 1: Flow Diagram of Trial Selection

Figure 2: Forest Plot of Meta-Analysis Results

Trials sorted based on person-years of follow-up, longest duration on top to shortest duration on bottom.

Table 1: Summary of Trials Conducted by Academic or Research Centers

Trial Name or description	Included in FDA meta-analysis	Total subjects randomized
ABCDE[16]	Yes	237
NEFA[17]	Yes	460
STEAL[18]	Yes	357
ABC-randomized substudy of CPCRA 058 (FIRST)[19]	Yes	182
BICOMBO[20]	Yes	333
ABC for d4T switch study[21]	No	112
RAVE[22]	No	105
Gilead NCT00270556[23]	No	105
Swiss HIV Cohort Study[24]	No	163
MITOX[25]	No	111
Treatment naïve strategy study[26]	No	180

ABCDE: Abacavir vs. d4T (stavudine) plus Efavirenz; NEFA: Nevirapine, Efavirenz and Abacavir; STEAL: Simplification of antiretroviral therapy with Tenofovir-Emtricitabine or Abacavir-Lamivudine; CPCRA: Community Programs for Clinical Research on AIDS; FIRST: Flexible Initial Retrovirus Suppressive Therapies; RAVE: Randomized Abacavir Viread Evaluation; MITOX: Mitochondrial Toxicity

Table 2: Summary of All 26 Trials Included in the Meta-analysis

Source	Trial Name	Total number randomized to ABC arm	Total number randomized to Non-ABC arm	Total follow-up (person-years)	Average follow-up (person-years)
GSK submitted data	CNA109586	192	193	354.8	0.92
	CNA30017	80	127	209.7	1.01
	CNA30024	324	325	766.4	1.18
	CNAA3006	102	103	215.8	1.05
	CNAB3001	49	50	75.4	0.76
	CNAB3002	91	93	199.9	1.09
	CNAB3014	165	164	306.7	0.93
	CNAC3003	156	80	402.4	1.71
	CNAC3005	262	264	701.3	1.33
	CNAF3007	96	91	176.4	0.94
	COL30305	58	29	42.2	0.49
	EPZ104057	343	345	1078.3	1.57
	ESS100327	137	141	239.5	0.86
	ESS40002	85	166	349.1	1.39
	ESS40003	51	44	50.9	0.54
	NZTA4002	150	152	319.3	1.06
ACTG data	ACTG 368	140	143	548	1.94
	ACTG 372A	116	113	1082	4.72
	ACTG 5095	758	376	3016	2.66
	ACTG A5110	48	53	107	1.06
	ACTG A5202	923	925	4779	2.59
Other sources	STEAL	178	175	647.2	1.83
	BICOMBO	167	166	540	1.62
	FIRST	93	89	812.7	4.47
	NEFA	149	311	1257.3	2.73
	ABCDE	115	122	418	1.76
	Total	**5028**	**4840**	**18695.3**	**1.62**

GSK: GlaxoSmithKline; ACTG: AIDS Clinical Trials Group

Table 3: Comparison of Baseline Subject Characteristics

	GSK		ACTG[1]		Other[2]	
	ABC	Non-ABC	ABC	Non-ABC	ABC	Non-ABC
N	2341	2367	1985	1610	702	863
Gender (% male)	78%	76%	81%	83%	82%	66%
Age[*]	36 (11.3)	37 (11.2)	38	39	42 (10)	42 (10)
BMI[* 3]	24.3 (7.0)	24.4 (7.8)	-	-	24.1 (4.5)	24.3 (4.1)
CD4 count[* 4]	360 (280)	360 (300)	237	235	255 (276)	250 (279)
Log viral load[* 5]	4.38 (1.08)	4.38 (1.08)	4.72	4.7	5.03 (0.73)	4.94 (0.71)

*Mean (SD), [1] Characteristics approximated from trial-level summaries, [2] other non-ACTG academic sources. [3]BMI not available for NEFA and BICOMBO, [4]CD4 count not available for NEFA, [5] Viral load not available for NEFA, STEAL and BICOMBO.

Table 4: Trial Level Analysis Results

Studies	Events / Subjects ABC	Non-ABC	RD (95% CI)[1]	OR (95% CI)[2]
Overall	24/5028	22/4840	0·008% (-0.26%, 0.27%)	1.02 (0.56, 1.84)
GSK	6/2341	9/2367	-0·11% (-0.43%, 0.21%)	0.70 (0.25, 2.00)
ACTG	12/1985	9/1610	0·03% (-0.45%, 0.51%)	1.06 (0.43, 2.61)
Other[3]	6/702	4/863	0·31% (-0.53%, 1.16%)	1.60 (0.46, 5.62)

[1] Mantel-Haenszel Risk Difference
[2] Mantel-Haenszel Odds Ratio
[3]Other non-ACTG academic sources

Table 5: Comparison of Average Duration of Follow-up between Groups by Trial

Source	Trial Name	Total number randomized to ABC group	Total number randomized to Non-ABC group	Average Follow-up in ABC arm (year)	Average Follow-up in Non-ABC arm (year)
GSK	CNA109586	192	193	0.875	0.968
	CNA30017	80	127	1.019	1.009
	CNA30024	324	325	1.206	1.156
	CNAA3006	102	103	1.025	1.081
	CNAB3001	49	50	0.732	0.79
	CNAB3002	91	93	1.076	1.097
	CNAB3014	165	164	0.955	0.910
	CNAC3003	156	80	1.659	1.795
	CNAC3005	262	264	1.337	1.329
	CNAF3007	96	91	0.956	0.930
	COL30305	58	29	0.469	0.517
	EPZ104057	343	345	1.605	1.530
	ESS100327	137	141	0.874	0.849
	ESS40002	85	166	1.409	1.381
	ESS40003	51	44	0.504	0.570
	NZTA4002	150	152	0.964	1.15
Other sources	STEAL	178	175	1.822	1.845
	BICOMBO	167	166	1.589	1.654
	FIRST	93	89	4.510	4.420
	NEFA	149	311	2.766	2.718
	ABCDE	115	122	1.765	1.762
	Total	**3043**	**3230**	**1.429**	**1.491**

Figure 1: Flow Diagram of Trial Selection