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Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis

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Abstract

Objective: Cardiovascular disease is one of the leading non-AIDS-defining causes of death among HIV-positive (HIV+) individuals. However, the evidence surrounding specific components of cardiovascular disease risk remains inconclusive. We conducted a systematic review and meta-analysis to synthesize the available evidence and estimate the relative risk (RR) of myocardial infarction (MI) among HIV+ compared with uninfected individuals.

Methods: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews until July 18, 2018. Furthermore, we scanned recent HIV conference abstracts (CROI, IAS/AIDS) and bibliographies of relevant articles. Original studies published after December 1999 and reporting comparative data relating to the rate of MI among HIV+ individuals were included. We examined MI risk within subgroups of HIV+ individuals according to exposure to combination antiretroviral therapy (ART), ART class/regimen, CD4 cell count and plasma viral load levels. Data were pooled using random-effects meta-analysis.

Results: Thirty-two of the 8,130 identified records were included in the review. The pooled RR suggests that HIV+ individuals have a greater risk of MI compared to uninfected individuals (RR=1.60; 95%CI: 1.38-1.85). Depending on risk stratification, there was moderate variation according to ART uptake (RR, ART-treated=1.80; 95%CI: 1.17-2.77; ART-untreated HIV+ individuals: 1.25; 95%CI: 0.93-1.67, both relative to uninfected individuals). We found certain ART characteristics including cumulative ART exposure, any/cumulative use of protease inhibitors as a class, and specific ART drugs (e.g. abacavir) to be importantly associated with a greater MI risk.

Conclusions: Our results indicate that HIV infection, low CD4, high plasma viral load, cumulative ART use in general including certain exposure to specific ART class/regimen are associated with increased risk of MI. The association with cumulative ART may be an index of the duration of HIV infection with its attendant inflammation, and not entirely the effect of cumulative exposure to ART per se.

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Keywords: Myocardial infarction, Cardiovascular disease, HIV, Combination antiretroviral therapy (ART), Relative risk, systematic review, meta-analysis

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Article Summary

Strengths and limitations of this study

- Strengths of this study includes the comprehensive search strategy as well as the independent and duplicate reviews employed for study selection and data extraction
- This systematic review and meta-analysis analyzed several additional drug exposure comparisons and clinical measures (e.g. CD4 cell count, plasma viral load) that had not been previously examined in relation to MI risk among HIV-positive individuals
- We observed heterogeneity across results of studies included in some of the meta-analyses, although this is a common limitation in meta-analysis especially those involving observational studies. Our *a priori* choice of employing the random-effects modeling strategy was driven in part by this expected variability among studies.

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading non-AIDS causes of death and disability among people living with HIV in the combination antiretroviral therapy (ART) era.[1 2] Although HIV-positive (HIV+) individuals are believed to be at higher risk of CVD compared to uninfected individuals,[3 4] the results and conclusions from the studies that have examined the nature of the risk of CVD, in particular myocardial infarction (MI) among HIV+ individuals have been conflicting. While some cohort studies have suggested a positive association between ART including specific drug (e.g. abacavir) or drug class (e.g. protease inhibitors [PI]) use and MI, or CVD risk,[5-9] others have not.[10-12] Furthermore, there has been a lack of agreement between observational studies,[8 11 13] and randomized controlled trials (RCT).[14 15] Clearly, the evidence regarding the nature of, and extent of the risk of MI and other CVD events among HIV+ individuals is far from uniform.

Five meta-analyses have been conducted in an attempt to synthesize the data on CVD risk among HIV+ individuals.[16-20] These have either been limited in scope by assessing only the association between ART use and risk of CVD;[16] included trials that lacked MI event adjudication;[17] included trials where CVD events were not among the pre-specified outcomes of interest;[18] provided incomplete results on MI risk;[19] or amalgamated all CVD events (e.g. MI, stroke) as a single outcome.[20] In addition, this latter meta-analysis was fraught with a number of methodological ambiguities.[21]

Given these limitations, coupled with the publication of several new and updated study reports on the topic, we sought to undertake an updated systematic review and meta-analysis of studies

assessing the risk of CVD among persons living with HIV. Considering the scope, diversity and differences in the etiology of CVD events, coupled with the complexity surrounding the available evidence, we have elected to focus primarily on MI as the outcome of interest for this meta-analysis, as it is the most widely researched CVD outcome among HIV+ individuals. The objective of our study was to estimate the risk of MI among HIV+ individuals relative to uninfected individuals. Additionally, we examined MI risk within subgroups of HIV+ individuals according to exposure to ART, ART class, specific ART regimen, CD4 cell count and plasma viral load levels.

METHODS

Search strategy and selection criteria

The systematic review and meta-analysis was performed in accordance with the PRISMA Statement.[22] A protocol describing the inclusion criteria and analysis methods for this systematic review was specified in advance, registered and published at the international prospective register of systematic reviews (PROSPERO, registration number CRD42014012977).[23]

The search strategy (see Appendix Table 1) was developed in consultation with a medical librarian at Simon Fraser University, BC, Canada. The search terms were based on a combination of indexed and free-text terms reflecting clinical outcomes of interest to the review, and included the following keywords: 'HIV, human immunodeficiency virus, acquired immunodeficiency syndrome, HIV/AIDS, stroke, myocardial infarction, cardiac death, cerebrovascular disease, ischemic heart disease, cardiovascular disease and CVD'. These terms were used in combination to execute the searches, which were up to July 18, 2018. Using the

Ovid platform, we searched the following electronic databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews. In addition, we screened the abstracts of the International AIDS Society conferences (AIDS 2012, 2014, 2016; IAS 2013) and the Conference on Retroviruses and Opportunistic Infections (CROI 2014, 2015, and 2016). We also searched the reference lists of relevant articles and previous systematic reviews for additional eligible publications. Finally, we set up automatic PubMed literature alerts to identify any new relevant article published while the manuscript was under development.

We included original research published in English where at least one of the participant groups were individuals living with HIV, and presenting comparative data on the incidence of MI. We included studies in which results were stratified according to HIV status; CD4 cell count; plasma viral load (pVL) levels; ART use; or exposure to particular ART class or regimen. Studies involving non-human populations, children, as well as those reporting only intermediate, surrogate or CVD biomarker outcomes were excluded (for additional information, see 'study selection' in the Appendix, p1). To reflect the current context of HIV treatment and disease management, we selected studies published from the year 2000 onwards. Although both observational studies and RCTs were eligible for inclusion, we did not include RCTs that were not designed to assess CVD events as a pre-specified outcome to avoid bias.

Working independently and in duplicate, two reviewers (OE and GB) scanned the titles and abstracts of the retrieved records for eligibility. The full-text articles of potentially eligible studies were obtained and reviewed in greater details. Disagreements in study selection were

resolved through discussion, and where necessary, a third investigator (RSH) was invited to facilitate consensus.

Data extraction and quality assessment

The same two reviewers (OE and GB) conducted data extraction independently using a pre-designed data abstraction sheet. We extracted data on study descriptors, sample characteristics, outcome assessment, risk estimate for relevant comparisons, and study quality features. Where necessary, we sought clarification directly from study authors through email contact. In cases where data from the same study described the same event risk in multiple publications, we extracted data from the most comprehensive report while supplementing missing study-level information from the others.

The quality of the included studies was assessed according to risk of bias criteria based on the type of study design. Briefly, we made this assessment by evaluating study design features including participant selection, comparability of groups, exposure and outcome assessments,[24] as only observational studies were eventually included in the meta-analysis since eligible RCTs were not identified.

Patient and public involvement

No patients were involved in this study. We used data from published materials only

Data analysis

We calculated the kappa statistic as a measure of the inter-reviewer agreement for the selection of articles meeting the inclusion/exclusion criteria. For interpretation, we defined *a priori* the interval for the kappa result using Landis and Koch criteria.[25] For effect measure, we assumed the incidence rate ratio (IRR), odds ratio (OR) and hazard ratio (HR) with corresponding sampling variance to be numerical approximate measures of the relative risk (RR) for a given association of interest with the underlying assumption of a generally low event risk (< 20%),[26-31] and thus combined them as previously described.[19 32-35] We tested this assumption in sensitivity analyses by performing separate meta-analyses where studies presenting results reported using a similar effect measure type were pooled. Given the expected variability among eligible studies, we pooled studies using the DerSimonian-Laird random-effects model.[36] To minimize bias in our pooled estimates, adjusted risk estimates were not combined with unadjusted estimates. The final set of studies that adjusted for confounders did not consistently adjust for the same set of confounders but were deemed to have sufficient internal validity to permit pooling. Given the limitations of the I^2 statistics with observational studies and Cochran Q test when the number of studies is small,[37 38] we assessed heterogeneity by visual inspection of the forest plots for overlap in the confidence intervals of the individual studies, although the I^2 and Cochran Q are reported in the forest plots for completeness sake. We were unable to perform meta-regression analyses to assess the potential effect of study-level covariates on the pooled estimate due to insufficient studies (< 10),[39] in each of the meta-analyses. A p-value < 0.05 was considered statistically significant. The meta-analysis was conducted using the *metafor* package of the R statistical program (version 3.3.1) [40].

RESULTS

Of 8,130 records identified through the database search, the final screening process yielded 64 potentially eligible publications on CVD outcomes, 32 of which had relevant data on MI and were included in this meta-analysis (Figure 1). Overall, there was near perfect agreement between reviewers on the inclusion of studies (kappa statistic = 0.94; 95% confidence interval (95%CI): 0.89, 0.99). The included studies, most of which were conducted in the United States and Europe, were published between 2000 and 2017 and involved approximately 383,471 HIV+ and > 798, 424 HIV- individuals (Appendix Table 2: characteristics of the included studies; *note: the number of individuals in cohorts with multiple publications was accessed only from one of the publication*s). The mean duration of follow-up varied across studies from approximately one to twenty years. All 32 publications were non-randomized studies and included two nested case-control studies,[11 41] one cohort/nested case-control study,[42] and 29 cohort studies; 15 of which were prospective studies, by design.[3 7 8 13 43-53] Twenty-nine studies were published as full-text journal articles, while three were available as conference abstracts.

In general, the reporting and quality of the methodological aspects of the included studies were variable. Three studies did not provide sufficient information necessary to assess the study quality, as they were reported and available as conference abstract/poster.[46 48 54] The eligibility criteria were clearly defined in the majority of studies (94%), description of study participants/ groups was sufficient (100%); however, the exposure or outcome was not adequately ascertained in 15 studies (47%);[8 12 42 45 47 51 54-62] one (7%) of which was published as an abstract [54] (see Appendix Table 3: risk of bias in the included studies).

Meta-analysis of the risk of MI

Below, we summarize the results of the meta-analyses of MI risk according to the various risk stratifications assessed. To avoid duplication of reporting, only statistically important RR are stated in text; although both statistically significant and insignificant results are presented in the figures (forest plots).

The pooled RR from the seven studies that met eligibility for this assessment of MI risk according to HIV serostatus suggests that HIV+ individuals are more likely to have an MI event compared to uninfected individuals (RR: 1.60; 95%CI: 1.38, 1.85).[3 42 43 47 61 63 64] Figure 2 shows the forest plots for the association between HIV serostatus and MI risk. Two studies assessed the risk of MI by HIV serostatus according to whether ART treatment was received.[51 65] Relative to uninfected individuals, the pooled RR of MI was significantly higher only among ART-treated individuals (RR: 1.80; 95%CI: 1.17, 2.77), and not the ART-untreated HIV+ individuals (RR: 1.25; 95%CI: 0.93, 1.67).

The pooled RR based on combining data from three studies suggests that low CD4 cell count (< 200 cells/mm^3) is associated with higher MI risk compared to CD4 ≥ 200 (RR: 1.60; 95%CI: 1.25, 2.04).[3 48 60] Conversely, a high pVL (≥ 100,000 copies/mL) was found to be associated with increased MI risk compared to pVL < 100,000 (RR: 1.45; 95%CI: 1.11, 1.90), based on the pooled results from two studies (Figure 3).[45 60]

With regards to *recent treatment exposure* (i.e. within the preceding six months), four eligible studies with data on nucleoside reverse transcriptase inhibitors (NRTI) exposure assessed the risk

of MI associated with recent compared to not recent abacavir exposure.[42 44 46 58] The pooled result from these four studies suggests that recent abacavir exposure is associated with increased risk of MI compared to not recent exposure (RR: 1.71; 95%CI: 1.39, 2.10). Similarly, recent didanosine (RR: 1.29; 95%CI: 1.04, 1.60),[42 49 58] and lamivudine (RR: 1.50; 95%CI: 1.18, 1.90),[13 42 58] exposure is associated with increased risk of MI compared to not recent exposures. In contrast, there was no association between recent tenofovir,[42 49 58] zidovudine,[13 42 58] stavudine,[13 42 58] emtricitabine,[42 58] and MI risk compared to not recent exposure (Figure 4). Based on pooling data from two studies with data on non-nucleoside reverse transcriptase inhibitors (NNRTI) exposure,[42 58] no association was found between recent efavirenz or nevirapine exposure and MI risk compared to not recent exposure (Figure 5). Based on pooled results from the studies assessing the MI risk of individual PIs, recent indinavir was associated with increased MI risk compared to not recent exposure (RR: 1.46; 95%CI: 1.08, 1.95).[42 58] Recent exposure to other PI regimens including atazanavir,[42 58] lopinavir,[42 58] ritonavir,[42 58] nelfinavir,[42 58] and saquinavir,[42 58] was not found to be significantly associated with MI risk compared to not recent exposure (Figure 6).

In terms of *any treatment exposure*, our meta-analysis did not find an association between exposure to ART and risk of MI compared to no exposure (Appendix Figure A1).[53 65] Based on the pooled results from six studies with data on NRTI exposure,[8 11 13 42 54 60] individuals receiving abacavir were more likely to have an MI compared to those who did not (RR: 1.58; 95%CI: 1.25, 2.00). We found a similar association between didanosine exposure and MI risk (RR: 1.48; 1.16, 1.90).[13 42 60] No important association was found between exposure to tenofovir,[42 60] zidovudine,[13 42] stavudine,[13 42 60] emtricitabine,[42 60] and MI risk, based on our pooled results

(Appendix Figure A2). The meta-analysis of studies with data on NNRTI exposure did not find any evidence of an association between either efavirenz,[42 56] or nevirapine exposure,[42 60] and MI risk compared to no exposure (Appendix Figure A3). The pooled RR from four studies demonstrates that PI exposure is associated with an increase in the risk of MI events compared to no exposure to PI (RR: 1.49; 95%CI: 1.16, 1.91).[3 6 52 54] When the analysis was limited to two studies comparing recent PI exposure to no exposure,[3 54] similar results were found (RR: 1.40; 95%CI: 1.16, 1.69 [data not shown]). For the individual PIs, there was no association between either atazanavir,[42 55 57 60] saquinavir,[42 60] or nelfinavir exposure,[42 60] and MI risk, compared to no exposure (Appendix Figure A4).

With regards to *cumulative treatment exposure*, three eligible studies provided relevant data regarding the risk of MI and cumulative ART exposure.[12 60 62] We found that cumulative exposure to ART was associated with an increase in the risk of MI per year of exposure (RR: 1.12; 95%CI: 1.06, 1.18) (Appendix Figure A5). For exposure to NRTI regimens, we estimated an increase in MI risk per year of exposure to abacavir (RR: 1.08; 95%CI: 1.01, 1.15) based on pooling data from two eligible studies.[12 49] Similar to abacavir, cumulative zidovudine exposure was associated with an increase in MI risk per year of exposure (RR: 1.05; 95%CI: 1.01, 1.10).[11 13] We found no association between cumulative exposure to either didanosine,[11 13] tenofovir,[11 49] lamivudine,[11 13] or stavudine,[11 13] and MI risk per year of exposure (Appendix Figure A6). The overall RR suggests that cumulative NNRTI exposure as a class (RR: 1.02; 95%CI: 0.97, 1.08),[50 62 65] or as individual drugs (nevirapine, and efavirenz),[11 49] is not significantly associated with increased risk of MI events per year of exposure (Appendix Figure A7). Three eligible studies reported data assessing the risk of MI associated with cumulative exposure to PIs as a class.[50 62]

[65] There was an increase in risk of MI per year of exposure to PIs (RR: 1.14; 95%CI: 1.03, 1.26). For individual drugs, cumulative exposure to lopinavir with ritonavir (RR: 1.19; 95%CI: 1.03, 1.39),[11 49] but not nelfinavir,[11 49] was found to be associated with increase in the risk of MI events per year of exposure (Appendix Figure A8).

