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Risk of cardiovascular disease associated with exposure to abacavir among individuals with HIV: A systematic review and meta-analyses of results from 17 epidemiologic studies

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Abstract

Objectives: Abacavir's potential to cause cardiovascular disease (CVD) among people living with HIV (PLWH) is debated. We conduct a systematic review and meta-analyses to assess CVD risk from recent and cumulative abacavir exposure.

Methods: We searched Medline, Embase, Web of Science, abstracts from Conference on Retroviruses and Opportunistic Infections, and International AIDS Society/AIDS Conferences and bibliographies of review articles to identify research studies published through 2018 on CVD risk associated with abacavir exposure among PLWH. Studies assessing risk of CVD associated with recent (exposure within last 6 months) or cumulative abacavir exposure across all age-groups were eligible. Risks were quantified using fixed- and random-effects models.

Results: Of 378 unique citations, 68 full-text research articles and abstracts were reviewed. Seventeen studies assessed risk of CVD from recent or cumulative abacavir exposure. Summary relative risk (sRR) is increased for recent exposure (n=16 studies, sRR=1.61; 95% confidence interval: 1.48–1.75), higher in antiretroviral-therapy-naive population (n=5, 1.91; 1.48–2.46) and

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Declarations

None.

Competing Interests

None.

Ethical Approval

This study received ethical approval from the University of California, Berkeley Office of Protection of Human Subjects.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.07.010.

all studies reported RR> 1. The sRR for recent exposure was similarly increased for the outcome of acute myocardial infarction, and for studies that adjusted for substance abuse, smoking, prior CVD, traditional CVD risk factors, and CD4 cell-count/HIV viral load. The sRR was increased for cumulative abacavir exposure (per year) (n=4, 1.12; 1.05–1.20) but no increase was seen after adjusting for recent exposure (n=5, 1.00; 0.93–1.08).

Conclusions: Our findings suggest an increased risk of CVD from recent abacavir exposure. The risk remained elevated after adjusting for potential confounders. Further investigations are needed to understand CVD risk from cumulative exposure.

Keywords

Abacavir; Human immunodeficiency virus; Cardiovascular disease

1. Introduction

In 2008, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study groups first reported that abacavir use is associated with an increased risk of acute myocardial infarction (AMI) among people living with HIV (PLWH) [1]. Subsequent studies conducted to investigate this risk have yielded conflicting results [2–10]. Although most recent studies have shown an increased risk of cardiovascular disease (CVD) associated with use of abacavir, many of the results did not reach statistical significance [3,11–14]. The studies that assessed the risk of CVD associated with exposure to abacavir were mostly observational, and there is a possibility that the study results are confounded and biased. For instance, PLWH may be preferentially prescribed abacavir or tenofovir based on the presence or absence of risk factors for CVD (i.e. hypertension, diabetes mellitus, renal dysfunction, dyslipidemia, and lipodystrophy), their cardiovascular safety profile, and the safety profile of companion antiretroviral (ARV) agents used. The results of epidemiologic studies also differed based on whether the study populations were antiretroviral therapy (ART) -naive or experienced, and using injection drugs. A previously conducted meta-analysis reported an increased risk of CVD exposure by pooling results across two studies and no conclusion was made on CVD risk from cumulative abacavir exposure due to inadequacy of studies [15]. Eight studies investigating the risk of CVD associated with exposure to abacavir have been published since that meta-analysis [10–14,16–18], one of which assessed the risk from specific abacavir-based ARV drug combinations. Therefore, we performed an updated systematic review and meta-analysis to summarize the relationship between recent (including current exposure) and cumulative exposure to abacavir or abacavir-based drug combinations and the risk of CVD among HIV-infected individuals. We also discuss the plausible biological mechanisms underlying the observed risk of CVD associated with exposure to abacavir. Finally, we address the biases potentially affecting the study results, the methodological challenges and inconsistencies we observed with regard to study design and analysis, and interpretation of these results.

2. Methods

2.1. Literature Search

Two authors (K.D. and T.C.) independently searched Medline, Embase, Web of Science, abstract books from the 2014–2018 Conference on Retroviruses and Opportunistic Infections (CROI) and 2014–2017 International AIDS Society (IAS) Conference and International AIDS Conference, and the bibliographies of five published reviews [15,19–22] to identify studies published through May 2018 that investigated the risk of CVD associated with exposure to abacavir. We used the keywords, ‘abacavir’, ‘cardiovascular disease’, ‘myocardial infarction’, and ‘heart disease’ for the search. PRISMA guidelines were followed in conducting the review.

2.2. Study Selection

We included randomized controlled trials (RCTs), and cohort and case-control studies, published in peer-reviewed journals or presented in conference proceedings that assessed abacavir exposure, either as an individual agent or in specific ARV drug combinations, and provided an estimate of a relative risk and variance. Outcome was defined as a new episode of CVD after the start of exposure. We required CVD to be defined as an ischemia-driven cardiac event/procedure such as AMI, angina pectoris, percutaneous coronary intervention or coronary artery bypass grafting. We included studies across all age-groups that assessed ischemic stroke as a component of the CVD definition, but excluded results that assessed only stroke as an outcome. We included conference abstracts if the data were unique (i.e. not included in the research articles chosen for the meta-analysis). We excluded from the meta-analysis studies that (1) assessed a class of ARV agents but did not specify abacavir as the exposure, (2) assessed possible risk factors for CVD including biomarkers as outcome but did not measure CVD, or (3) that reported only crude estimates and did not adjust for basic confounders, such as age. Two authors (K.D. and T.C.) independently evaluated each study and abstracted relative risk estimates. Discrepancies were resolved through open deliberation.

2.3. Data abstraction and definitions

We reviewed each study in detail and categorized them based on the type of exposure, outcome, study design, study population, data year, comparator ARV agent/group used, and adjustment for potential causal mediators and specific covariates. We performed meta-analyses of the results for the risk of CVD associated with (1) recent exposure to abacavir, defined as exposure within the last 6 months, including current exposure, and (2) cumulative exposure, defined as the accumulated sum of the total duration of exposure at pre-specified time points. CVD risk from cumulative abacavir exposure was calculated separately for models that did and did not adjust for recent exposure. We performed pertinent sub-group analyses for the risk of CVD from recent exposure. For studies that reported multiple risk estimates using marginal structural models and traditional models, we chose the marginal structural model estimates because of its potential to address channeling bias and difference in the exposure groups [23]. In a sensitivity analysis, we assessed the risk of CVD associated with recent exposure by excluding the 2008 D:A:D study that initiated the other studies.

2.4. Statistical analysis and evaluation of bias

We have calculated and reported summary estimates from both fixed- and random-effects models [24]. We assessed heterogeneity across studies using Cochran's Q-test (χ^2 P<0.10) [25] and I^2 statistics (I^2 >30%) [26]. Some believe that the random-effects model is more conservative than the fixed-effects model because it accounts for variance between studies. However, unlike the fixed- effects model, the random-effects model does not weight studies directly on precision; it assigns smaller, less precise studies greater relative weight than does the fixed-effect model. Fixed-effects model weight studies directly on precision while still incorporating between-study variance. Therefore, we used the fixed-effects model to calculate the sRRs and then adjusted their 95% confidence intervals (CIs) for between-study heterogeneity using the method described by Shore et al. [27]. Random effects model may also be used in the event of heterogeneity [28]. The calculations were performed in Microsoft Office Excel 2016 (Microsoft corporation, Redmond, WA, USA). The P-values are two-sided. We analysed publication bias using funnel plots and Begg's and Egger's test. Quality of each cohort and case-control study was assessed using the Newcastle-Ottawa assessment scales and each RCT using the PRISMA guidelines.

3. Results

We identified 377 unique articles/abstracts from the searches of Medline, Embase, Web of Science, and abstract books of 2014–2018 CROI, and 2014–2017 IAS/AIDS conferences. Of these, we reviewed the full texts of 65 research articles (Fig. 1). Seventeen studies meeting our inclusion criteria were used for the meta-analysis. Six studies assessed the risk associated with cumulative exposure to abacavir. There were 13 cohort studies, three case-control studies, and one RCT. Table 1 summarizes these studies.

3.1. Recent exposure

All 16 studies that met our inclusion criteria for recent exposure showed an increased risk of CVD from recent exposure to abacavir; 13 were statistically significant (Fig. 2). We obtained an sRR (95% Cl) of 1.61 (1.48, 1.75) for recent exposure (Table 2). We excluded the study by Bedimo et al. [2] in the above analysis because the estimate adjusted only for chronic kidney disease and not for any other variable including age and gender. In a sensitivity analysis, the risk continued to be elevated (sRR: 1.56; 95% Cl; 1.40, 1.74) when Bedimo et al.'s study was included in the meta-analysis (Table 2). In addition to reporting risk of CVD from abacavir as an individual antiretroviral agent, Desai et al. obtained the following results (hazard ratio (HR) (95% Cl)) for CVD risk from exposure to abacavir-based ARV drug combinations: abacavir + atazanavir + lamivudine: 2.08 (1.41–3.06); abacavir + efavirenz + lamivudine: 1.94 (1.34–2.79); abacavir + Iamivudine + zidovudine: 1.60 (1.21–2.11); abacavir + lamivudine + lopinavir: 1.44 (0.91–2.28); and abacavir + lamivudine + nevirapine: 1.49 (0.81–2.73) [11]. We have not included the above results of Desai et al. into our analyses because each of the abacavir-based combinations represents a unique exposure, and it would be misleading to pool the study results of specific abacavir-based drug combinations with studies that assessed abacavir's risk as an individual agent. Table 2 lists the results of our group and sub-group analyses for recent and cumulative exposure to abacavir. The summary estimate for risk of CVD associated with recent abacavir

exposure remained elevated for ART-naive populations (*n*=5 studies) (sRR: 1.91; 95% Cl: 1.48, 2.46) and for studies conducted in the pre-2008 (*n*=8; sRR:1.77; 95% Cl: 1.51, 2.07) and post-2008 periods (*n*=2; sRR: 1.53; 95% Cl: 1.14, 2.06) (Fig. 4). Meta-analysis of two studies that used tenofovir as the comparator ARV agent showed a greater risk of CVD in the abacavir groups (sRR: 2.94; 95% Cl: 0.88, 9.76) as compared to the result for all studies, but the sRR was not statistically significant (Fig. 4). The results for recent exposure in subgroup analyses based on outcome, study design, adjustment for causal intermediates, and adjustment of other specific covariates including substance abuse/HIV acquisition through injection drug use are similar to the result for all studies (Table 2, Fig. 3). In a sensitivity analysis for recent exposure, the risk remained elevated after excluding the 2008 D:A:D study (HR: 1.58; 95% Cl: 1.45, 1.72). Egger's (*P*=0.648) and Begg's (*P*=0.153) tests for publication bias were not statistically significant (funnel plot in Fig. 5). The Newcastle-Ottawa scores (highest possible score=9) for qualitative bias analyses for cohort and case-control studies ranged from 6 to 9, with a median score of 9 (Supplementary Tables S1, S2).

3.2. Cumulative exposure

Results for CVD risk from cumulative abacavir exposure have varied across studies based on whether the model was adjusted for recent exposure. We obtained an increased sRR (95% Cl) of CVD of 1.12 (1.05, 1.20) from cumulative abacavir exposure (per year) for studies that did not adjust for recent exposure and no increased risk (sRR: 1.00; 95% Cl: 0.93, 1.08) for studies that adjusted for recent exposure (Fig. 6). The D:A:D study groups reported an increased risk (RR: 1.14; 95% Cl: 1.08, 1.21) of AMI in the cumulative exposure only model but the risk normalized after adjusting for recent exposure [1]. However, Dorjee et al. recently reported that the risk of CVD from abacavir exposure followed a dose-response pattern, with the risk peaking between 13 and 24 months and leveling off thereafter, after adjusting for recent exposure [10]. Earlier, Young et al. had also reported an increased risk of AMI (HR: 1.22; 95% Cl: 0.98, 1.52) beyond 6 months from a cumulative exposure for up to 36 months after adjusting for recent exposure [16]. Findings by Dorjee et al. and Young et al. highlight the importance of continued investigation into the risk of CVD from a cumulative abacavir exposure beyond 6 months, despite a pooled estimate showing no risk for CVD after adjusting for recent exposure.

4. Discussion

We calculated a 61% increased pooled risk of CVD among PLWH who were recently exposed to abacavir. A higher summary estimate calculated for ART-naive PLWH or individuals observed to initiate ART (sRR: 1.91), that was not affected by confounding by prior ART use, may more closely estimate the causal effect from exposure to abacavir. Earlier, Bavinger et al. had also reported an increased CVD risk (HR: 1.92; 95% Cl: 1.50, 2.42) from recent abacavir exposure by pooling results across two studies; however, fewer studies were available for them to review as part of that meta-analysis. [15] Two studies had reported results using patient data post-March 2008 when the D:A:D study associating abacavir with AMI was first published; both the studies observed increased risk with a sRR of 1.53. This may refute the argument that CVD risk from abacavir exposure could be due to a channeling bias wherein PLWH having renal dysfunction, a risk factor for CVD, may have

been preferentially prescribed abacavir as compared to tenofovir, a phenomenon described as confounding by indication, which we have further discussed below. The prescription of abacavir declined after March 2008, especially among individuals with moderate to severe risk factors for CVD [13,18,29], leading to the possibility of a reverse channeling bias.

Desai et al. [11] have reported increased risk of CVD associated with three specific abacavir based ARV drug combinations: abacavir + lamivudine + atazanavir, abacavir + lamivudine + efavirenz, and abacavir + lamivudine + zidovudine. They observed different CVD risk estimates for specific drug combinations as compared to the risk calculated for the drugs individually, suggesting interaction between the drugs. While it is important to understand CVD risk from ARV drug combinations, especially as ARTs are prescribed in combinations, all the above three abacavir-based combinations contained lamivudine. Therefore, teasing apart the individual drug effects is necessary.

We noted that the results across studies for cumulative exposure to abacavir were inconsistent in terms of magnitude and direction of association. There is ongoing controversy regarding whether the CVD risk from abacavir is limited to individuals who were recently exposed in the previous 6 months and studies have reported results for cumulative exposure by including and not including a recent exposure variable in the estimating model. As such, we conducted meta-analyses for cumulative exposure risk separately for models that did and did not adjust for recent exposure. In our pooled analysis, we observed no increased risk of CVD associated with cumulative exposure after adjusting for recent exposure, i.e. no increased risk in PLWH exposed to abacavir prior to 6 months ago and not recently exposed. However, we note that recent studies by Dorjee et al. and Young et al. found an increased risk of CVD from a cumulative abacavir exposure beyond the last 6 months in an inverted U-shaped dose-response pattern after adjusting for recent exposure [10,16]. Dorjee et al. reported that CVD risk peaked between 13 and 24 months of exposure and leveled off thereafter. Such results could suggest a reversible but more gradual underlying mechanism with a longer lasting effect that regresses slowly after removal of the exposure rather than an acute underlying mechanism [10]. We note here, as was previously explained, that when a model contains both cumulative exposure and recent exposure, the parameter for cumulative exposure captures the risk only among the exposed group [15]. Additional studies are needed to better understand this relationship.