The strength and direction of the overall RR from the various meta-analyses remained robust in sensitivity analyses where estimates reported using similar effect measures were pooled. For example, HIV+ individuals continued to have higher risk of MI events compared to uninfected individuals when pooled using either IRRs (overall effect: 1.51; 95%CI: 1.13, 2.01) or HRs (overall effect: 1.75; 95%CI: 1.24, 2.48) effect measures, compared to a RR of 1.60; 95%CI: 1.38, 1.85, obtained from pooling results reported using multiple relative effect measures (Appendix Figure A9).

DISCUSSION

This updated systematic review and meta-analysis assessing the risk of MI among people living with HIV reflects contemporary ART era and found the following: (1) HIV+ individuals have a greater risk of MI compared to uninfected individuals; and among HIV+ individuals, (2) low CD4 cell count (< 200 cells/mm^3) and high pVL (> 100,000 copies/mL) are associated with increases in MI risk compared to higher CD4 or lower pVL respectively; (3) cumulative ART exposure is associated with a greater risk of MI per year of exposure; (4) among NRTIs, any type of exposure to abacavir; cumulative exposure to zidovudine; and recent exposure to either didanosine or lamivudine are significantly associated with higher risk of MI; (5) compared to no exposure, any or cumulative exposure to PIs as a class; cumulative exposure to lopinavir with

ritonavir; and recent indinavir exposure was associated with higher risk of MI; (6) NNRTIs assessed either as a class or individually were not associated with increased MI risk.

Previous meta-analyses comparing CVD risk among HIV+ and uninfected individuals reported estimates for the association between HIV-seropositivity and MI (RR: 1.75)[19] or CVD (RR: 1.61)[20] risk that are similar to our findings (RR: 1.60). Relative to uninfected individuals and similar to what we found (RR: 1.80), one of these studies also reported a higher risk of CVD among ART-treated individuals (RR: 2.00).[20] As has been previously hypothesized,[3 66-69] the probable mechanistic pathway through which HIV infection can induce MI may include a cascade of events involving chronic inflammation, immunodeficiency/CD4 cell depletion, endothelial dysfunction, increased thrombosis and accelerated atherosclerosis that typically accompany both controlled and uncontrolled HIV disease. We suspect that the higher MI risk among ART-treated HIV+ individuals may not necessarily be attributable to ART alone but rather to the combined effect from a host of factors including HIV itself, ART, and other comorbid risk factors which have been individually shown to contribute to MI risk.[3 5 70 71] Furthermore, the risk associated with cumulative ART exposure may be an index of the duration of HIV infection with its attendant inflammation, and not entirely the effect of cumulative exposure to ART per se.

Specific to abacavir and MI risk, our findings were similar to reports from a previous meta-analysis of observational studies of MI,[16] but different from those of the meta-analysis of RCTs,[17 18] or reports from aggregate clinical trial studies,[14 15] that suggested no risk associated with abacavir exposure. Although observational studies and RCT results regarding MI and CVD

risk due to abacavir exposure among people living with HIV are largely at odds, the Simplification with Tenofovir-Emtricitabine or Abacavir-Lamivudine (STEAL) trial is the first RCT to support observational studies finding of increased risk of CVD with exposure to abacavir.[72] Based on the available evidence to date, the controversy regarding the potential association between abacavir use and risk of MI will likely continue to plague the field of HIV therapeutics until such a time when definitive evidence describing the underlying mechanism can be produced.[73 74] A sufficiently powered RCT with long follow-up and including real-world populations reflective of those typically seen clinically may be needed to fully resolve this clinical controversy.

Unlike our results where a class-level effect was evident for PIs, pooled aggregate clinical trial data after one year of treatment with four different PI-based regimens did not find evidence of an increased risk associated with PI compared to NRTI regimen (RR: 1.69; 95%CI: 0.54, 7.48).[75] When we pooled data of individual PIs separately, we did not observe the same 'class-level' results. In our analysis, different PI regimens carried different risks. For example, while recent indinavir and cumulative lopinavir-ritonavir exposure were associated with increased MI risk, nelfinavir or atazanavir did not appear to contribute to MI risk irrespective of the type of exposure data that were pooled.

In terms of the scope and design, our study differs from previous meta-analyses on this topic in several ways. First, we used an expanded search strategy that included more data sources and search of conference archives compared to prior meta-analyses.[16-20] Second, as the association of HIV and ART may affect the risk of MI and other CVD events differently, we did not assess the

risk of CVD in general, as was done in previous meta-analysis.[20] Third, we have used more recent risk estimates from studies with longer follow-up such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Fourth, we have included studies published between 2000 and 2017 with reported data from the post-ART era. The historical nature of some of the studies included in previous meta-analysis may have limited their relevance in contemporary times. Finally, this systematic review analyzed several additional drug exposure comparisons and clinical measures (e.g. CD4 cell count, plasma viral load) in relation to MI risk that had not been previously examined.

There are several important considerations that should be taken into account in the interpretation of the results of this study. Accurate characterization of the risk of MI and CVD outcomes in general may be confounded by a number of factors that may have affected our conclusions. The first concern has to do with the differences in the risk factors, drug exposure, HIV-related variables, or population considered in the included studies. No two studies of HIV+ individuals can have participants with the same demographic, clinical and drug exposure profile – all of which play a role in overall health outcomes. Therefore, heterogeneity arising from differences in study design features may have influenced the results and thus the overall conclusions drawn. Although we observed heterogeneity across results of studies included in some of the meta-analyses, this is a common limitation in meta-analysis especially those involving observational studies.[37] Our *a priori* choice of employing the random-effects modeling strategy was driven in part by this expected variability among studies.[76] It is unclear how differences in MI definition may have affected our results. While some studies retrospectively assessed MI and relied on International Classification of Diseases (ICD) codes alone, others followed participants over time

and prospectively assessed and validated the MI events.[5 44] Furthermore, our study combined results presented using several different relative effect measures with the assumption that these represent approximately the same numerical value.[26-31] In sensitivity analyses, we did not find any evidence of bias in our pooled estimates, as these did not differ importantly from the pooled estimates we obtained when we combined studies reporting results using the same effect measure. Moreover, we reached comparable conclusions with previous meta-analyses that combined,[19] or did not combine HR estimates with OR, and RR.[16]

CONCLUSIONS

In summary, this updated systematic review and meta-analysis suggests that HIV infection, ART use in general including exposure to specific ART class (e.g. PIs) and regimen (e.g. abacavir) are associated with increased risk of MI. We found the totality of the evidence for an association between HIV infection and MI to be compelling. With respect to ART and MI risk, HIV treatment strategies should certainly consider cardiovascular risk factors including exposure to particular ART drugs as part of patient-tailored care. However, given what we currently know about ART's effectiveness, the benefits of ART for the treatment of HIV infection in terms of viral suppression and immune reconstitution should be balanced against its potential unfavorable impact on MI. Specific to abacavir and MI risk where there is conflicting evidence between observational studies and RCTS, additional rigorously conducted studies in real-world populations are needed to definitively validate our findings and strengthen the existing evidence on this topic. Given the multiple potential contributory and mechanistic pathways to developing MI among HIV+ individuals and the complexity/feasibility of designing a large enough study to completely tease apart the potential contributions of each of the factors believed to increase the

risk of MI, managing known modifiable risk factors for CVD outcomes (e.g. smoking) through behavioural/lifestyle interventions, would be an excellent first step in reducing the incidence and risk of MI among people living with HIV.

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Author contributions

OE, MWH, SAL, JSGM and RSH conceived and designed the study. OE, GB, and RSH acquired the data. OE performed the statistical analysis with input from CHG, CF, and EM. All authors contributed to the interpretation of the data. OE drafted the manuscript. All authors reviewed the manuscript critically for important intellectual content and approved the final version submitted for publication.

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Competing interests

We declare no competing interests

Patient consent

None required

Data sharing statement

All data and materials used in this research are available in Medline/PubMed. References have been provided.

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Figure Titles and Legends

Figure 1. Flow diagram of study selection

Legend: *, Includes several conference abstract records captured through the database search

ART, Combination antiretroviral therapy; CVD, Cardiovascular disease

Figure 2. Forest plot of the meta-analysis of the risk of MI according to HIV status

Legend: *, this was a general population comparison group and may not have consisted of HIV- individuals only. Although including this study could potentially be considered a weakness in this meta-analysis, the overall pooled estimate did not change significantly when it was excluded from the meta-analysis in a sensitivity analysis, likely due to the low prevalence of HIV in the general population of the USA (RR: 1.60 [95%CI: 1.38, 1.85] including the study compared to 1.67 [95%CI: 1.45, 1.94] excluding the study); ART, Antiretroviral therapy; CI, Confidence interval

Figure 3. Forest plot of the meta-analysis of CD4 cell count, plasma viral load levels and risk of MI

Legend: CI, Confidence interval

Figure 4. Forest plot of the meta-analysis of recent exposure to drugs of the NRTI class and risk of MI

Legend: CI, Confidence interval

Figure 5. Forest plot of the meta-analysis of recent exposure to drugs of the NNRTI class and risk of MI

Legend: CI, Confidence interval

Figure 6. Forest plot of the meta-analysis of recent exposure to drugs of the protease inhibitor class and risk of MI

Legend: CI, Confidence interval

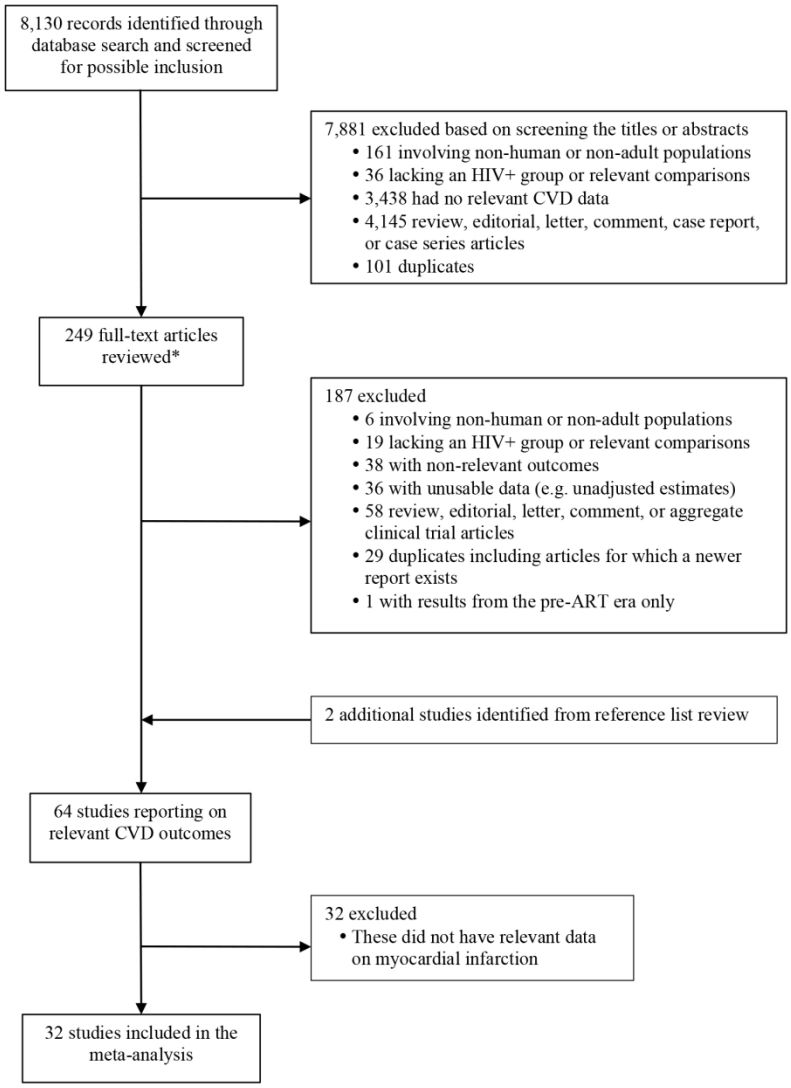


Figure 1. Flow diagram of study selection
Legend: *, Includes several conference abstract records captured through the database search
ART, Combination antiretroviral therapy; CVD, Cardiovascular disease

Figure 1. Flow diagram of study selection

152x205mm (300 x 300 DPI)

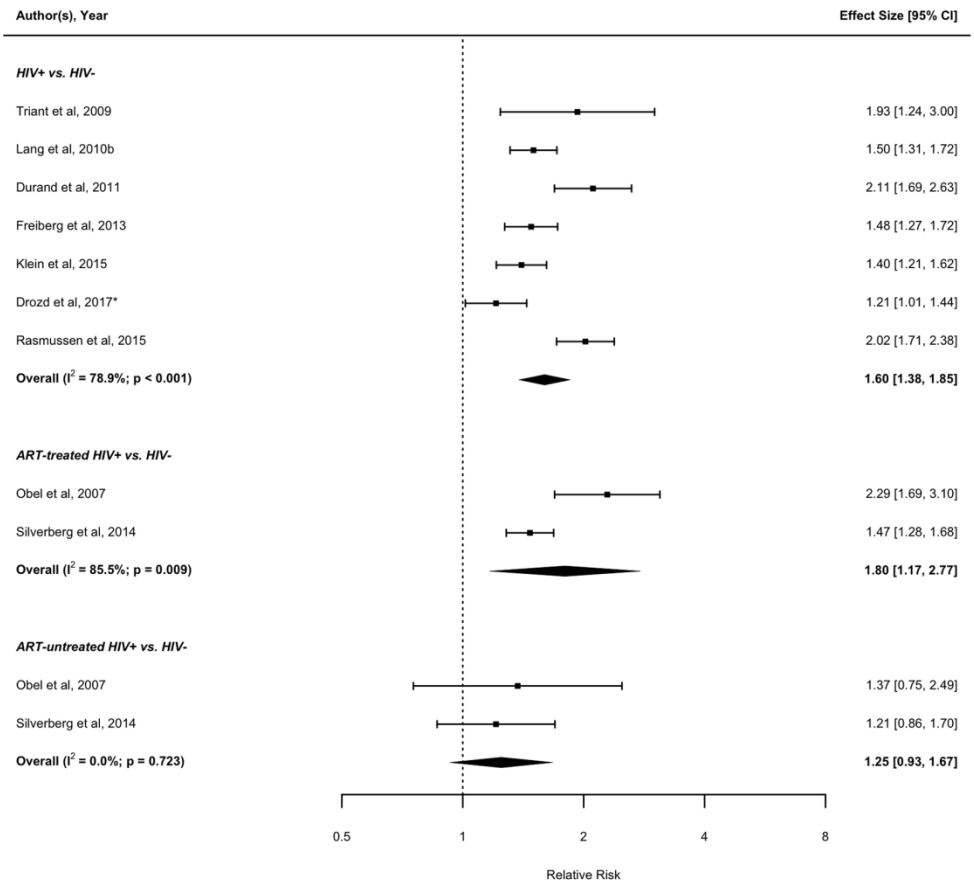


Figure 2. Forest plot of the meta-analysis of the risk of MI according to HIV status

152x136mm (300 x 300 DPI)