Three meta-analyses with significant overlap in the data they included, have assessed the risk of CVD using RCT data and all showed no increase in risk of CVD associated with abacavir exposure [9,30,31]. However, these studies were of limited duration, lacking in generalizability because of healthier study populations, and had low power, owing to their primary objective being to assess the efficacies of various ARV drugs, instead of measuring CVD as an outcome. Therefore, we did not include the results from these trial data in our meta-analyses. An RCT conducted by Martin et al. (STEAL trial) assessed the risk of CVD as a study outcome and reported an increased risk of CVD in the abacavir group [32]. However, it was a small RCT and lacked adequate discriminatory power to detect a difference in effects [18]. Therefore, we conducted a subgroup analysis of only the observational studies excluding the study by Martin et al.; the summary estimate did not change. Lang et al., in a case-control study using a French hospital database, reported a

significantly increased risk of AMI (HR: 1.62, 95% Cl: 0.93, 2.81) associated with exposure to abacavir; however, they did not see the effect when the study population was restricted to those not using cocaine or injection drugs (HR: 1.27, 95% Cl: 0.64, 2.49) [6]. This finding by Lang et al. was not re-produced in other studies, which continued to show an increased risk of CVD in association with abacavir exposure after adjusting for substance use [4,5,10,16,17]. A recent study conducted in the NA-ACCORD cohort by Elion et al. with robust ascertainment and adjudication of outcomes has also shown an increased risk of Type I (adjusted hazard ratio (aHR): 1.62) and Type II AMI (aHR: 2.11) associated with abacavir exposure. The risk persisted even after adjusting for injection drug use warranting screening for not just traditional CVD risk factors associated with Type I MI, but also for risk factors of type II AMI such as sepsis and illicit substance use including cocaine [17]. In our meta-analysis, the summary risk pooled from studies that adjusted for substance abuse as a confounder (n=12) remained elevated (sRR: 1.64). Elion et al. observed a statistically significant association between AMI and CD4 cell-count <200 cells/mm^3 whereas the 2008 D:A:D study found that CD4 cell-count did not influence the association between abacavir use and AMI risk. In our analysis, the summary estimate for CVD risk did not significantly change in the sub-group of studies that adjusted for CD4 cell-count.

In 2011, Bedimo et al. argued that the 2008 D:A:D study results linking abacavir exposure to AMI could be due to a channeling bias, whereby individuals having renal dysfunction were preferentially put on abacavir to avoid additional nephrotoxicity from tenofovir. In a study in a US Veteran population, they reported that renal dysfunction is a significant risk factor for AMI (HR: 3.85; 95% Cl: 2.74, 5.42) and that the HR for AMI associated with current exposure to abacavir decreased from 0.73 (P = 0.013) to 0.67 (P = 0.07) after adjusting for renal dysfunction [2]. We note that this is only a slight decrease in risk and, moreover, the model adjusted for only renal dysfunction as a covariate. The result may be less vulnerable to confounding if the model had been adjusted for additional covariates including age and gender, which are two of several important risk factors for CVD. Subsequently, the D:A:D study groups showed through separate pre- and post-March 2008 analyses that the risk of CVD continued to remain elevated (HR: 1.98; 95% Cl: 1.72–2.29) after adjusting for pertinent covariates, including chronic kidney disease (CKD) [18,29]. They demonstrated that individuals at moderate and high risk for CVD were, in fact, channeled away from abacavir use after 2008. Other studies, including two studies in the veteran population [4,11], have confirmed elevated risk of CVD associated with abacavir use after adjusting for renal dysfunction [4,5,7,10–12,16,32].

Although we observed variations across studies in terms of study designs, confounder adjustment set of confounders, statistical methods, and populations, all 16 studies (100%) that met our inclusion criteria for recent exposure reported RR>1, suggesting homogeneity in the data. We explored whether a number of factors were related to heterogeneity, including difference in study design (observational vs. interventional), outcomes assessed (AMI only vs. all CVD), study populations (ART naive vs not), year of publication (pre- vs. post-2008), comparison group (tenofovir vs. other), the extent of adjustment for potential confounding, and other factors (Table 2). Analysis of all studies combined showed moderate heterogeneity (I^2 value =44%, P-value for heterogeneity =0.03). However, when removing the study by Bedimo [2], or when limiting studies to those that only assessed AMI (vs. all

CVD combined), heterogeneity was markedly reduced (I^2 values of 0%). Heterogeneity was more marked for results from cumulative abacavir exposure. In our analyses, we combined odds ratios and rate ratios because the former approximate the latter for rare outcomes such as AMI [33]. We combined rate ratio and hazard ratio because most studies had discrete time data and the estimate from a logistic or a Poisson model for such data yielding ORs or RRs is an approximation of a hazard ratio from a Cox model [34,35]. Additionally, we thoroughly reviewed each study, and where we saw important differences between any two studies in terms of definition of exposure, study population, covariates, and outcome, we performed appropriate subgroup analyses and accordingly reported the results. Where heterogeneity *P*-values (Table 2) were <0.20, we recommend using the Shore-adjusted confidence interval for the estimate from the fixed-effects model or the estimates from the random-effects model.

4.1. Plausible biological mechanisms

The D:A:D study result showing a reversal of risk of CVD within 6 months of discontinuation of abacavir prompted investigators to search for a relatively rapidly acting underlying biological mechanism for the risk of CVD associated with abacavir exposure. While the SMART/INSIGHT study investigators, Kristoffersen et al. and Hileman et al. [8,36,37], showed evidence for a possible role of inflammatory biomarkers (e.g. increased levels of high sensitivity c-reactive protein (hsCRP) and interleukin-6 (IL-6)) in association with CVD among abacavir users, several other studies showed that levels of biomarkers such as hsCRP, IL-6, selectin P and E, D-dimer, vascular adhesion molecule-1, intercellular adhesion molecule-1, and tumor necrosis factor alpha are not elevated in the setting of abacavir exposure [38–50].

Studies that evaluated abacavir's role in causing endothelial dysfunction have also yielded mixed results [46,51,52]. Endothelial dysfunction, induced by both traditional cardiovascular risk factors and chronic inflammation [53], increases the risk of CVD by promoting atherosclerosis [54]. Hsue et al. reported that abacavir use independently predicts lower brachial artery flow mediated vasodilation, a measure of endothelial dysfunction [52]. Sinn et al. observed lower arterial stiffness and improvement in Framingham risk score when individuals on abacavir were switched to tenofovir [51]. However, in an RCT, Wohl et al. found no evidence of endothelial dysfunction from abacavir use as compared to tenofovir [46].

Baum et al., Satchell et al., and Falcinelli et al. showed that abacavir increases platelet aggregation and reactivity, that could potentially lead to thrombosis and myocardial infarction [55–57]. Satchell et al. demonstrated that among abacavir recipients, platelet aggregation increased upon exposure to various platelet agonists, such as, adenosine diphosphate (ADP), collagen, epinephrine, and thrombin receptor-activating peptide [57]. Baum et al. further showed that abacavir causes platelet hyper-reactivity by competitive inhibition of a nitric oxide-induced soluble guanylyl cyclase via its active metabolite, carbovir-triphosphate, leading to a decreased production of cyclic guanosine monophosphate, an inhibitor of platelet aggregation and secretion [53,55]. Falcinelli et al., confirmed these findings in both in vivo and ex vivo settings [56]. In an RCT, switching

from abacavir-lamivudine to tenofovir-emtricitabine resulted in decreased platelet reactivity to thrombin receptor-activating peptide (TRAP), ADP, and collagen, suggesting that the endothelial-platelet pathway may be a possible underlying mechanism for the AMI risk associated with abacavir exposure [58].

A recent review has discussed in more detail the existing literature on plausible underlying biological mechanisms [21]. The review summarizes that results from in vivo and in vitro experiments and abacavir's structural similarity to endogenous purines possessing pro-inflammatory and pro-thrombotic potential may stand to support abacavir's role as an inducer of vascular inflammation via leucocyte-endothelia cell interactions with resultant cardiovascular implications [21,59–61]. It is unclear how such mechanisms and accompanying effects, which are acute and reversible, may reconcile with recent clinical findings of CVD risk from cumulative exposure beyond 6 months [10,16]. With the literature demonstrating that abacavir does not affect lipid profile, insulin sensitivity, limb fat mass, or traditional cardiovascular risk factors [21,62,63], the search for plausible biological underpinnings continues.

Recent exposure to abacavir is associated with ~60% increased risk of CVD that was not attenuated after adjusting for substance use, renal dysfunction, and several other potential confounders. The finding of an increased risk of CVD associated with abacavir use among ART-naive individuals may be more suggestive of a causal relationship. We note that because of the observational nature of most studies in our analysis, the study results may be subject to confounding from unmeasured risk factors. While this risk appears to be reversible upon discontinuation of abacavir, further research is necessary to confirm this in view of recent studies that showed evidence of increased risk from cumulative exposure beyond 6 months.

5. Conclusion

In view of the increased risk of CVD associated with exposure to abacavir among HIV-infected individuals, risks and benefits for PLWH must be carefully weighed in prescribing abacavir-based regimens taking into account existing risk factors for CVD, a detailed history of prior exposure to ART, the patient's clinical status, and the availability of other ARV drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

Abacavir, a nucleoside reverse transcriptase inhibitor, is a backbone antiretroviral drug for people living with HIV (PLWH). Its prescription had declined after reports showed that people receiving abacavir experience increased risk of acute myocardial infarction (AMI). Most recent studies have shown that abacavir use is associated with an increased risk of AML. However, it has been strongly argued that this observed risk is due to a higher prevalence of risk factors for cardiovascular disease (CVD), such as renal dysfunction and substance abuse, among abacavir recipients. There is ongoing confusion about whether the risk of CVD is for exposure to abacavir within the recent time (~last 6 months) only or if there is cumulative risk beyond 6 months of exposure. Inability to identify an underlying biological mechanism for such a risk has added to the dilemma.

Added value of this study

To our knowledge, this is the first systematic review and meta-analyses to investigate and summarize all existing evidence to date on the CVD risk associated with recent and cumulative abacavir exposure. We found an approximately 60% increased risk of CVD from recent exposure to abacavir as compared to PLWH not receiving abacavir. We found a higher summary risk among antiretroviral therapy naive PLWH who were recently exposed to abacavir. The pooled risk remained significantly elevated after studies adjusted for risk factors of CVD including renal dysfunction and substance abuse. The risk remained similarly elevated when studies adjusted for smoking, prior CVD, CD4 cell-count, and HIV viral load. Summary risk for cumulative exposure to abacavir was elevated for studies that did not adjust for recent exposure, but no increased cumulative risk was seen when the studies adjusted for recent exposure. This may suggest a reversible acute underlying biological mechanism. However, there are fewer studies that have investigated the CVD risk from cumulative abacavir exposure and two recent studies have argued with findings that risk of CVD from abacavir exposure may persist beyond 6 months of exposure.

Implications of all the available evidence

Risk and benefits should be weighed in prescribing abacavir-based antiretroviral regimens to PLWH. Research is needed to identify a clear underlying biological mechanism that corroborates the clinical evidence. The majority of evidence on CVD risk from abacavir exposure to date is among PLWH in the high-income countries.

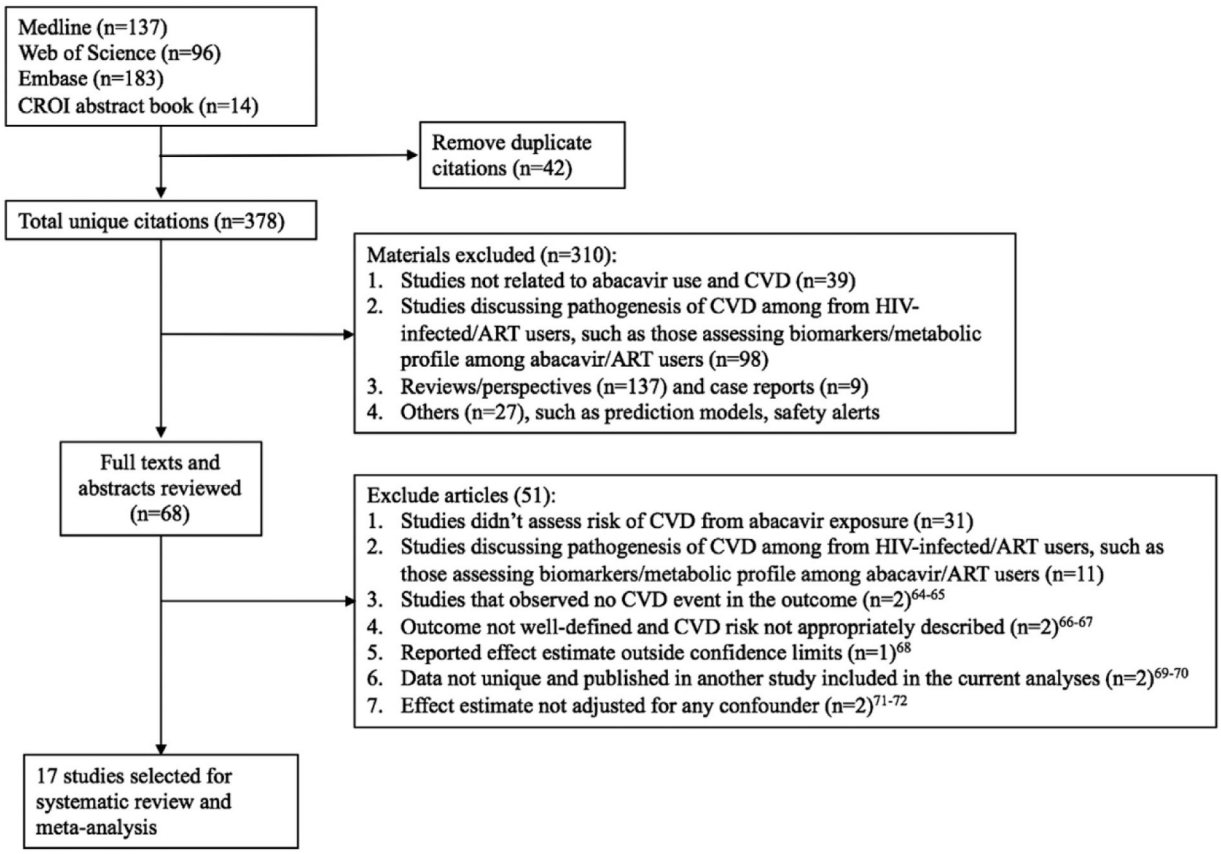

Fig. 1.

Flow diagram showing the search strategy and algorithm for identification of studies. ART, antiretroviral therapy; CVD, cardiovascular disease (See Refs. [64–72]).