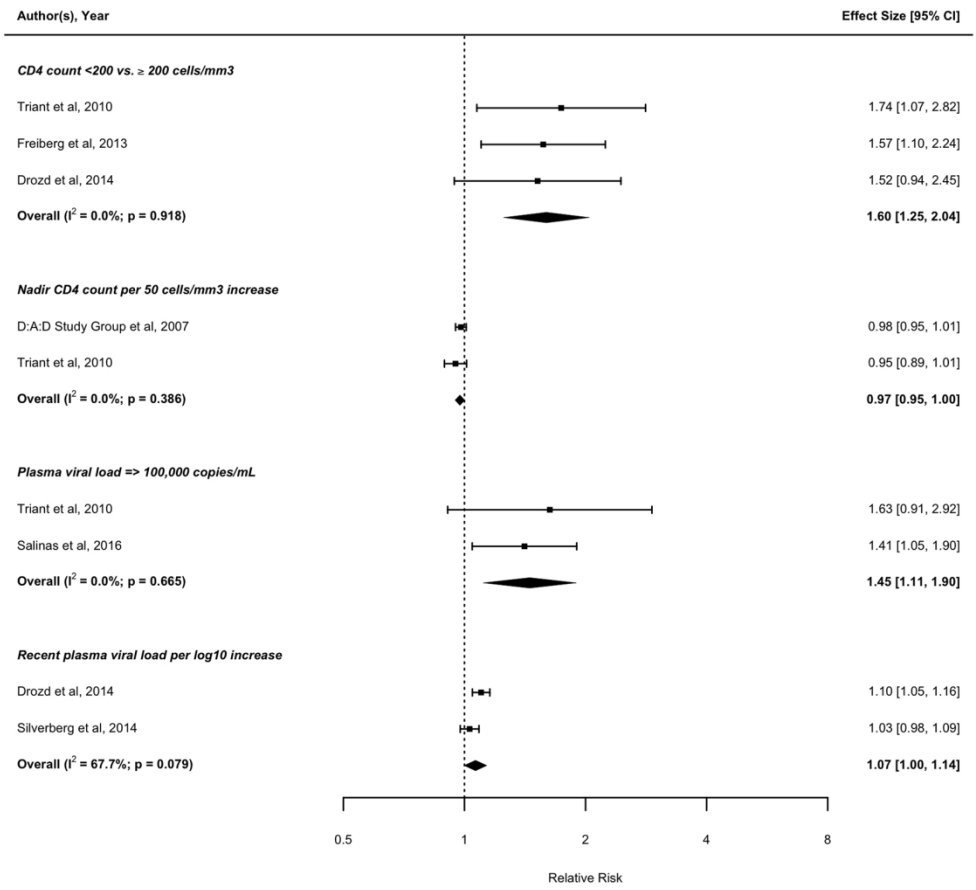


Figure 3. Forest plot of the meta-analysis of CD4 cell count, plasma viral load levels and risk of MI

152x135mm (300 x 300 DPI)

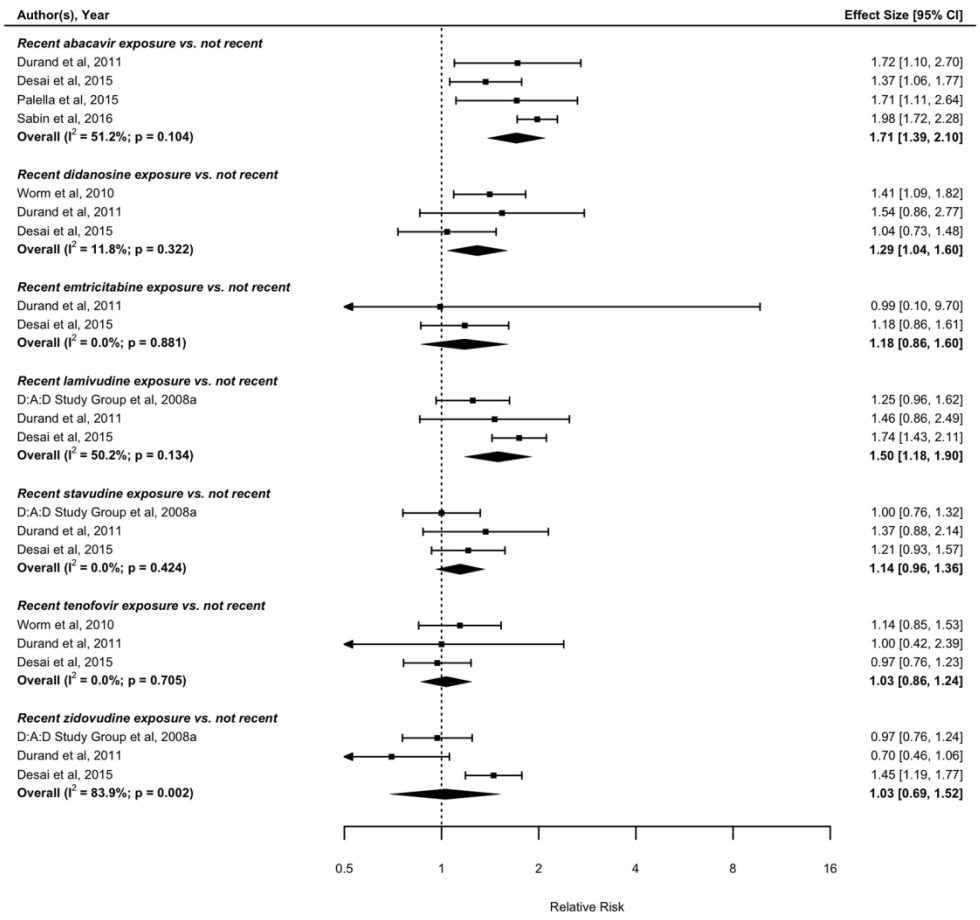


Figure 4. Forest plot of the meta-analysis of recent exposure to drugs of the NRTI class and risk of MI

152x140mm (300 x 300 DPI)

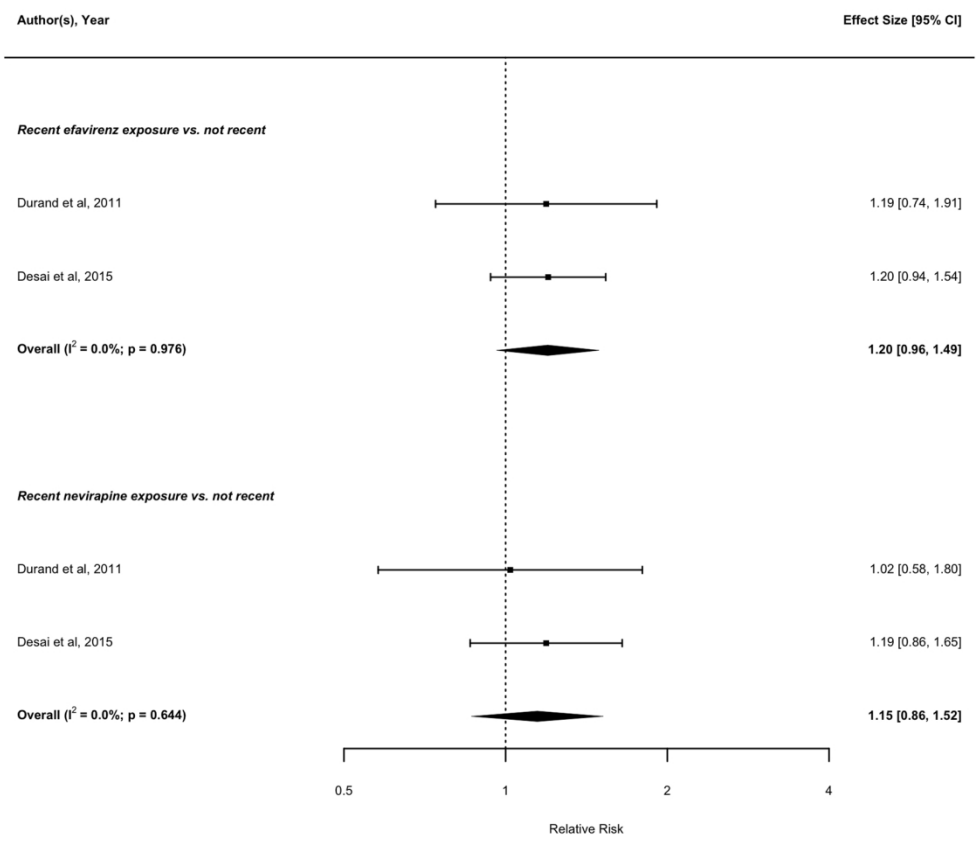
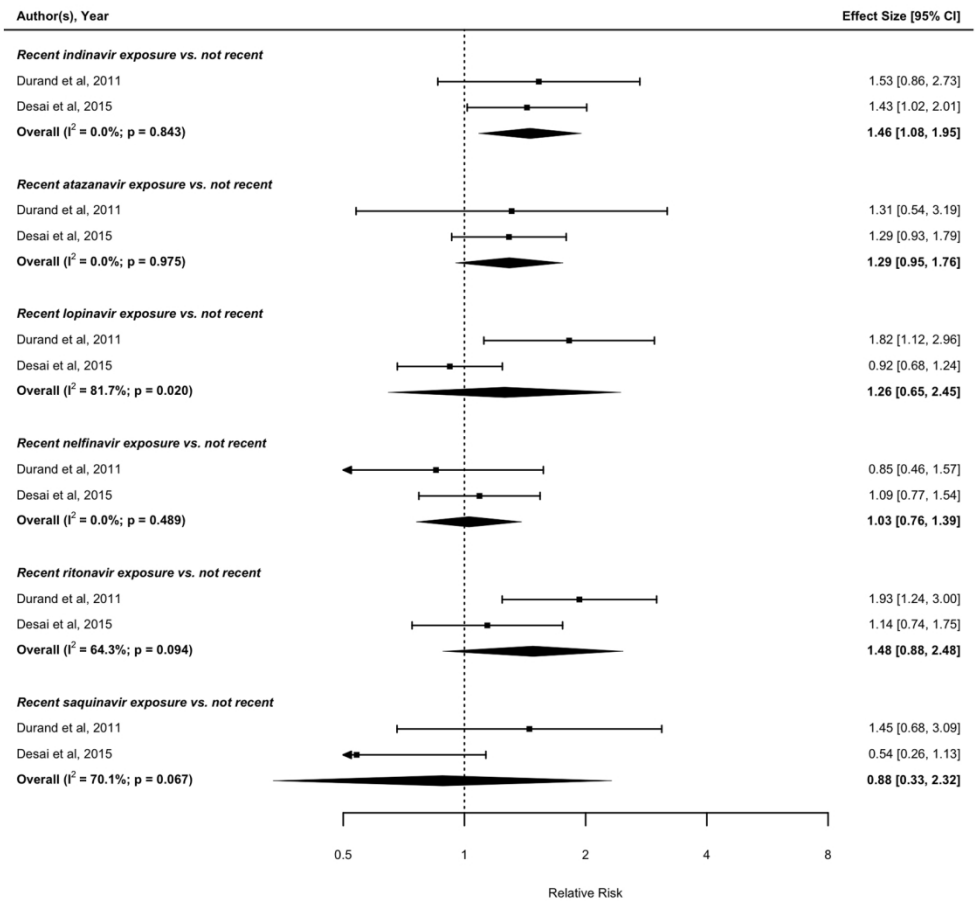


Figure 5. Forest plot of the meta-analysis of recent exposure to drugs of the NNRTI class and risk of MI

152x128mm (300 x 300 DPI)



152x138mm (300 x 300 DPI)

Appendix

Appendix Table 1. Search strategy

1	hiv.af.
2	human immunodeficiency virus.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
3	acquired immunodeficiency syndrome.af.
4	hiv aids.af.
5	1 or 2 or 3 or 4
6	stroke.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
7	(myocardial infarction or heart attack).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
8	cardiac death.af.
9	cerebrovascular disease.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
10	(ischemic heart disease or Ischaemic heart disease).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
11	(cardiovascular disease or cvd).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
12	6 or 7 or 8 or 9 or 10 or 11
13	5 and 12
14	limit 13 to human
15	limit 14 to english language
16	Limit 15 to yr= "2000 – Current"
17	remove duplicates from 16

Note: The searches were executed in the following four databases: (1) EBM Reviews - Cochrane Central Register of Controlled Trials <June 2018>, (2) EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 11, 2018>, (3) Embase <1974 to 2018 July 17>, (4) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily <1946 to July 17, 2018>

Study selection

The excluded studies included several key CVD review articles,[1–8] and aggregate clinical trial studies,[9–12] whose bibliographies were screened for identification of additional relevant studies. We also excluded a number of potentially eligible records when more comprehensive or updated results for the same participants and risk comparison were published in another report;[13–16] risk associations were reported in a way that would not allow for pairwise grouping with other studies reporting similar associations to facilitate pooling of results;[17–21] or results were reported as number of events or unadjusted risk estimates only.[22–25]

Note: the references cited in the paragraph above are listed at the end of the appendix