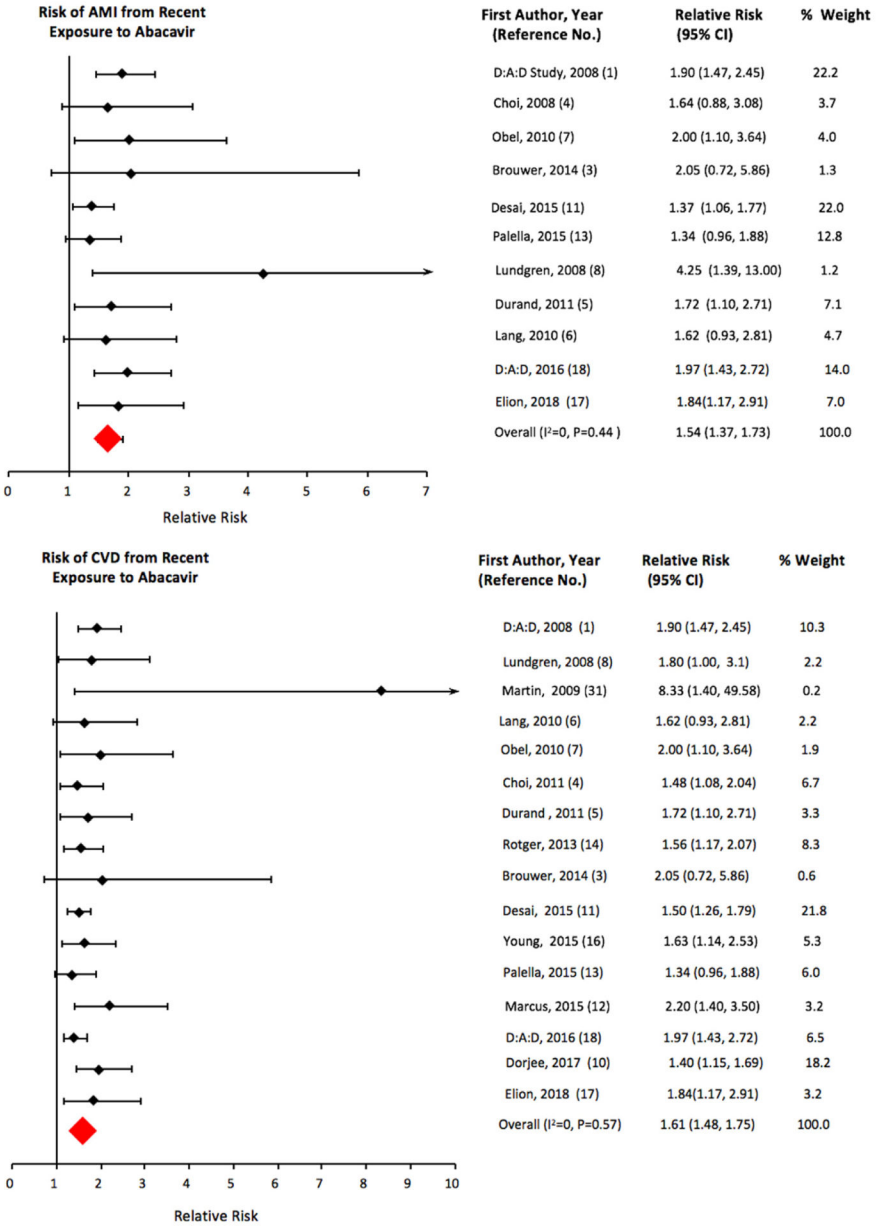

Fig. 2.

Pooled risk of cardiovascular disease and acute myocardial infarction from recent exposure to abacavir.

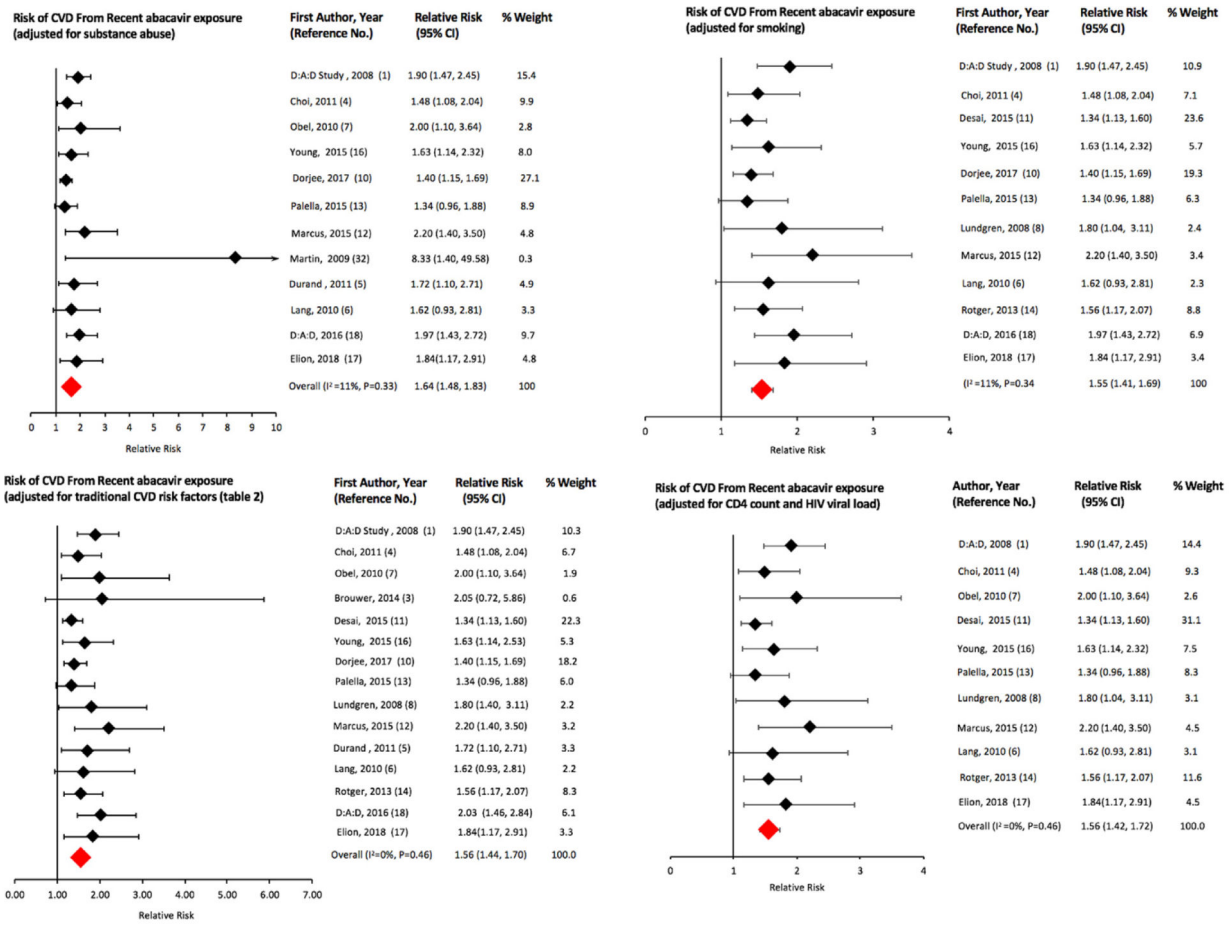

Fig. 3.

Pooled risk of cardiovascular disease from recent exposure to abacavir in various sub-groups of HIV-infected individuals.