Appendix Table 2. Characteristics of included studies

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
LaFleur *et al* 2017[55]	Cohort	USA	ATV-cohort: 12 months Non-ATV: 13 months	HIV+	ATV-cohort: 1,529 (96) Non-ATV: 7,971 (92)	50 years	MI	ATV exposure vs. not exposed	HR[β]
Drozd *et al* 2017[43]	Cohort	North America	HIV+: 4.5 years HIV-: 19.7 years	HIV+/HIV- (NA-ACCORD / ARIC)	HIV+: 28,912 (81) HIV-: 14,308 (44)	HIV+: 80% were < 50 years HIV-: 27% were < 50 years	Type 1 MI	HIV+ vs. HIV-**	IRR[β]
Rosenblatt *et al* 2016a[56]	Cohort	USA	EFV-cohort: 23.2 months EFV-free: 19.3 months	HIV+	EFV-cohort: 11,978 (86) EFV-free: 10,234 (79)	EFV-cohort: 40.2 years EFV-free: 40.7 years	MI	EFV exposure vs. not exposed	HR[β]
Rosenblatt *et al* 2016b[57]	Cohort	USA	ATV-cohort: 24 months ATV-free: 21 months	HIV+	ATV-cohort: 2,437 (76) ATV-free: 19,774 (84)	ATV-cohort: 41.0 years ATV-free: 40.4 years	MI	ATV exposure vs. not exposed	HR[β]
Sabin *et al* 2016[44]	Cohort	Multi-national	7.0 (4.4-11.1) years[α]	HIV+	49,717 (74)	38 (32-44) years[α]	MI	Current ABC exposure vs. not current (1999-2013)	IRR[β]
Salinas *et al* 2016[45]	Cohort	USA	1996-2012 (follow-up)	HIV+	8,168 (97)	46 (40-53) years[α]	AMI	VL at ART initiation ≥ 100,000 copies/mL vs. < 100,000	HR[β]
Desai *et al* 2015[58]	Cohort	USA	~6.7 years	HIV+	24,510 (98)	46.5	MI	Current exposure to ABC vs. not currently exposed Current exposure to DDI vs. not currently exposed Current exposure to ATV vs. not currently exposed Current exposure to TDF vs. not currently exposed Current exposure to LPV vs. not currently exposed Current exposure to FTC vs. not currently exposed Current exposure to 3TC vs. not currently exposed Current exposure to d4T vs. not currently exposed Current exposure to ZDV vs. not currently exposed Current exposure to IDV vs. not currently exposed	OR[β] / HR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Current exposure to NFV vs. not currently exposed Current exposure to SQV vs. not currently exposed Current exposure to RTV vs. not currently exposed Current exposure to EFV vs. not currently exposed Current exposure to NVP vs. not currently exposed	
Klein *et al* 2015[63]	Cohort	USA	HIV+: 4.8years HIV-: 5.8 years	HIV+/HIV-	282,368 (91)	HIV+: 41 years HIV-: 40 years	MI	HIV+ vs HIV-	IRR[β]
Palella *et al* 2015[46]	Cohort	USA	~3.9 years	HIV+	16,733 (81)	Reported proportion of individuals by age categories	MI	Recent ABC use vs. non-recent use	HR[β]
Rasmussen *et al* 2015[47]	Cohort	Denmark	HIV+: 55,050–57,631 PYs HIV-: 638,204–659,237 PYss	HIV+/HIV-	HIV+: 5,897 (76) HIV-: 53,073 (76)	HIV+: 36.8 years[α] HIV-: 36.8 years[α]	MI	HIV+ vs. HIV-	IRR[β]
Drozd *et al* 2014[48]	Cohort	USA	1996-2012 (follow-up) NR	HIV+ HIV+	18,155 (NR) 17,626 (79)	NR Reported proportion of individuals by age categories	MI Primary MI	Current HIV RNA (log (copies/mL)+1) CD4 < 200 vs ≥ 200	OR[β] HR[β]
Silverberg *et al* 2014[65]	Cohort	USA	HIV+: 4.5 years HIV-: 5.4 years	HIV+/HIV-	HIV+: 22,081 (90.6) HIV-: 230,069 (90.5)	Reported proportion of individuals by age categories	MI	ART-treated HIV+ vs. HIV- ART-untreated HIV+ vs. HIV- Recent HIV RNA (per 1 log increase) Prior ART (yes vs no) Duration of PI use per year increase Duration of NNRTI use per year increase	IRR[β]
Freiberg *et al* 2013 [3]	Cohort	USA	5.9 years[α]	HIV+/HIV-	HIV+: 27,350 (97.3) HIV-: 55,109 (97.2)	HIV+: 48.2 years HIV-: 48.8 years	AMI	HIV+ vs. HIV- Recent CD4 < 200 (yes/no) Recent PI use (yes/no)	HR[β]
Lang *et al* 2012[41]	Nested case control	France	4.0 years	HIV+	Cases: 289 (88.9) Controls: 884 (89.1)	Cases: 47 (41-54) years[α]	MI	Current ABC vs not current HIV RNA per log10 increase	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
						Controls: 46 (40-54) years[α]			
Bedimo *et al* 2011[12]	Cohort	USA	3.9 years[α]	HIV+	19,424 (98)	46 years[α]	AMI	Cumulative ABC HAART per year of exposure Current ABC HAART vs. neither ABC/TDF Cumulative ARV per year of exposure	HR[β]
Choi *et al* 2011[59]	Cohort	USA	4.5 years[α]	HIV+	10,931 (98)	46 to 49 years (within subgroups by ART use)	MI	Recent ABC vs. not recent ABC or TDF	HR[β]
Durand *et al* 2011[42]	Cohort	Canada	4.0 years	HIV+/HIV-	HIV+: 7,053 (78); HIV-: 27,681 (78)	HIV+: 39.5 years HIV-: 39.7 years	AMI	HIV+ vs. HIV-	HR[β]
	Nested case control			HIV+	Cases: 125 (91.2); Controls: 1,084 (92.2)	Cases: 49.0 years Controls: 47.5 years	AMI	ABC exposure vs. no exposure Recent ABC vs. not recent DDI exposure vs. no exposure Recent DDI vs. not recent TDF exposure vs. no exposure Recent TDF vs. not recent ATV exposure vs. no exposure Recent ATV vs. not recent Recent LPV vs. not recent Recent RTV vs. not recent Recent EFV vs. not recent NVP exposure vs. no exposure Recent NVP vs. not recent FTC exposure vs. no exposure Recent FTC vs. not recent Recent 3TC vs. not recent d4T exposure vs. no exposure Recent d4T vs. not recent ZDV exposure vs. no exposure Recent ZDV vs. not recent Recent IDV vs. not recent	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								NFV exposure vs. no exposure Recent NFV vs. not recent SQV exposure vs. no exposure Recent SQV vs. not recent	
Carman *et al* 2011[54]	Cohort	USA	1998-2007 (follow-up)	HIV+	66,286 (NR)	NR	AMI	Recent ABC use vs. no use Recent PI use vs. no use	IRR[β]
Lang *et al* 2010b[64]	Cohort	France	2000-2006 (follow-up)	HIV+/ general population	HIV+: ~ 74,958 General population: unclear	35 to 64 years	MI	HIV+ vs general population	SMR
Lang *et al* 2010a[11]	Nested case control	France	2000-2006 (follow-up)	HIV+	Cases: 289 (89) Controls: 884 (89)	Cases: 47 (41-54) years[α] Controls: 46 (40-54) years[α]	MI	Recent ABC exposure vs. no exposure Cumulative ABC exposure vs. no exposure Cumulative DDI per year of exposure Cumulative TDF per year of exposure Cumulative ZVD per year of exposure Cumulative EFV per year of exposure Cumulative NVP per year of exposure Cumulative LPV + RTV per year of exposure Cumulative NFV per year of exposure Cumulative 3TC exposure per year Cumulative d4T exposure per year	OR[β]
Obel *et al* 2010[8]	Cohort	Denmark	~ 6.5 years	HIV+	2,952 (76.4)	39.1 (33.0-46.6) years[α]	MI	ABC exposure vs. no exposure	IRR[β]
Worm *et al* 2010[49]	Cohort	Multi-national	5.8 (3.9-7.5) years[α]	HIV+	33,308 (74)	With MI: 49 (43-65) years[α] Without MI: 44 (38-50) years[α]	MI	Cumulative ABC exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent TDF exposure vs. not recent Cumulative TDF exposure per year Recent DDI exposure vs. not recent Cumulative LPV-RTV exposure per year Cumulative NFV exposure per year Cumulative NVP exposure per year Cumulative EFV exposure per year	
Triant *et al* 2010[60]	Cohort	USA	5.1 years[α]	HIV+	6,517 (69)	46 years	AMI	CD4 count < 200/mm^3 vs ≥ 200 Nadir CD4 per 50/mm^3 increase VL > 100,000 copies/mL vs. ≤ 100,000 HIV RNA per log 10 increase ART per year since first ART use TDF use vs. none ABC use vs. none DDI use vs. none FTC use vs. none d4T use vs. none NVP use vs. none ATV use vs. none NFV use vs. none SQV use vs. none	OR[β]
Triant *et al* 2009[61]	Cohort	USA	HIV+: 6.0 years HIV-: 5.8 years	HIV+/HIV-	HIV+: 487 (62.8) HIV-: 69,870 (45.6)	HIV+/HIV-: Reported proportion by age categories	AMI	HIV+ vs. HIV-	OR[β]
D:A:D Study Group *et al* 2008a[13]	Cohort	Multi-national	5.1 years[α]	HIV+	33,347 (74)	With MI: 49 (range: 24-92) years[α] Without MI: 44 (range: 12-95) years[α]	MI	Recent ABC exposure vs. never exposed to ABC Recent DDI exposure vs. never exposed Cumulative DDI exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent ZDV exposure vs. never exposed Recent ZDV exposure vs. not recent Cumulative ZDV exposure per year Recent 3TC exposure vs. not recent Cumulative 3TC exposure per year Recent d4T exposure vs. not recent Recent d4T exposure vs. never exposed Cumulative d4T exposure per year	
D:A:D Study Group *et al* 2008b[50]	Cohort	Multi-national	4.5 years[α]	HIV+	28,985 (NR)	Reported by calendar period	MI	Cumulative exposure to PIs per year Cumulative exposure to NNRTIs per year	Relative rate[β]
D:A:D Study Group *et al* 2007[7]	Cohort	Multi-national	4.5 years[α]	HIV+	23,437 (76)	39 (34-45) years[α]	MI	Nadir CD4 per 50 cells/mm^3 increase	Relative rate[β]
Obel *et al* 2007[51]	Cohort	Denmark	HIV+: 6.9years[α] HIV-: 8.1 years[α]	HIV+/ HIV-	HIV+: 3,953 (76.8) HIV-: 373,856 (76.3)	HIV+: 36.8 (30.8-44.6) years[α] HIV-: 36.4 (30.6-44.0) years[α]	MI	HIV+, on HAART+ vs. HIV- HIV+ not on HAART- vs. HIV-	IRR[β]
Kwong *et al* 2006[62]	Cohort	USA and Netherlands	3.49 (range: 0.02-18.46) years[α]	HIV+	18,603 (82.63)	36 (range: 18-92) years[α]	MI	PI per year of exposure NNRTI per year of exposure HAART per year of exposure	RR[β]
Mary-Krause *et al* 2003[6]	Cohort	France	With MI: 28 (18-39) months[α] Without MI: 33 (15-48) months[α]	HIV+ men	34,976 (100)	With MI: 41.9 years Without MI: 37.7 years	MI	Exposure to PI	Relative hazard[β]
Holmberg *et al* 2002[52]	Cohort	USA	~ 3.1 years	HIV+	5,672 (82)	42.6 years	MI	PI use (yes vs no)	HR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
Rickerts *et al* 2000*[53]	Cohort	Germany	24.6 ± 18.1 months	HIV+	2,861 (78)	36.6 ± 9.5 years	MI	Prior HAART (yes vs. no)	OR[β]

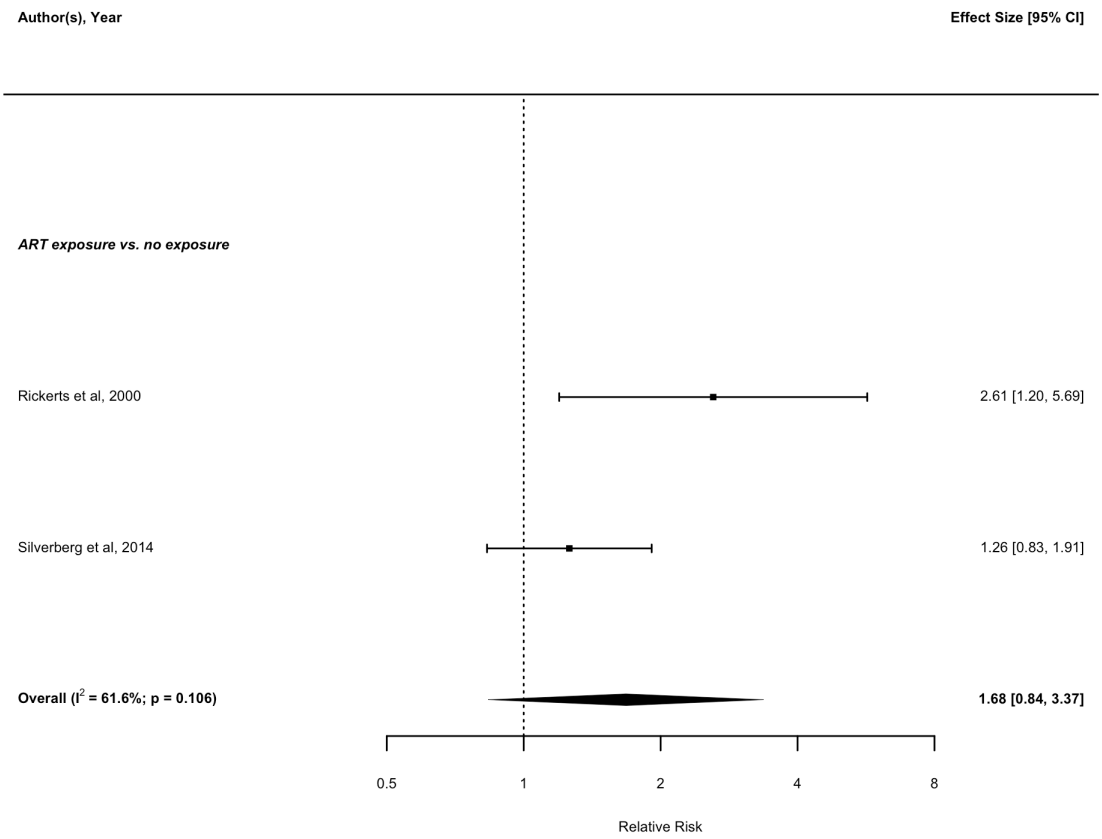
Legend: [α], median (including lower and upper quartiles, where reported); [β], adjusted estimate; *, extracted data from the ART era only; **, this was a general population comparison group and may not have consisted of HIV- individuals only; Note: a superscript alongside the author name/year is used to denote the reference number of the study; **ABC**, abacavir; **AMI**, acute myocardial infarction; **ARIC**, Atherosclerosis Risk in Communities; **ART**, antiretroviral therapy; **ATV**, atazanavir; **DDI**, didanosine; **d4T**, stavudine; **EFV**, efavirenz; **FTC**, emtricitabine; **HAART**, highly active antiretroviral therapy; **HR**, Hazard ratio; **IDV**, indinavir; **IRR**, incidence rate ratio; **LPV**, lopinavir; **LPV-RTV**, lopinavir-ritonavir; **MI**, myocardial infarction; **NA-ACCORD/ARIC**, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)/Atherosclerosis Risk in Communities (ARIC) cohorts; **NFV**, nelfinavir; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **NR**, not reported; **NRTI**, nucleoside reverse transcriptase inhibitor; **NVP**, nevirapine; **OR**, Odds ratio; **PI**, protease inhibitor; **RR**, relative risk; **RTV**, ritonavir; **SMR**, standardized morbidity ratio; **SQV**, saquinavir; **TDF**, tenofovir; **VL**, viral load; **ZDV**, zidovudine; **3TC**, lamivudine

Appendix Table 3. Risk of bias in the included studies

Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
LaFleur *et al* 2017[55]	Journal	Cohort (R)	+	+	No	+	-	-	Public. industry
Drozd *et al* 2017[43]	Journal	Cohort (P & R)	+	+	Yes*	-	+	+	Public
Rosenblatt *et al* 2016a[56]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Rosenblatt *et al* 2016b[57]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Sabin *et al* 2016[44]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Salinas *et al* 2016[45]	Journal	Cohort (P)	+	+	No	+	-	+	Public
Desai *et al* 2015[58]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Klein *et al* 2015[63]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Palella *et al* 2015[46]	Abstract	Cohort (P & R)	+	+	No	-	+	+	-
Rasmussen *et al* 2015[47]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Drozd *et al* 2014[48]	Abstract	Cohort (P)	-	+	No	-	+	-	Public
Silverberg *et al* 2014[65]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Freiberg *et al* 2013[3]	Journal	Cohort (P)	+	+	No	+	+	+	Public
Lang *et al* 2012[41]	Journal	Nested case-control	+	+	No	+	+	+	Public
Bedimo *et al* 2011[12]	Journal	Cohort (R)	+	+	No	+	-	+	-
Choi *et al* 2011[59]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Durand *et al* 2011[42]	Journal	Cohort (R), & nested case-control	+	+	No	+	-	+	Industry
Carman *et al* 2011[54]	Abstract	Cohort (R)	-	+	-	-	-	+	-

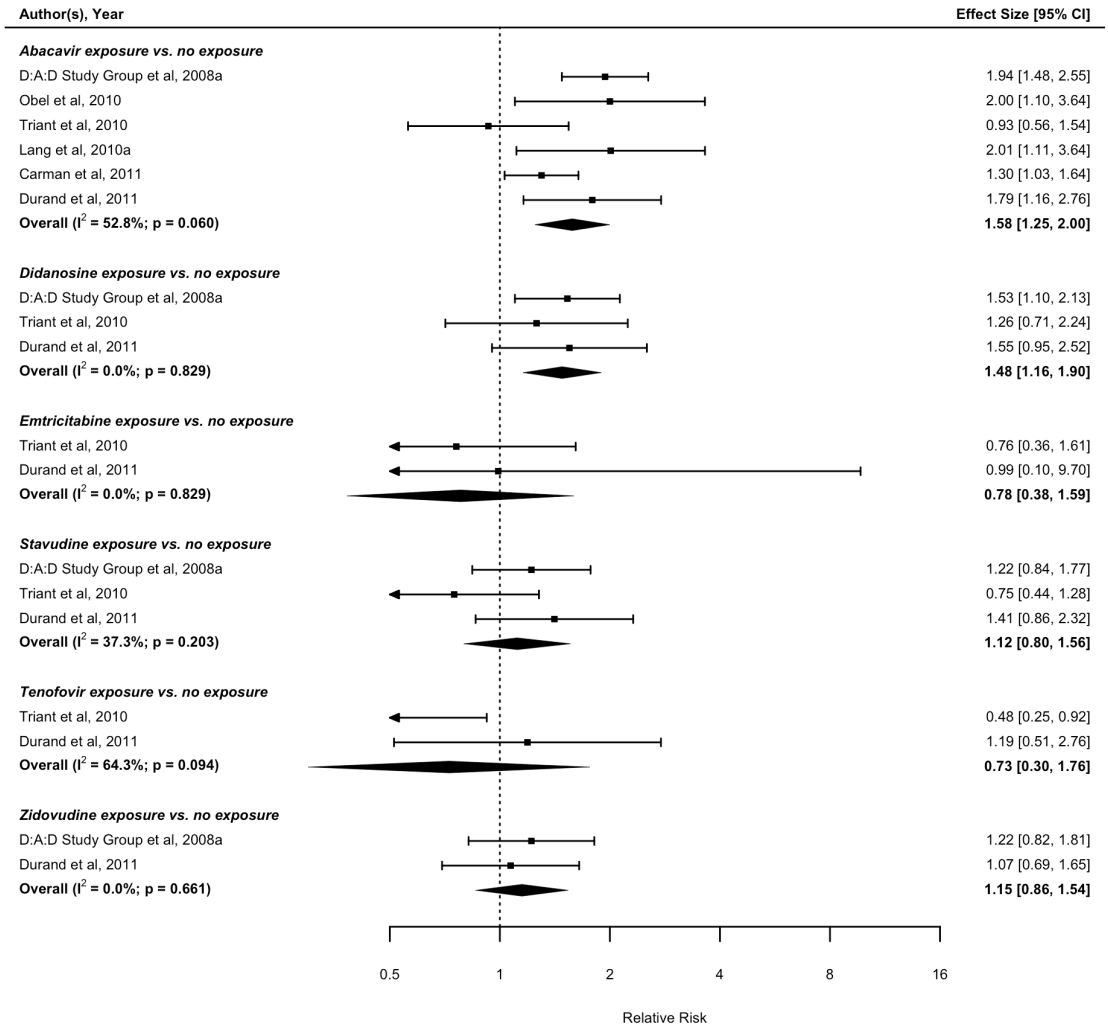
Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
Lang *et al* 2010a[64]	Journal	Nested case-control	+	+	No	+	+	+	Public
Lang *et al* 2010b[11]	Journal	Cohort (R)	+	+	No	-	+	+	Public
Obel *et al* 2010[8]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Worm *et al* 2010[49]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Triant *et al* 2010[60]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Triant *et al* 2009[61]	Journal	Cohort (R)	+	+	No	+	-	+	Public
D:A:D Study Group *et al* 2008a[13]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2008b[50]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2007[7]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Obel *et al* 2007[51]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Kwong *et al* 2006[62]	Journal	Cohort (R)	+	+	No	+	-	+	Public, industry
Mary-Krause *et al* 2003[6]	Journal	Cohort (R)	+	+	No	+	+	+	Public
Holmberg *et al* 2002[52]	Journal	Cohort (P)	+	+	No	-	+	+	Public
Rickerts *et al* 2000[53]	Journal	Cohort (P)	+	+	No	+	+	+	-

Legend: + means this is clearly described and adequate; - means this is unclear, inadequate or not reported; *, The HIV+ cohort (NA-ACCORD study) was compared to a general population cohort from a different study (Atherosclerosis Risk in Communities [ARIC] study); Note: a superscript alongside the author name/year is used to denote the reference number of the study; **NA**, Not applicable; **P**, Prospective; **R**, Retrospective



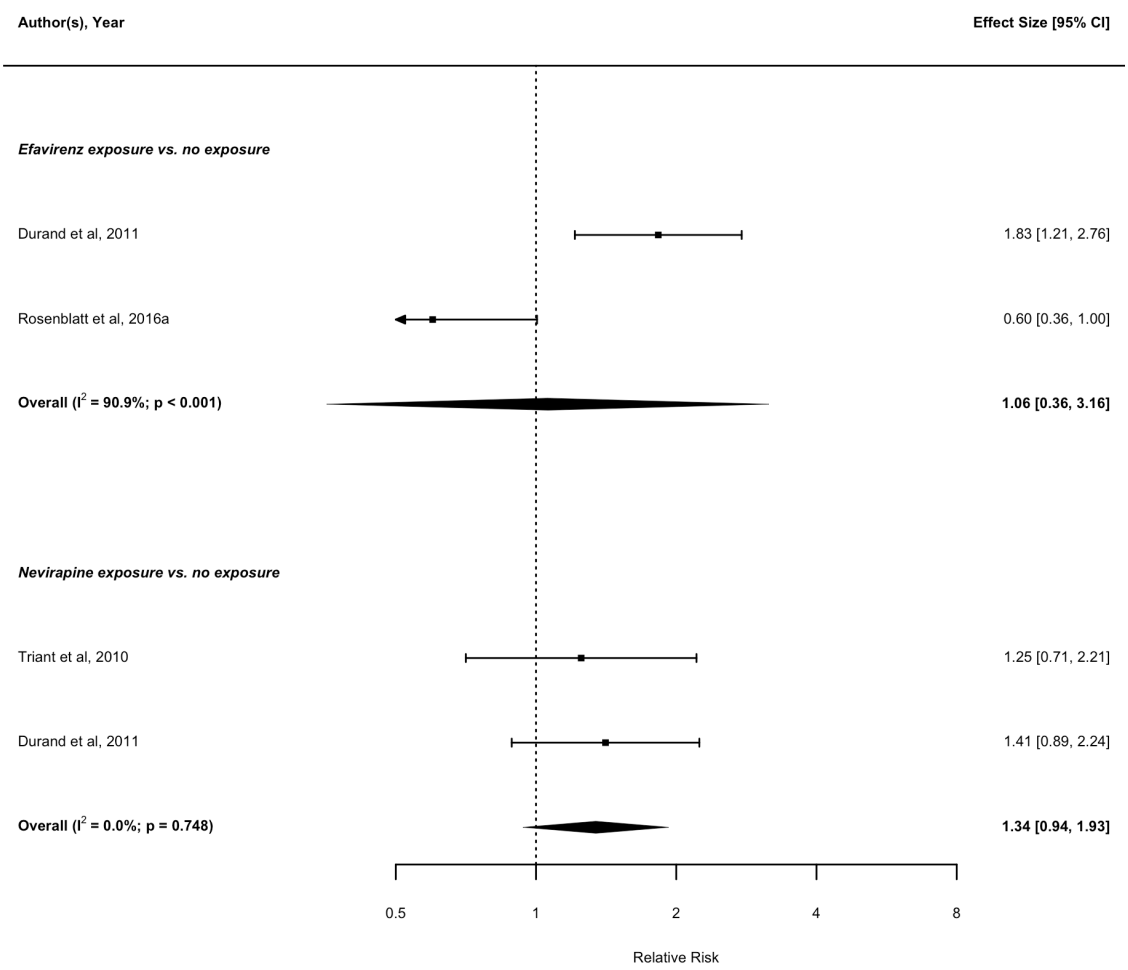
Appendix Figure A1. Forest plot of the meta-analysis of any exposure to antiretroviral therapy and risk of MI

Legend: CI, Confidence interval



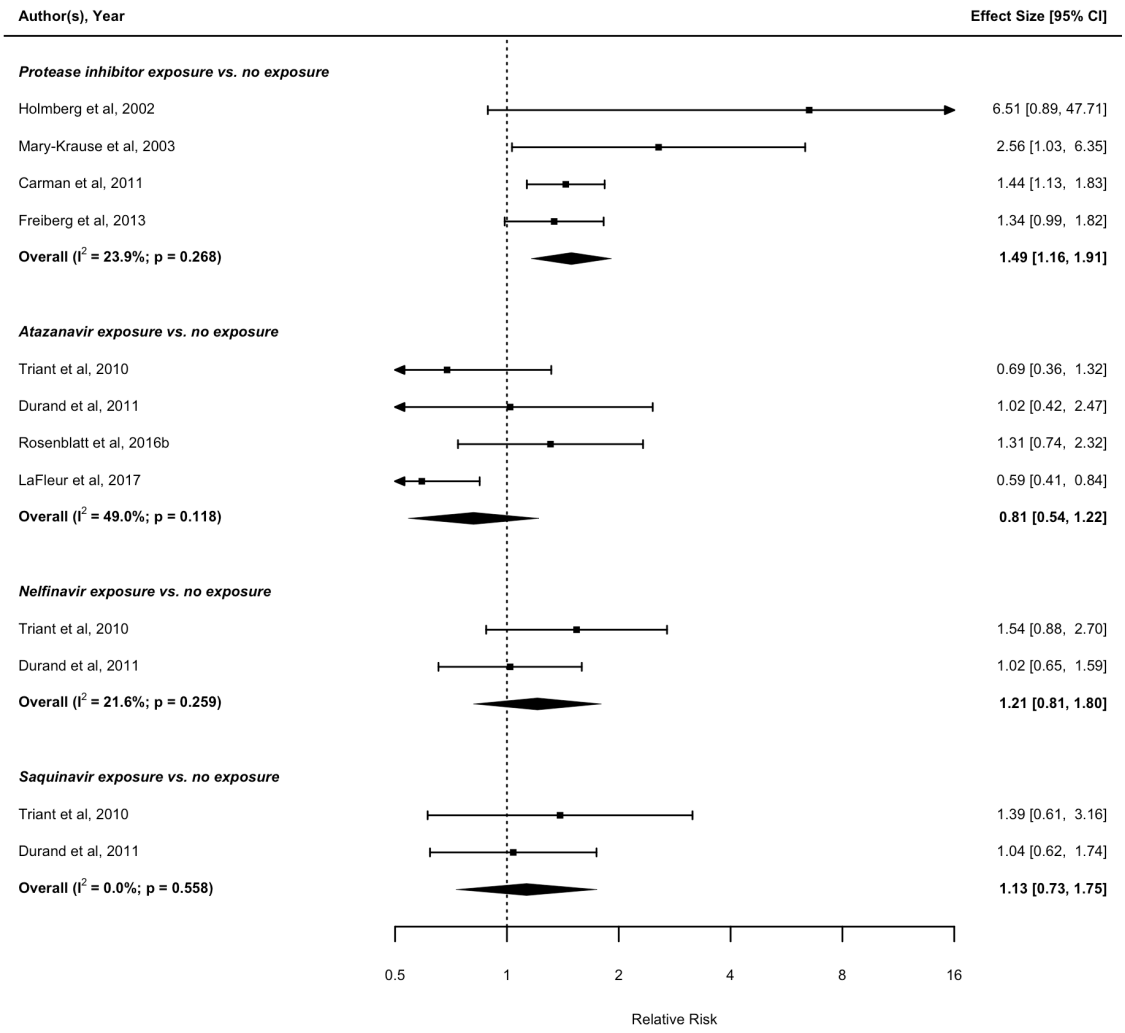
Appendix Figure A2. Forest plot of the meta-analysis of any exposure to drugs of the NRTI class and risk of MI

Legend: CI, Confidence interval

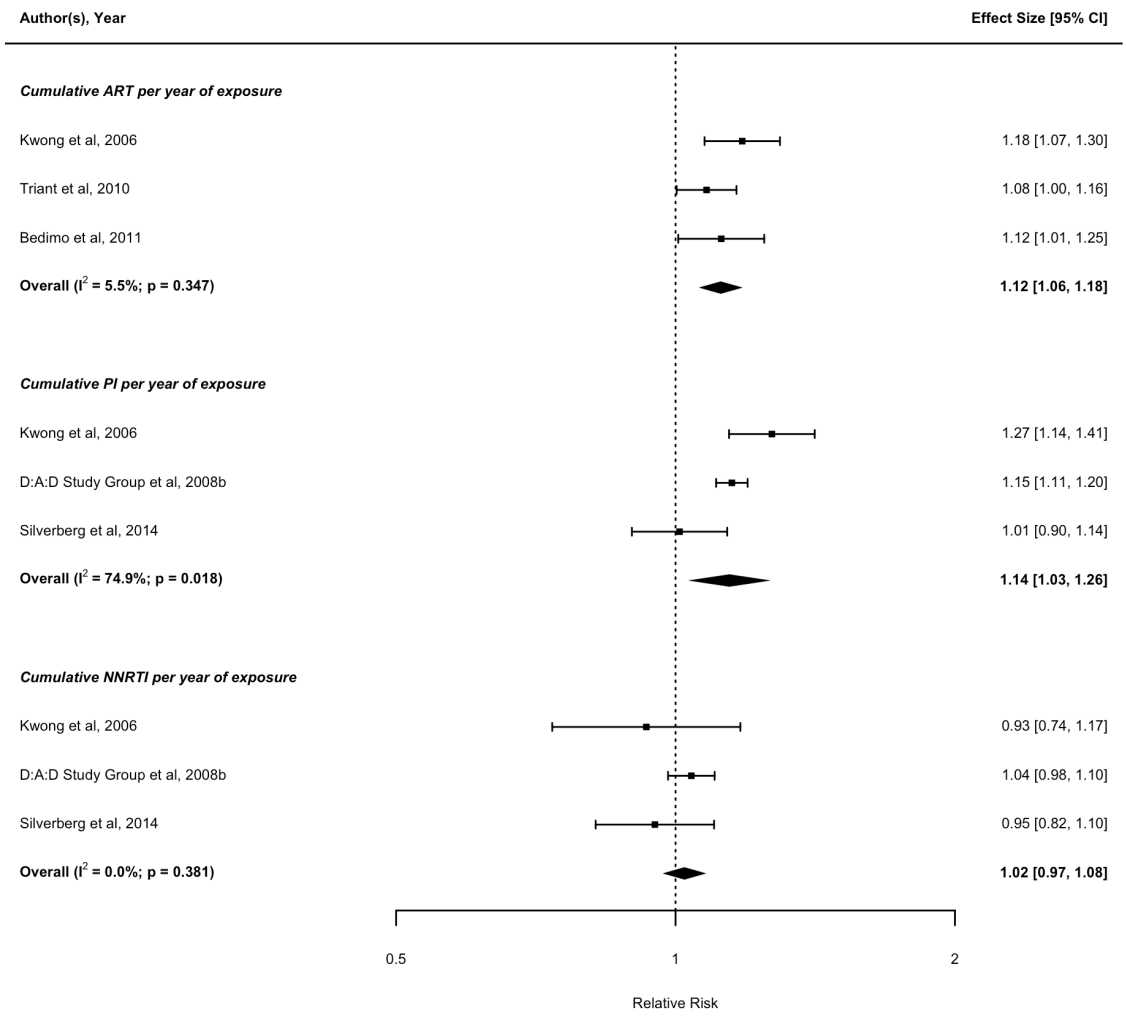


Appendix Figure A3. Forest plot of the meta-analysis of any exposure to drugs of the NNRTI class and risk of MI