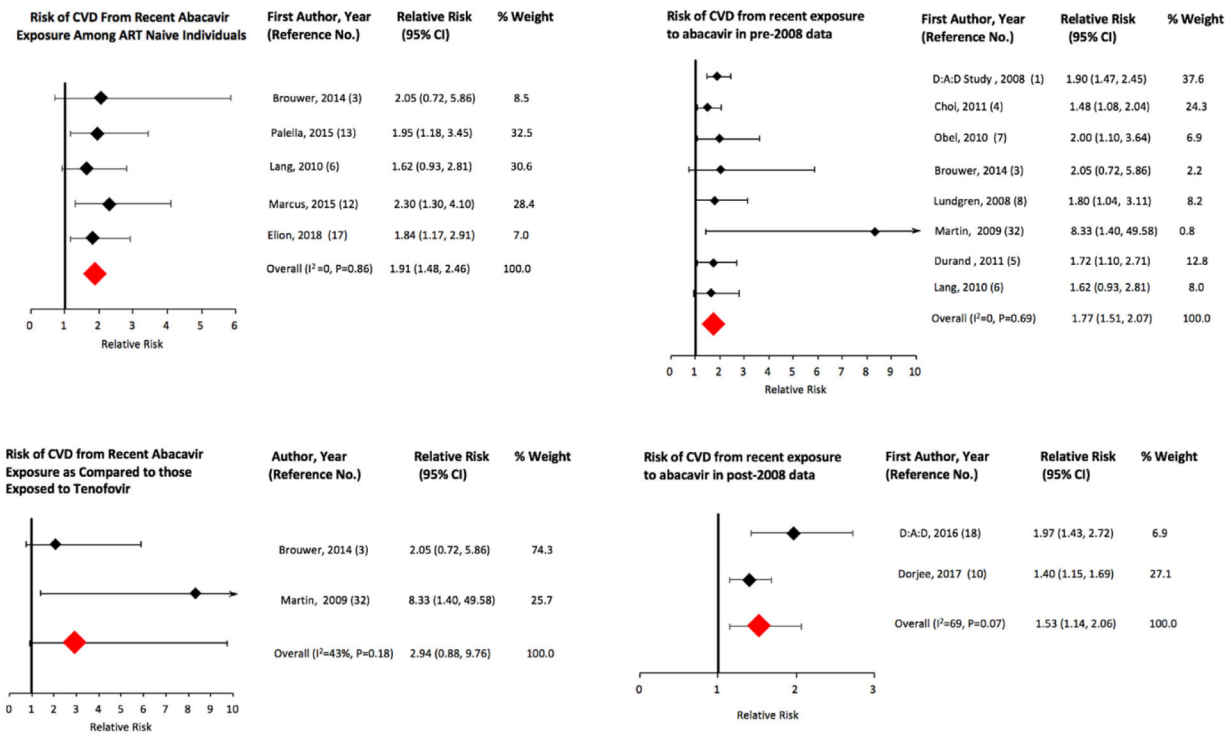

Fig. 4.

Pooled risk of cardiovascular disease from recent exposure to abacavir in sub-groups of HIV-infected individuals.

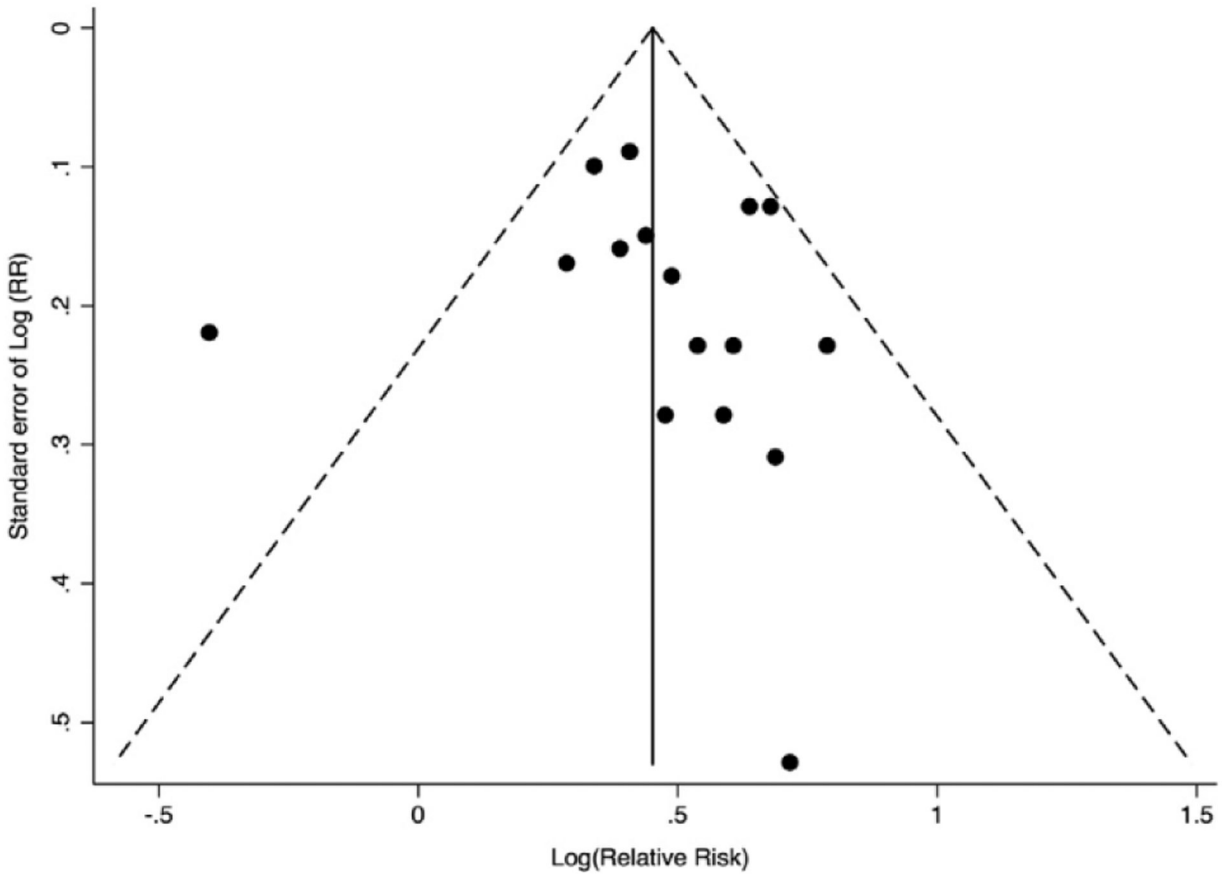

Fig. 5.
Funnel plot of 16 observational studies to assess publication bias for risk of CVD associated with recent exposure to abacavir.