Legend: CI, Confidence interval

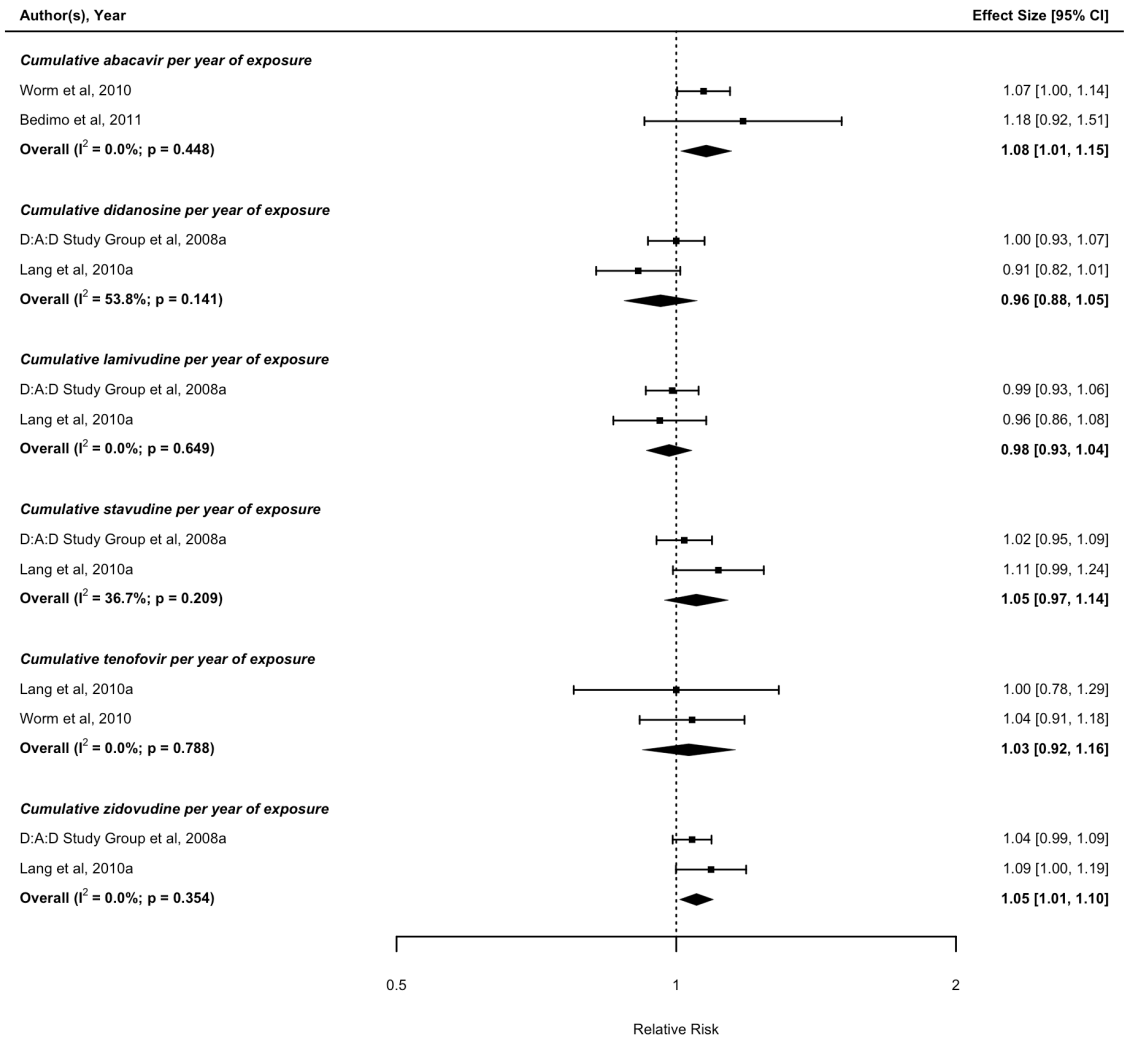


Appendix Figure A4. Forest plot of the meta-analysis of any exposure to protease inhibitors (both as a class and individually) and risk of MI
Legend: CI, Confidence interval

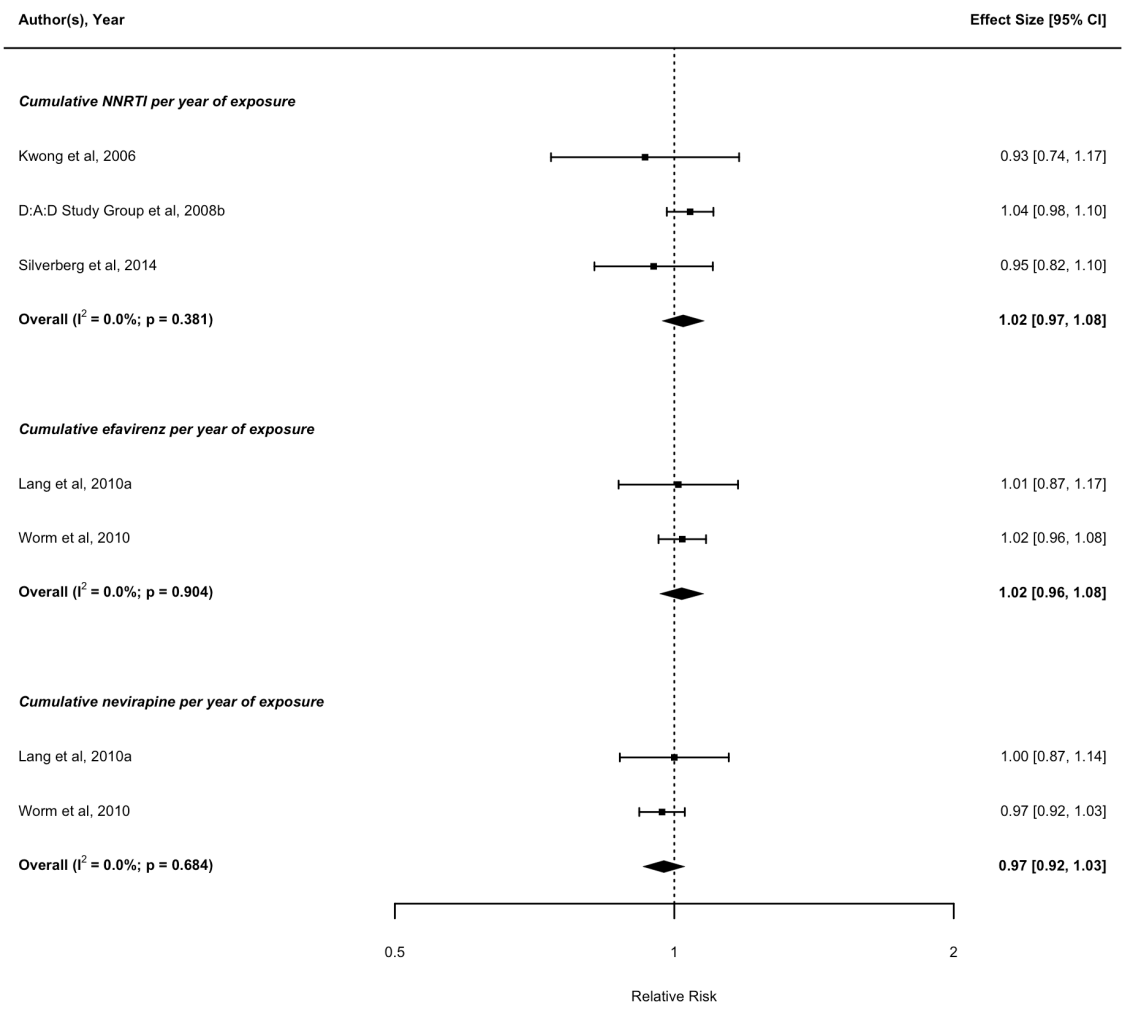


Appendix Figure A5. Forest plot of the meta-analysis of cumulative exposure to antiretroviral therapy (ART) including class of ART and risk of MI per year of exposure

Legend: ART, Antiretroviral therapy; CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease inhibitors

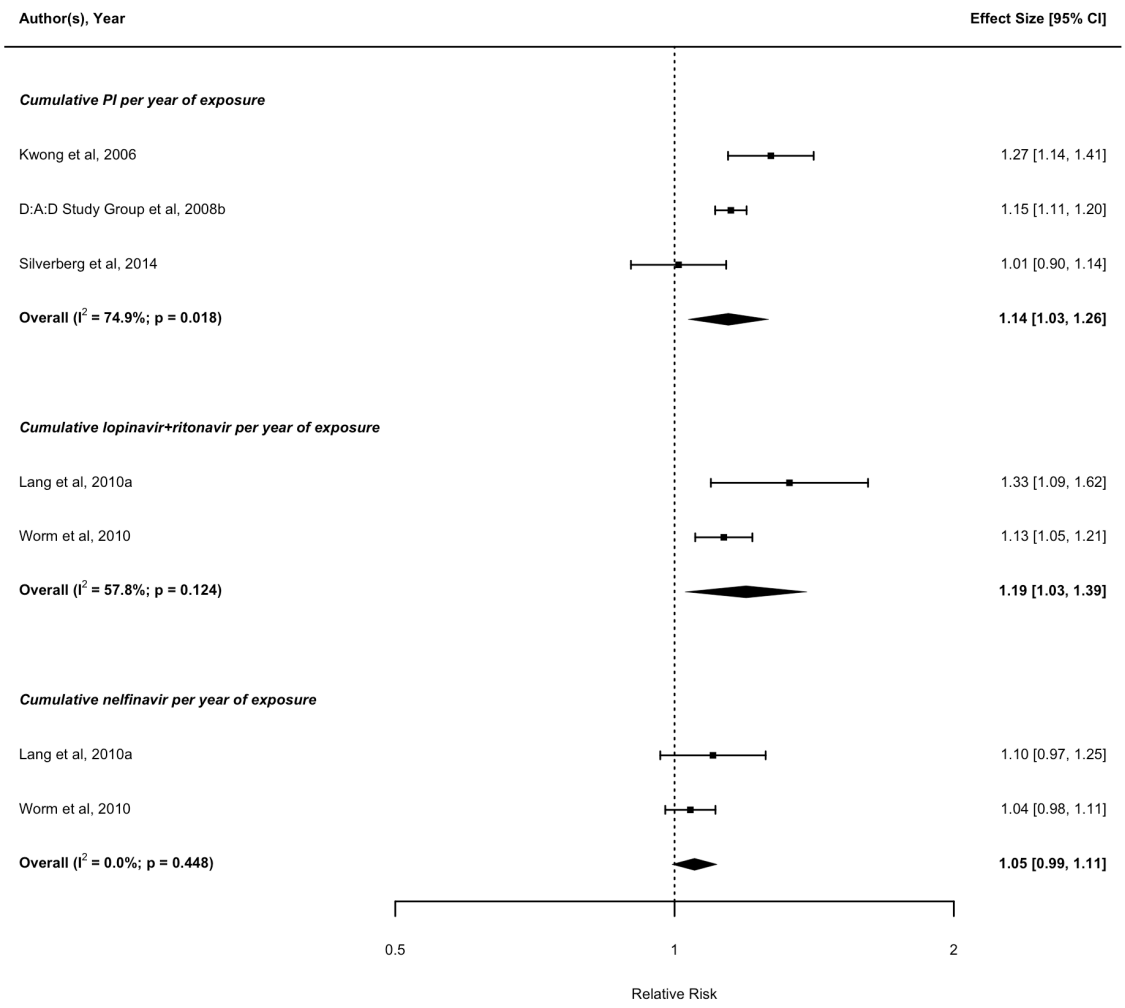


Appendix Figure A6. Forest plot of the meta-analysis of cumulative exposure to drugs of the NRTI class and risk of MI per year of exposure
Legend: CI, Confidence interval

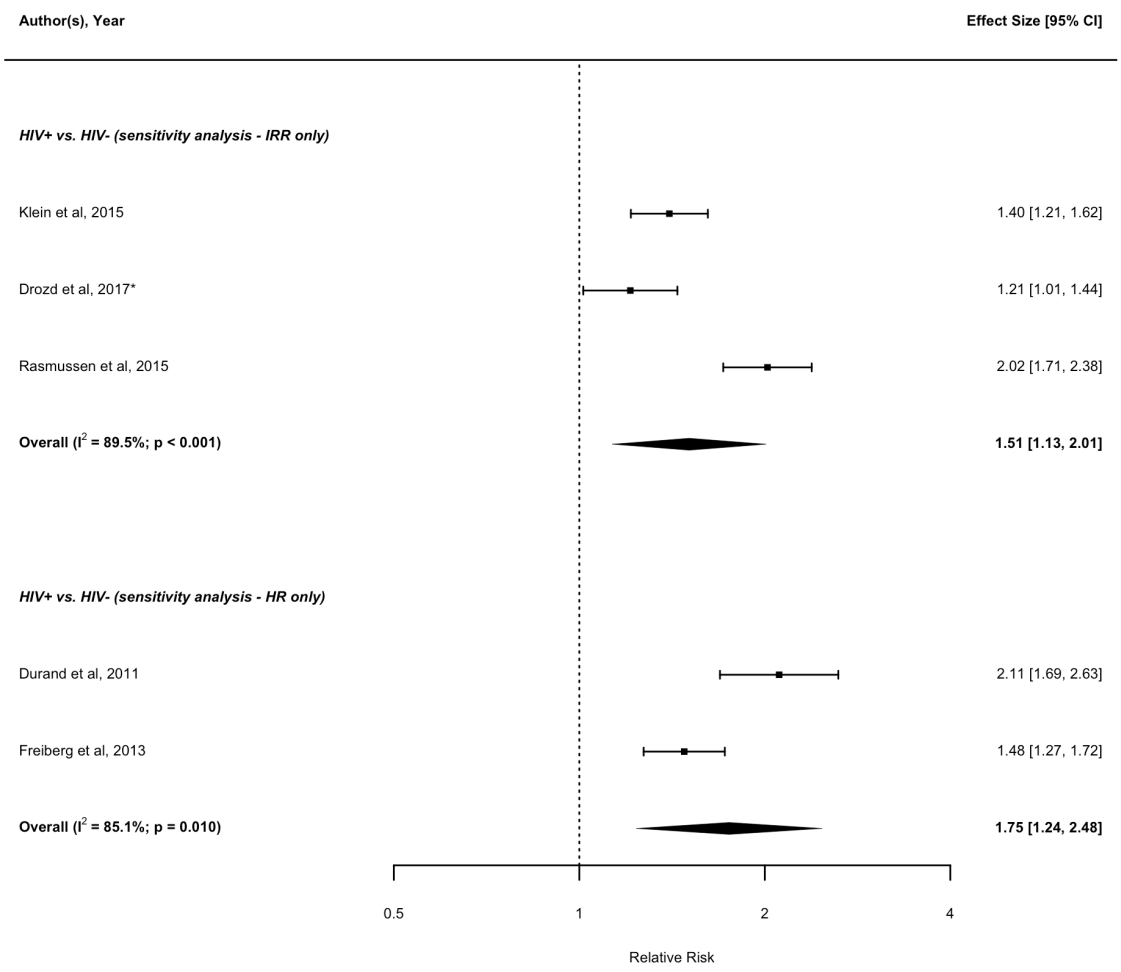


Appendix Figure A7. Forest plot of the meta-analysis of cumulative exposure to NNRTI (both as a class and individually) and risk of MI per year of exposure

Legend: CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors



Appendix Figure A8. Forest plot of the meta-analysis of cumulative exposure to protease inhibitors (both as a class and individually) and risk of MI per year of exposure
Legend: CI, Confidence interval; PI, Protease inhibitors



Appendix Figure A9. Forest plot of the sensitivity analyses for the meta-analysis of the risk of MI according to HIV status, where estimates reported using similar relative effect measures were pooled
Legend: CI, Confidence interval; HR, Hazard ratio; IRR, Incidence rate ratio

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Risk of cardiovascular disease events among HIV-positive individuals compared to HIV-negative individuals: a systematic review and meta-analysis

Oghenowede Eyawo, Gwenyth Brockman, Scott Lear, Charles Goldsmith, Robert Hogg

Citation

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Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42014012977

Review question

How does the risk of cardiovascular disease (CVD) events compare between HIV-positive and HIV-negative adults and what are the potential reasons underlying these differences (if any)?
Does the risk of CVD events differ between subgroups of HIV-positive individuals, for example, among those receiving antiretroviral therapy (ART) compared to those not on ART?
How does the risk of CVD events compare between particular subgroup of HIV-positive individuals (e.g., those on ART) versus HIV-negative individuals?

Searches

We will search the following bibliographic databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Databases of Systematic Reviews up to July 2014. Records published from 2000 onwards will be included. This update was necessary to enable us include several key papers that were published between 2000 and 2004.
Abstracts from two major HIV/AIDS conferences (Conference on Retroviruses and Opportunistic Infections [CROI] and the International AIDS Society [IAS] conferences) for the last two years (CROI 2013 & 2014; AIDS 2012 & IAS 2013) will also be reviewed for inclusion.
Search terms will include a combination of free and indexed terms containing keywords relating to disease and topic of interest. The keywords will include: "HIV", "HIV/AIDS", "stroke", "myocardial infarction", "cardiac death", "cardiovascular disease", "cerebrovascular disease", and "ischemic heart disease".

Types of study to be included

Inclusion criteria: Randomized controlled trials (RCT) and observational studies

Condition or domain being studied

Cardiovascular disease and HIV/AIDS

Participants/population

Inclusion: Adults only. Study inclusion requires that at least one of the studied groups/study arm includes HIV-positive individuals.
Exclusion: Non-adult population. Studies without an HIV-positive comparison group

Intervention(s), exposure(s)

HIV-seropositivity in at least one of the studied groups/arms

Comparator(s)/control

At least one of the study groups/arms should include HIV-positive individuals

Context

We would like to summarize evidence examining the risk of incident CVD events among HIV-positive adults compared to HIV-negative adults

Primary outcome(s)

Incident (new) cardiovascular disease events

Timing and effect measures

For this review, we define cardiovascular disease event to include stroke, myocardial infarction and cardiac death

Secondary outcome(s)

None

Data extraction (selection and coding)

Two independent reviewers will be involved in the screening and extraction of data for this review. Discrepancies will be resolved through discussion and, where necessary, a third reviewer will be invited to assist in achieving consensus

Risk of bias (quality) assessment

The quality of the included studies will be assessed according to the type of study design (RCT or observational study).
For RCTs, we will use a modified Cochrane Risk of Bias tool and will evaluate several key domains including adequacy of randomization/sequence generation, allocation concealment, blinding, use of intention to treat analysis and other sources of bias.

For observational studies, we will make this assessment using the Newcastle-Ottawa Scale which will evaluate study design features including participant selection, comparability of groups, exposure and outcomes.

Strategy for data synthesis

Our approach to the conduct and reporting of the data synthesis will follow the guidelines in the PRISMA Statement. A flow diagram will be used to describe the study selection process. Meta-analysis of the extracted data will be performed only if there is sufficient homogeneity between studies to allow for such quantitative synthesis

Analysis of subgroups or subsets

Depending on the results, we intend to perform subgroup analyses to investigate the effect of study-level variables. The specific subgroup analyses will be informed by the nature of the evidence in the included studies.

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Revision note for this version
The anticipated completion date was revised based on when we now expect to complete the review.The search time frame (only records from the last 10 years) was changed. It now states that: records published from 2000 onwards will be included. This update was necessary to enable us include several key papers that were published between 2000 and 2004.

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note
The anticipated completion date was revised based on when we now expect to complete the review.The search time frame (only records from the last 10 years) was changed. It now states that: records published from 2000 onwards will be included. This update was necessary to enable us include several key papers that

were published between 2000 and 2004.

Versions

14 August 2014
13 November 2014

Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the MOOSE reporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

	Reporting Item	Page Number
#1	Identify the study as a meta-analysis of observational research	1
#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2
#3a	Problem definition	5
#3b	Hypothesis statement	6
#3c	Description of study outcomes	5
#3d	Type of exposure or intervention used	5, 6

	#3e	Type of study designs used	6
	#3f	Study population	7
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	6
	#4b	Search strategy, including time period included in the synthesis and keywords	6
	#4c	Effort to include all available studies, including contact with authors	7
	#4d	Databases and registries searched	7
	#4e	Search software used, name and version, including special features used (eg, explosion)	7
	#4f	Use of hand searching (eg, reference lists of obtained articles)	7
	#4g	List of citations located and those excluded, including justification	See note 1
	#4h	Method of addressing articles published in languages other than English	6
	#4i	Method of handling abstracts and unpublished studies	7
	#4j	Description of any contact with authors	8
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	6-8
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5-8
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	7,8
	#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	n/a
	#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	8,9
	#5f	Assessment of heterogeneity	9
	#5g	Description of statistical methods (eg, complete description of fixed or	8, 9

	random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
#5h	Provision of appropriate tables and graphics	9, 10
#6a	Graphic summarizing individual study estimates and overall estimate	10-14
#6b	Table giving descriptive information for each study included	36
#6c	Results of sensitivity testing (eg, subgroup analysis)	32
#6d	Indication of statistical uncertainty of findings	32
#7a	Quantitative assessment of bias (eg. publication bias)	9
#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	10
#7c	Assessment of quality of included studies	8, 10
#8a	Consideration of alternative explanations for observed results	18
#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	18
#8c	Guidelines for future research	18
#8d	Disclosure of funding source	19

Author notes

1. 10, Appendix

BMJ Open

Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis

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Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis

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Abstract

Objective: Cardiovascular disease is one of the leading non-AIDS-defining causes of death among HIV-positive (HIV+) individuals. However, the evidence surrounding specific components of cardiovascular disease risk remains inconclusive. We conducted a systematic review and meta-analysis to synthesize the available evidence and establish the risk of myocardial infarction (MI) among HIV+ compared with uninfected individuals. We also examined MI risk within subgroups of HIV+ individuals according to exposure to combination antiretroviral therapy (ART), ART class/regimen, CD4 cell count and plasma viral load levels.

Design: Systematic review and meta-analysis

Data sources: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews until July 18, 2018. Furthermore, we scanned recent HIV conference abstracts (CROI, IAS/AIDS) and bibliographies of relevant articles.

Eligibility criteria: Original studies published after December 1999 and reporting comparative data relating to the rate of MI among HIV+ individuals were included.

Data extraction and synthesis: Two reviewers working in duplicate, independently extracted data. Data were pooled using random-effects meta-analysis and reported as relative risk (RR) with 95% confidence intervals (CI).

Results: Thirty-two of the 8,130 identified records were included in the review. The pooled RR suggests that HIV+ individuals have a greater risk of MI compared to uninfected individuals (RR: 1.67, 95%CI: 1.45, 1.94). Depending on risk stratification, there was moderate variation according to ART uptake (RR, ART-treated=1.80; 95%CI: 1.17, 2.77; ART-untreated HIV+ individuals: 1.25; 95%CI: 0.93, 1.67, both relative to uninfected individuals). We found low CD4 count, high

plasma viral load, and certain ART characteristics including cumulative ART exposure, any/cumulative use of protease inhibitors as a class, and exposure to specific ART drugs (e.g. abacavir) to be importantly associated with a greater MI risk.

Conclusions: Our results indicate that HIV infection, low CD4, high plasma viral load, cumulative ART use in general including certain exposure to specific ART class/regimen are associated with increased risk of MI. The association with cumulative ART may be an index of the duration of HIV infection with its attendant inflammation, and not entirely the effect of cumulative exposure to ART per se.

PROSPERO registration number: CRD42014012977

Keywords: Myocardial infarction, Cardiovascular disease, HIV, Combination antiretroviral therapy (ART), Relative risk, Systematic review, Meta-analysis

Word count: 4,480

Article Summary

Strengths and limitations of this study

- We used explicit eligibility criteria and a comprehensive search strategy for this systematic review and meta-analysis
- Adjudication of studies for eligibility and the data extraction was performed by two independent reviewers working in duplicate
- This systematic review and meta-analysis analyzed several additional drug exposure comparisons and clinical measures (e.g. CD4 cell count, plasma viral load) that had not been previously examined in relation to MI risk among HIV-positive individuals
- Some of the comparisons were based on a small number of studies which is a limitation
- Variability in the quality of the included studies may have influenced the results and thus the conclusions drawn.

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading non-AIDS causes of death and disability among people living with HIV in the combination antiretroviral therapy (ART) era.[1 2] Although HIV-positive (HIV+) individuals are believed to be at higher risk of CVD compared to uninfected individuals,[3 4] the results and conclusions from the studies that have examined the nature of the risk of CVD, in particular myocardial infarction (MI) among HIV+ individuals have been conflicting. While some cohort studies have suggested a positive association between ART including specific drug (e.g. abacavir) or drug class (e.g. protease inhibitors [PI]) use and MI, or CVD risk,[5-9] others have not.[10-12] Furthermore, there has been a lack of agreement between observational studies,[8 11 13] and randomized controlled trials (RCT).[14 15] Clearly, the evidence regarding the nature of, and extent of the risk of MI and other CVD events among HIV+ individuals is far from uniform.

Five meta-analyses have been conducted in an attempt to synthesize the data on CVD risk among HIV+ individuals.[16-20] These have either been limited in scope by assessing only the association between ART use and risk of CVD;[16] included trials that lacked MI event adjudication;[17] included trials where CVD events were not among the pre-specified outcomes of interest;[18] provided incomplete results on MI risk;[19] or amalgamated all CVD events (e.g. MI, stroke) as a single outcome.[20] In addition, this latter meta-analysis was fraught with a number of methodological ambiguities.[21]

Given these limitations, coupled with the publication of several new and updated study reports on the topic, we sought to undertake an updated systematic review and meta-analysis of studies

assessing the risk of CVD among persons living with HIV. Considering the scope, diversity and differences in the definition,[22-25] etiology and clinical picture of different CVD events,[26] coupled with the strong body of literature related to HIV and MI and the ongoing debate around potential MI risk associated with use of specific ART medications such as abacavir, we have elected to focus primarily on MI as the outcome of interest for this meta-analysis, as it is the most widely researched CVD outcome among HIV+ individuals. The objective of our study was to estimate the risk of MI among HIV+ individuals relative to uninfected individuals. Additionally, we examined MI risk within subgroups of HIV+ individuals according to exposure to ART, ART class, specific ART regimen, CD4 cell count and plasma viral load levels.

METHODS

Search strategy and selection criteria

The systematic review and meta-analysis was performed in accordance with the PRISMA Statement.[27] A protocol describing the inclusion criteria and analysis methods for this systematic review was specified in advance, registered and published at the international prospective register of systematic reviews (PROSPERO, registration number CRD42014012977).[28]

The search strategy (see Appendix Table 1) was developed in consultation with a medical librarian at Simon Fraser University, BC, Canada. The search terms were based on a combination of indexed and free-text terms reflecting clinical outcomes of interest to the review, and included the following keywords: 'HIV, human immunodeficiency virus, acquired immunodeficiency syndrome, HIV/AIDS, stroke, myocardial infarction, cardiac death, cerebrovascular disease, ischemic heart disease, cardiovascular disease and CVD'. These terms were used in combination

to execute the searches, which were up to July 18, 2018. Using the Ovid platform, we searched the following electronic databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews. In addition, we screened the abstracts of the International AIDS Society conferences (AIDS 2012, 2014, 2016; IAS 2013) and the Conference on Retroviruses and Opportunistic Infections (CROI 2014, 2015, and 2016). We also searched the reference lists of relevant articles and previous systematic reviews for additional eligible publications. Finally, we set up automatic PubMed literature alerts to identify any new relevant article published while the manuscript was under development.

We included original research published in English where at least one of the participant groups were individuals living with HIV, and presenting comparative data on the incidence of MI. We included studies in which results were stratified according to HIV status; CD4 cell count; plasma viral load (pVL) levels; ART use; or exposure to particular ART class or regimen. Studies involving non-human populations; children; as well as those reporting only unadjusted estimates, intermediate, surrogate or CVD biomarker outcomes were excluded (for additional information, see 'study selection' in the Appendix, p1). To reflect the current context of HIV treatment and disease management, we selected studies published from the year 2000 onwards. Although both observational studies and RCTs were eligible for inclusion, we did not include RCTs that were not designed to assess CVD events as a pre-specified outcome to avoid bias.

Working independently and in duplicate, two reviewers (OE and GB) scanned the titles and abstracts of the retrieved records for eligibility. The full-text articles of potentially eligible studies were obtained and reviewed in greater details. Disagreements in study selection were resolved

through discussion, and where necessary, a third investigator (RSH) was invited to facilitate consensus.

Data extraction and quality assessment

The same two reviewers (OE and GB) conducted data extraction independently using a pre-designed data abstraction sheet. We extracted data on study descriptors, sample characteristics, outcome assessment, risk estimate for relevant comparisons, and study quality features. Where necessary, we sought clarification directly from study authors through email contact. In cases where data from the same study described the same event risk in multiple publications, we extracted data from the most comprehensive report while supplementing missing study-level information from the others. In keeping with characterizations in the included studies, exposure to ART was categorized as any (or prior/some *compared to none*), recent (or within the preceding six months *compared to not recent*) and cumulative ART exposure per year of exposure.

The quality of the included studies was assessed according to risk of bias criteria based on the type of study design. As only observational studies were eventually included in the meta-analysis since eligible RCTs were not identified, we made this assessment by evaluating study design features of the eligible observational studies. Following guidelines in the Newcastle-Ottawa Scale (NOS) for assessing the quality of observational studies in meta-analyses[29] and with slight modification of the scoring system to simplify reporting, the risk of bias assessment was performed based on the adequacy of three key domains of the study design features namely: the group/participant selection; comparability of groups; and the exposure and outcome assessments in the individual

studies. For each of these key features, we assigned a "+" (plus) sign when this was clearly and adequately described in the study, and a "–" (minus) sign when it was not clearly described or was missing. A detailed description of the results of the quality assessment is available in the appendix.

Patient and public involvement

No patients were involved in this study. We used data from published materials only

Data analysis

We calculated the kappa statistic as a measure of the inter-reviewer agreement for the selection of articles meeting the inclusion/exclusion criteria. For interpretation, we defined *a priori* the interval for the kappa result using Landis and Koch criteria.[30] For effect measure, we assumed the incidence rate ratio (IRR), odds ratio (OR) and hazard ratio (HR) with corresponding sampling variance to be numerical approximate measures of the relative risk (RR) for a given association of interest with the underlying assumption of a generally low event risk (< 20%),[31-36] and thus combined them as previously described.[19 37-40] We tested this assumption in sensitivity analyses by performing separate meta-analyses where studies presenting results reported using a similar effect measure type were pooled. Given the expected variability among eligible studies, we pooled studies using the DerSimonian-Laird random-effects model.[41] To minimize bias in our pooled estimates, adjusted risk estimates were not combined with unadjusted estimates. The final set of studies that adjusted for confounders did not consistently adjust for the same set of confounders but were deemed to have sufficient internal validity to permit pooling. For the analysis that quantified the overall RR of MI associated with HIV infection, we performed a sensitivity analysis where we

examined the appropriateness of the comparison group by repeating the meta-analysis and including one additional study that involved a general population comparison group,[42] as opposed to an HIV-uninfected comparison group. Given the limitations of the I^2 statistics with observational studies and Cochran Q test when the number of studies is small,[43 44] we assessed heterogeneity by visual inspection of the forest plots for overlap in the confidence intervals of the individual studies, although the I^2 and Cochran Q are reported in the forest plots for completeness sake. We were unable to perform meta-regression analyses to assess the potential effect of study-level covariates on the pooled estimate due to insufficient studies (< 10),[45] in each of the meta-analyses. Although we assessed publication bias by visually inspecting and testing for funnel plot asymmetry,[46] its interpretation was limited by a lack of sufficient number of studies per meta-analysis.[47 48] A p-value < 0.05 was considered statistically significant. The meta-analysis was conducted using the *metafor* package of the R statistical program (version 3.3.1) [49].

RESULTS

Of 8,130 records identified through the database search, the final screening process yielded 64 potentially eligible publications on CVD outcomes, 32 of which had relevant data on MI and were included in this meta-analysis (Figure 1). Overall, there was near perfect agreement between reviewers on the inclusion of studies (kappa statistic = 0.94; 95% confidence interval (95%CI): 0.89, 0.99). The included studies, most of which were conducted in the United States and Europe, were published between 2000 and 2017 and involved approximately 383,471 HIV+ and > 798, 424 HIV- individuals (Appendix Table 2: characteristics of the included studies; *note: the number of individuals in cohorts with multiple publications was accessed only from one of the publication*s). The mean duration of follow-up varied across studies from approximately one to

twenty years. All 32 publications were non-randomized studies and included two nested case-control studies,[11 50] one cohort/nested case-control study,[51] and 29 cohort studies; 15 of which were prospective studies, by design.[3 7 8 13 42 52-61] Twenty-nine studies were published as full-text journal articles, while three were available as conference abstracts.