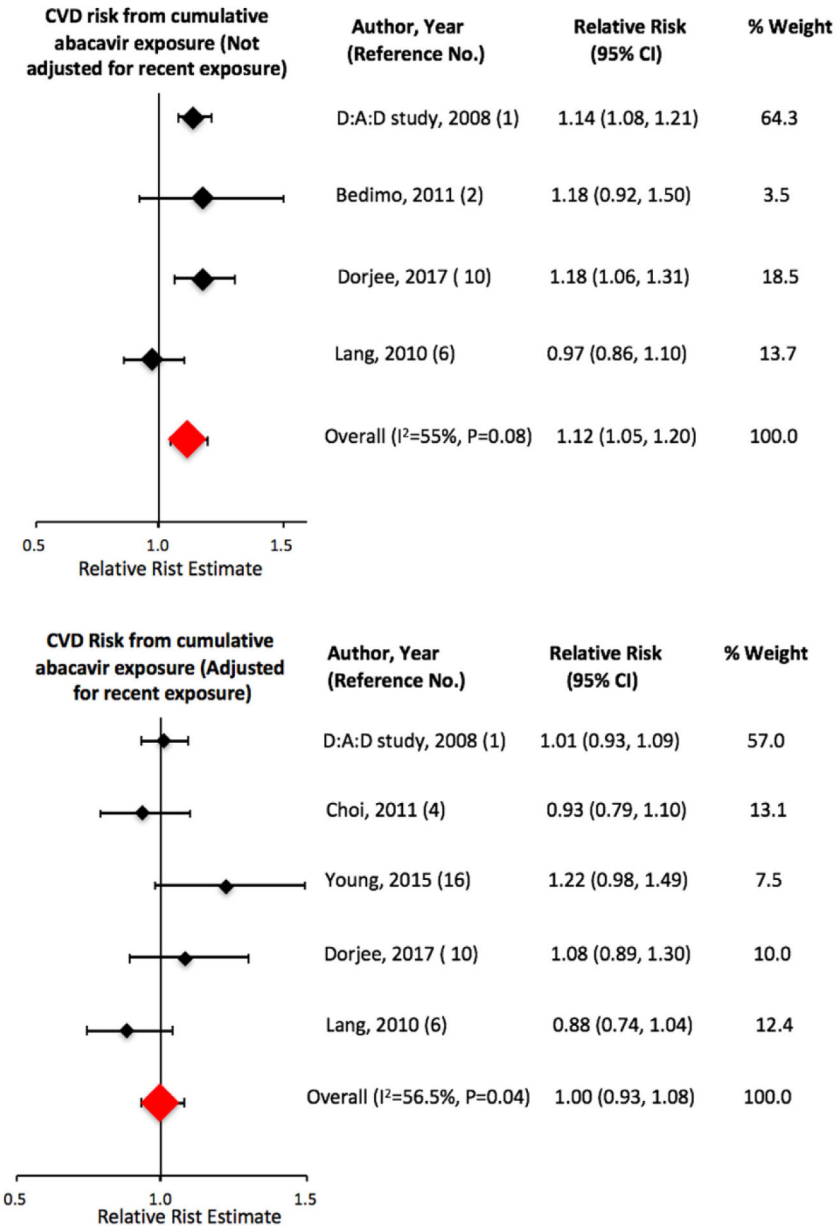

Fig. 6.

Pooled risk of cardiovascular disease from cumulative exposure to abacavir.

Table 1

Studies assessing the risk of acute myocardial infarction (AMI) or cardiovascular disease (CVD) from recent or cumulative exposure to abacavir.

Author, year of publication	Study period	Cohort/Location	Study Design	Sample size (n)	Outcome (*n*)	Exposure (recent or cumulative)	Reference group	Statistics (95% CI)	Covariates included in the model and comments
D:A:D Study Groups, 2008	1999–2007	Multinational D:A:D cohort	Prospective cohort	33 347	AMI (517) AMI (517)	Recent Cumulative	Other ARV agents Other ARV agents	RR: 1.90 (1.47, 2.45) RR: 1.14 (1.08, 1.21)	Age, sex, risk group, ethnicity, calendar year, cohort, smoking, family history of CVD, prior CVD, BMI, cumulative exposure to other ARV drugs. Further adjustment for CD4 cell count, viral load, lipid and glucose levels, blood pressure, diabetes, and lipodystrophy made little difference to the result.
D:A:D study Groups, 2016	1999–2013	Multinational D:A:D cohort	Prospective cohort	49 717	AMI (941)	Current	Other ARV agents	RR: 1.98 (1.72–2.29)	Time-fixed covariates: gender, mode of HIV acquisition, ethnicity, participating clinical cohort: time-updated covariates: age, smoking status, family history of CVD, previous CVD event, BMI, cumulative exposure to the main protease inhibitors and non-NRTIs, and cumulative and current exposure to other NRTIs.
	1999-Feb 2008	Multinational D:A:D cohort	Prospective cohort	210250 person-years	AMI (672)	Current	Other ARV agents	RR: 1.97 (1.68–2.33)	Sensitivity analyses separately carried out adjusting potential causal mediators: diabetes mellitus, total and high-density lipoprotein cholesterol, triglycerides, blood pressure, antihypertensive drugs, blood glucose, Framingham score, body weight, and renal function
	March 2008–2013	Multinational D:A:D cohort	Prospective cohort	157 309 person-years	AMI (269)	Current	Other ARV agents	RR: 1.97 (1.43–2.72)	
Lundgren et al., 2008	2002–2007	Multinational (SMART study)	Prospective cohort	4544	AMI (19) CVD (70)	Recent Recent	Other NRTIs Other NRTIs	HR: 4.25 (1.39, 13) HR: 1.80 (1.04, 3.11)	Age, sex, race, baseline viral load and CD4 cell count, smoking, prior CVD, diabetes, BP-lowering drugs, hepatitis B or C virus infection, baseline use of NNRTI and PI.
Martin et al., 2009	2005–2008	STEAL study, Australia	Randomized controlled trial	357	CVD (9)	Recent	Tenofovir-Emtricitabir	HR: 8.33 (1.40, 1649.58)	
Lang et al., 2010	2000–2006	French Hospital Database	Case-control	1173	AMI (289)	Recent Cumulative	Not exposed to abacavir Not exposed to abacavir	OR: 1.62 (0.93, 2.81) OR: 0.97 (0.87, 1.10)	Cases and controls were matched for age and sex and the models were adjusted for hypertension, smoking, family history of premature coronary artery disease, cocaine or IVDU, HIV viral load, CD4:CD8 cell ratio, and exposure to other ARV drugs.
Obel et al., 2010	1995–2005	Danish HIV Cohort Study	Prospective cohort	2952	AMI (67)	Current	Not exposed to abacavir	HR: 2.00 (1.10, 3.64)	Age, sex, year of diagnosis, year of HAART initiation, CD4 cell count, viral load, race, injection drug use, use of other ARV drugs, diabetes, alcoholism, COLD, hypertension, liver disease, and kidney disease.
Choi et al., 2011	1997–2007	VA HIV Clinical Case Registry, USA	Retrospective cohort	10 931	CVD (501) CVD (501) AMI (NS)	Recent Cumulative Recent	ARV agents other than	HR: 1.48 (1.08, 2.04) HR: 0.93	Age, sex, race, calendar year, diabetes, hypertension, dyslipidemia, prevalent CVD, smoking, drug abuse, hepatitis B and C virus

Author, year of publication	Study period	Cohort/Location	Study Design	Sample size (n)	Outcome (*n*)	Exposure (recent or cumulative)	Reference group	Statistics (95% CI)	Covariates included in the model and comments
							tenofovir and abacavir	(0.79, 1.10) HR: 1.64 (0.88, 3.08)	infection, cancer, eGFR, proteinuria, BMI, CD4 cell count, viral load, and cumulative exposure to other ARV drugs.
Bedimo et al., 2011	1996–2004	VA HIV Clinical Case Registry, USA	Retrospective cohort	19 424	AMI (267) AMI (278)	Current Cumulative	ARV agents other than tenofovir and abacavir Not exposed to abacavir	HR: 0.67 (0.43, 1.03) HR: 1.18 (0.92, 1.50)	Model for current exposure was adjusted for only chronic kidney disease. Model for cumulative exposure was adjusted for age, hypercholesterolemia, hypertension, diabetes, and smoking.
Durand et al., 2011	1985–2007	RAMQ and Med-Echo Databases, Quebec	Case-control	1209	AMI (125)	Recent	Not exposed to abacavir	OR: 1.72 (1.10, 2.71)	Age, sex, past AMI, past stroke, chronic kidney disease, anti-diabetic drug use, lipid-lowering drug use, anti-platelet or warfarin use, hepatitis C infection, illicit drug use.
Rotger et al., 2013	2000–2009	MAGNIFICENT Consortium	Case-control	1875	CAD (571)	Current	Not specified	OR: 1.56 (1.17, 2.11)	Sex-matched study and restricted to people without prior CAD. Adjusted for age, smoking, family history of CAD, cholesterol levels, hypertension or anti-hypertensives, diabetes mellitus and anti-diabetic medication, current ART exposure, cumulative exposure to lopinavir and indinavir, CD4 cell count, and HIV viral load.
Brouwer et al., 2014	2002–2008	North Carolina Medicaid Beneficiaries	Retrospective cohort	3481	AMI (38)	Recent	Tenofovir	HR: 2.05 (0.72, 5.86)	Age, sex, race, calendar year, cardiovascular medication use (β-blockers, ACEI, ARB, CCB, statins), hospitalization, comorbidities including heart failure, diabetes, renal disease, cerebrovascular disease, peripheral vascular disease, and ART-regimen type.
Desai et al., 2015	1996–2009	VA HIV Clinical Case Registry, USA	Retrospective cohort	24 510	CVD (934)	Current	All other ARV agents	HR: 1.50 (1.26, 1.79)	Age, year of exposure, viral load, CD4 cell count, exposure to statins, and follow up time.
Young et al., 2015	2000–2012	Swiss HIV Cohort Study	Prospective cohort	11856	CVD (365)	Recent Cumulative	Not exposed to abacavir	HR: 1.63 (1.14, 2.32) HR: 1.22 (0.98, 1.52)	Age, sex, injection drug use, Caucasian ethnicity, family history of CAD, prior CVD, smoking, BMI, calendar year, cumulative exposure to other ARV drugs, hypertension, diabetes, Framingham risk score categories, CD4 cell count and viral load.
Palella et al., 2015	1995–2010	NA-ACCORD, North America	Prospective cohort	16733 (full study population) 6485 (ART-naive)	AMI (301) AMI (93)	Recent Recent	Not recently exposed Not recently exposed	HR: 1.34 (0.96, 1.88) HR: 1.95 (1.18, 3.45)	Model for full study population (ART-naive and ART-experienced) was adjusted for age, sex, race, risk group, calendar year, smoking, hypertension, diabetes, renal impairment, cholesterol and triglyceride levels, statin use, CD4 count, viral load, previous PI use, and cohort. In addition to above covariates, the model for restricted study population (ART-naive) was adjusted for hepatitis C infection and history of clinical AIDS diagnosis.

Author, year of publication	Study period	Cohort/Location	Study Design	Sample size (n)	Outcome (*n*)	Exposure (recent or cumulative)	Reference group	Statistics (95% CI)	Covariates included in the model and comments
Marcus et al., 2016	1998–2011	Kaiser (KPNC&KPSC), California	Retrospective cohort	8154	CVD (178)	Recent	All other ARV agents	HR: 2.2 (1.4, 3.5)	Age, sex, calendar era, years known to be HIV-infected at ART initiation, race/ethnicity, CD4 cell count, HIV viral load, risk group, previous ART experience, alcohol use, smoking, overweight/obesity, diabetes, lipid-lowering therapy, renal function, and indicator for pre-2008 and post-2008.
Dorjee et al., 2017	2009–2014	US Insurance Claims Data	Retrospective cohort	72 733	CVD (714) CVD (714)	Recent Cumulative	All other ARV agents All other ARV agents	HR: 1.40 (1.16, 1.69) HR: 1.08 (0.89, 1.30)	Age, sex, calendar year, smoking, body weight, substance abuse, alcohol abuse, hepatitis B and C infection, prior CVD, chronic kidney disease, hypertension, diabetes, dyslipidemia, anti-hyperglycemic agents, cardiovascular medications (ACEI, ARB, CCB, β-blockers, statins, aspirin), stroke, cancer, symptomatic HIV-disease, and exposure to specific ARV drugs.
Elion et al., 2018	2001–2013	NA-ACCORD, North America	Prospective cohort	8265	AMI (123)	Recent	All other ARV agents	HR: 1.84 (1.17, 2.91)	Age, sex, race/ethnicity, acquisition, calendar year, smoking, hepatitis C infection, hypertension, diabetes, renal function, lipid levels, statin use, CD4 cell count, HIV viral load, history of clinical AIDS

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARV, antiretroviral; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; Cl, confidence interval; COLD, chronic obstructive lung disease; eGFR, estimated glomerular filtration rate; HAART, highly active antiretroviral agent; IVDU, intravenous drug use; NNRTI, non nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

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Table 2

Results of meta-analyses for the risk of cardiovascular disease (CVD) from exposure to abacavir in HIV-infected individuals.

Group and subgroup[$] (uutcome = CVD, unless specified)	No. of studies	Fixed effects		Shore-adjusted[#]	Random effects[#]		Heterogeneity		
		sRR	95% CI	95% CI	sRR	95% CI	χ^2	*P*	I^2 value (%)
Recent exposure									
All studies	17	1.56	1.44, 1.69	1.40, 1.74	1.35	1.20, 1.53	28.5	0.03	44
Excluding Bedimo et al., 2011	16	1.61	1.48, 1.75	NA	NA	NA	13.6	0.57	0
Outcome									
AMI	11	1.68	1.49, 1.90	NA	NA	NA	9.30	0.50	0
Study population									
ART-naïve	5	1.91	1.48, 2.46	NA	NA	NA	0.79	0.94	0
Study design									
Observational studies	15	1.60	1.48, 1.74	NA	NA	NA	10.30	0.74	0
Data year[$]									
Pre-2008	8	1.85	1.63, 2.10	NA	NA	NA	5.63	0.58	0
Post-2008	2	1.53	1.30, 1.81	1.14, 2.06	1.62	1.16, 2.25	3.19	0.07	69
Comparator agent									
Tenofovir	2	2.94	1.19, 7.25	0.88, 9.76	3.41	0.91,12.76	1.76	0.18	43
Confounder adjustment									
Potential causal mediators or traditional CVD risk factors[*]	15	1.56	1.44, 1.70	NA	NA	NA	13.84	0.46	0
Substance abuse	12	1.64	1.49, 1.82	1.48, 1.83	1.26	1.13, 1.41	12.39	0.33	11
Smoking status	12	1.55	1.42, 1.68	1.41, 1.69	1.37	1.25, 1.51	12.32	0.34	11
Prior CVD	12	1.57	1.43, 1.71	1.41, 1.73	1.41	1.26, 1.57	14.87	0.19	26
CD4 cell count and HIV viral load	11	1.56	1.42, 1.72	NA	NA	NA	9.78	0.46	0
Cumulative exposure (per year)									
Model not adjusted for recent exposure	4	1.12	1.07, 1.18	1.05, 1.20	1.11	1.02, 1.21	6.71	0.08	55
Model adjusted for recent abacavir exposure	5	1.00	0.94, 1.06	0.93, 1.08	1.00	0.92, 1.10	6.75	0.15	41

AMI, acute myocardial infarction; ART, antiretroviral therapy; Cl, confidence interval; sRR, summary relative risk.

[*]Studies included in this group adjusted for at least three of five potential factors (hypertension, diabetes mellitus, renal dysfunction, dyslipidemia, and lipodystrophy) that may lie on the causal pathway between abacavir exposure and risk of CVD.

[#] Shore-adjusted confidence intervals and random-effects models may be used when the χ^2 statistic was greater than the degrees of freedom (number of studies minus 1).

[$] Studies included in the group and subgroup analyses are shown in the Figs. 2, 3, 4, and 6 with corresponding reference numbers.