In general, the reporting and quality of the methodological aspects of the included studies were variable. Three studies did not provide sufficient information necessary to assess the study quality, as they were reported and available as conference abstract/poster.[54 56 62] The eligibility criteria were clearly defined in the majority of studies (94%), description of study participants/ groups was sufficient (100%); however, the exposure or outcome was not adequately ascertained in 15 studies (47%);[8 12 24 51 53 55 59 62-69] one (7%) of which was published as an abstract [62] (see Appendix Table 3: risk of bias in the included studies).

Meta-analysis of the risk of MI

Below, we summarize the results of the meta-analyses of MI risk according to the various risk stratifications assessed. To avoid duplication of reporting, only statistically important RR are stated in text; although both statistically significant and insignificant results are presented in the figures (forest plots).

Risk of MI associated with HIV infection

The pooled RR from the six studies that met eligibility for this assessment of MI risk according to HIV serostatus suggests that HIV+ individuals are more likely to have an MI event compared to uninfected individuals (RR: 1.67; 95%CI: 1.45, 1.94).[3 51 55 68 70 71] In sensitivity analysis (Appendix

Figure S1) where we repeated the meta-analysis and included one additional study that involved a general population comparison group,[42] the overall pooled RR was 1.60; 95%CI: 1.38, 1.85. Figure 2 shows the forest plots for the association between HIV infection and MI risk. Two studies assessed the risk of MI by HIV serostatus according to whether ART treatment was received.[59 72] Compared to uninfected individuals, the pooled RR of MI was significantly higher among HIV+ individuals on ART (RR: 1.80; 95%CI: 1.17, 2.77), but not the ART-untreated HIV+ individuals (RR: 1.25; 95%CI: 0.93, 1.67).

Risk of MI associated with CD4 cell count and plasma viral load levels

The pooled RR based on combining data from three studies suggests that low CD4 cell count (< 200 cells/mm^3) is associated with higher MI risk compared to CD4 ≥ 200 (RR: 1.60; 95%CI: 1.25, 2.04).[3 56 67] Conversely, a high pVL (≥ 100,000 copies/mL) was found to be associated with increased MI risk compared to pVL < 100,000 (RR: 1.45; 95%CI: 1.11, 1.90), based on the pooled results from two studies (Figure 3).[53 67]

Risk of MI associated with recent ART exposure

With regards to *recent treatment exposure* (i.e. within the preceding six months), four eligible studies with data on nucleoside reverse transcriptase inhibitors (NRTI) exposure assessed the risk of MI associated with recent compared to not recent abacavir exposure.[51 52 54 66] The pooled result from these four studies suggests that recent abacavir exposure is associated with increased risk of MI compared to not recent exposure (RR: 1.71; 95%CI: 1.39, 2.10). Similarly, recent didanosine (RR: 1.29; 95%CI: 1.04, 1.60),[51 57 66] and lamivudine (RR: 1.50; 95%CI: 1.18, 1.90),[13 51 66] exposure is associated with increased risk of MI compared to not recent exposures. In contrast,

there was no association between recent tenofovir,[51 57 66] zidovudine,[13 51 66] stavudine,[13 51 66] emtricitabine,[51 66] and MI risk compared to not recent exposure (Figure 4). Based on pooling data from two studies with data on non-nucleoside reverse transcriptase inhibitors (NNRTI) exposure,[51 66] no association was found between recent efavirenz or nevirapine exposure and MI risk compared to not recent exposure (Figure 5). Based on pooled results from the studies assessing the MI risk of individual PIs, recent indinavir was associated with increased MI risk compared to not recent exposure (RR: 1.46; 95%CI: 1.08, 1.95).[51 66] Recent exposure to other PI regimens including atazanavir,[51 66] lopinavir,[51 66] ritonavir,[51 66] nelfinavir,[51 66] and saquinavir,[51 66] was not found to be significantly associated with MI risk compared to not recent exposure (Figure 6).

Risk of MI associated with any ART exposure

In terms of *any treatment exposure*, our meta-analysis did not find an association between exposure to ART and risk of MI compared to no exposure (Appendix Figure A1).[61 72] Based on the pooled results from six studies with data on NRTI exposure,[8 11 13 51 62 67] individuals receiving abacavir were more likely to have an MI compared to those who did not (RR: 1.58; 95%CI: 1.25, 2.00). We found a similar association between didanosine exposure and MI risk (RR: 1.48; 1.16, 1.90).[13 51 67] No important association was found between exposure to tenofovir,[51 67] zidovudine,[13 51] stavudine,[13 51 67] emtricitabine,[51 67] and MI risk, based on our pooled results (Appendix Figure A2). The meta-analysis of studies with data on NNRTI exposure did not find any evidence of an association between either efavirenz,[51 64] or nevirapine exposure,[51 67] and MI risk compared to no exposure (Appendix Figure A3). The pooled RR from four studies demonstrates that PI exposure is associated with an increase in the risk of MI events compared to no exposure to PI (RR: 1.49; 95%CI: 1.16, 1.91).[3 6 60 62] When the analysis was limited to two studies comparing recent PI

exposure to no exposure,[3 62] similar results were found (RR: 1.40; 95%CI: 1.16, 1.69 [data not shown]). For the individual PIs, there was no association between either atazanavir,[51 63 65 67] saquinavir,[51 67] or nelfinavir exposure,[51 67] and MI risk, compared to no exposure (Appendix Figure A4).

Risk of MI associated with cumulative ART exposure

With regards to *cumulative treatment exposure*, three eligible studies provided relevant data regarding the risk of MI and cumulative ART exposure.[12 67 69] We found that cumulative exposure to ART was associated with an increase in the risk of MI per year of exposure (RR: 1.12; 95%CI: 1.06, 1.18) (Appendix Figure A5). For exposure to NRTI regimens, we estimated an increase in MI risk per year of exposure to abacavir (RR: 1.08; 95%CI: 1.01, 1.15) based on pooling data from two eligible studies.[12 57] Similar to abacavir, cumulative zidovudine exposure was associated with an increase in MI risk per year of exposure (RR: 1.05; 95%CI: 1.01, 1.10).[11 13] We found no association between cumulative exposure to either didanosine,[11 13] tenofovir,[11 57] lamivudine,[11 13] or stavudine,[11 13] and MI risk per year of exposure (Appendix Figure A6). The overall RR suggests that cumulative NNRTI exposure as a class (RR: 1.02; 95%CI: 0.97, 1.08),[58 69 72] or as individual drugs (nevirapine, and efavirenz),[11 57] is not significantly associated with increased risk of MI events per year of exposure (Appendix Figure A7). Three eligible studies reported data assessing the risk of MI associated with cumulative exposure to PIs as a class.[58 69 72] There was an increase in risk of MI per year of exposure to PIs (RR: 1.14; 95%CI: 1.03, 1.26). For individual drugs, cumulative exposure to lopinavir with ritonavir (RR: 1.19; 95%CI: 1.03, 1.39),[11 57] but not nelfinavir,[11 57] was found to be associated with increase in the risk of MI events per year of exposure (Appendix Figure A8).

Sensitivity analyses

The strength and direction of the overall RR from the various meta-analyses remained robust in sensitivity analyses where estimates reported using similar effect measures were pooled. For example, HIV+ individuals continued to have higher risk of MI events compared to uninfected individuals when pooled using either IRRs (overall effect: 1.68; 95%CI: 1.17, 2.40) or HRs (overall effect: 1.75; 95%CI: 1.24, 2.48) effect measures, compared to a RR of 1.67; 95%CI: 1.45, 1.94, obtained from pooling results reported using multiple relative effect measures (Appendix Figure S2).

DISCUSSION

This updated systematic review and meta-analysis assessing the risk of MI among people living with HIV reflects contemporary ART era and found the following: (1) HIV+ individuals have a greater risk of MI compared to uninfected individuals; and among HIV+ individuals, (2) low CD4 cell count (< 200 cells/mm^3) and high pVL (> 100,000 copies/mL) are associated with increases in MI risk compared to higher CD4 or lower pVL respectively; (3) cumulative ART exposure is associated with a greater risk of MI per year of exposure; (4) among NRTIs, any type of exposure to abacavir; cumulative exposure to zidovudine; and recent exposure to either didanosine or lamivudine are significantly associated with higher risk of MI; (5) compared to no exposure, any or cumulative exposure to PIs as a class; cumulative exposure to lopinavir with ritonavir; and recent indinavir exposure was associated with higher risk of MI; (6) NNRTIs assessed either as a class or individually were not associated with increased MI risk.

Previous meta-analyses comparing CVD risk among HIV+ and uninfected individuals reported estimates for the association between HIV-seropositivity and MI (RR: 1.79, 95%CI: 1.54, 2.08)[19] or CVD (RR: 1.61, 95%CI: 1.43, 1.81);[20] risk that are similar to our findings for MI (RR: 1.67, 95%CI: 1.45, 1.94). Regarding studies that quantified the risk of MI associated with HIV infection, the appropriateness of the HIV-uninfected group used for comparison purposes is critical; an issue that has been extensively reviewed elsewhere.[73] In sensitivity analysis, the overall RR of MI associated with HIV infection was reduced when we included one additional study involving a 'general population' comparison group, therefore highlighting the importance of using an appropriate control group. As has been previously hypothesized,[3 23 74-76] the probable mechanistic pathway through which HIV infection can induce MI may include a cascade of events involving chronic inflammation, immunodeficiency/CD4 cell depletion, endothelial dysfunction, increased thrombosis and accelerated atherosclerosis that typically accompany both controlled and uncontrolled HIV disease. Relative to uninfected individuals and similar to what we found (RR: 1.80, 95%CI: 1.17, 2.77), one of the previous meta-analysis also reported a higher risk of CVD among ART-treated individuals (RR: 2.00, 95%CI: 1.70, 2.37).[20] We suspect that the higher MI risk among ART-treated HIV+ individuals may not necessarily be attributable to ART alone but rather to the combined effect from a host of factors including HIV itself, ART, and other comorbid risk factors which have been individually shown to contribute to MI risk.[3 5 77 78] Furthermore, the risk associated with cumulative ART exposure may be an index of the duration of HIV infection with its attendant inflammation, and not entirely the effect of cumulative exposure to ART per se.

Specific to abacavir and MI risk, our findings were similar to reports from a previous meta-analysis of observational studies of MI,[16] but different from those of the meta-analysis of RCTs,[17 18] or reports from aggregate clinical trial studies,[14 15] that suggested no risk associated with abacavir exposure. Although observational studies and RCT results regarding MI and CVD risk due to abacavir exposure among people living with HIV are largely at odds, the Simplification with Tenofovir-Emtricitabine or Abacavir-Lamivudine (STEAL) trial is the first RCT to support observational studies finding of increased risk of CVD with exposure to abacavir.[79] Based on the available evidence to date, the controversy regarding the potential association between abacavir use and risk of MI will likely continue to plague the field of HIV therapeutics until such a time when definitive evidence describing the underlying mechanism can be produced.[80 81] A sufficiently powered RCT with long follow-up and including real-world populations reflective of those typically seen clinically may be needed to fully resolve this clinical controversy.

Unlike our results where a class-level effect was evident for PIs, pooled aggregate clinical trial data after one year of treatment with four different PI-based regimens did not find evidence of an increased risk associated with PI compared to NRTI regimen (RR: 1.69; 95%CI: 0.54, 7.48).[82] When we pooled data of individual PIs separately, we did not observe the same 'class-level' results. In our analysis, different PI regimens carried different risks. For example, while recent indinavir and cumulative lopinavir-ritonavir exposure were associated with increased MI risk, nelfinavir or atazanavir did not appear to contribute to MI risk irrespective of the type of exposure data that were pooled.

In terms of the scope and design, our study differs from previous meta-analyses on this topic in several ways. First, we used an expanded search strategy that included more data sources and search of conference archives compared to prior meta-analyses.[16-20] Second, as the association of HIV and ART may affect the risk of MI and other CVD events differently, we did not assess the risk of CVD in general, as was done in previous meta-analysis.[20] Third, we have used more recent risk estimates from studies with longer follow-up such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Fourth, we have included studies published between 2000 and 2017 with reported data from the post-ART era. The historical nature of some of the studies included in previous meta-analysis may have limited their relevance in contemporary times. Finally, this systematic review analyzed several additional drug exposure comparisons and clinical measures (e.g. CD4 cell count, plasma viral load) in relation to MI risk that had not been previously examined.

There are several important considerations that should be taken into account in the interpretation of the results of this study. Accurate characterization of the risk of MI and CVD outcomes in general may be confounded by a number of factors that may have affected our conclusions. The first concern has to do with the differences in the risk factors, drug exposure, HIV-related variables, or population considered in the included studies. No two studies of HIV+ individuals can have participants with the same demographic, clinical and drug exposure profile – all of which play a role in overall health outcomes. There is also the potential for residual, unmeasured confounding given the observational nature of the included studies. For example, we noted that the included studies did not consistently control for the exact same set of confounders which may have undermine their internal validity. Therefore, heterogeneity arising from differences in study design

or other features may have influenced the results and thus the overall conclusions drawn. Although we observed heterogeneity across results of studies included in some of the meta-analyses, this is a common limitation in meta-analysis especially those involving observational studies.[43] Our *a priori* choice of employing the random-effects modeling strategy was driven in part by this expected variability among studies.[83] It is unclear how differences in MI definition may have affected our results. While some studies retrospectively assessed MI and relied on International Classification of Diseases (ICD) codes alone, others followed participants over time and prospectively assessed and validated the MI events.[5 52] Furthermore, our study combined results presented using several different relative effect measures with the assumption that these represent approximately the same numerical value.[31-36] In sensitivity analyses, we did not find any evidence of bias in our pooled estimates, as these did not differ importantly from the pooled estimates we obtained when we combined studies reporting results using the same effect measure. Moreover, we reached comparable conclusions with previous meta-analyses that combined,[19] or did not combine HR estimates with OR, and RR.[16] In terms of the critical appraisal and its impact on the interpretation of the results, variability in the quality of the included studies may have influenced the results of the meta-analyses and thus the conclusions drawn. Also, some of the comparisons in our study were based on a small number of studies which is a limitation. Therefore, additional rigorously conducted studies with extensive confounding factor stratification/adjustment are needed to confirm our findings. Furthermore, considering that the majority of the studies on this topic are carried out in North America and Europe, our study highlights the need for more research to be conducted in resource limited settings where most people living with HIV reside.

CONCLUSIONS

In summary, this updated systematic review and meta-analysis suggests that HIV infection, ART use in general including exposure to specific ART class (e.g. PIs) and regimen (e.g. abacavir) are associated with increased risk of MI. We found the totality of the evidence for an association between HIV infection and MI to be compelling. With respect to ART and MI risk, HIV treatment strategies should certainly consider cardiovascular risk factors including exposure to particular ART drugs as part of patient-tailored care. However, given what we currently know about ART's effectiveness, the benefits of ART for the treatment of HIV infection in terms of viral suppression and immune reconstitution should be balanced against its potential unfavorable impact on MI. Specific to abacavir and MI risk where there is conflicting evidence between observational studies and RCTS, additional rigorously conducted studies in real-world populations are needed to definitively substantiate our findings and strengthen the existing evidence on this topic. Given the multiple potential contributory and mechanistic pathways to developing MI among HIV+ individuals and the complexity/feasibility of designing a large enough study to completely tease apart the potential contributions of each of the factors believed to increase the risk of MI, managing known modifiable risk factors for CVD outcomes (e.g. smoking) through behavioural/lifestyle interventions, would be an excellent first step in reducing the incidence and risk of MI among people living with HIV.

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Author contributions

OE, MWH, SAL, JSGM and RSH conceived and designed the study. OE, GB, and RSH acquired the data. OE performed the statistical analysis with input from CHG, CF-V, and EM. OE, GB, CHG, MWH, SAL, MB, SG, CF-V, AA, EM, JSGM, and RSH contributed to the interpretation of the data. OE drafted the manuscript. OE, GB, CHG, MWH, SAL, MB, SG, CF-V, AA, EM, JSGM, and RSH reviewed the manuscript critically for important intellectual content and approved the final version submitted for publication.

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Competing interests

We declare no competing interests

Patient consent

None required

Data sharing statement

All data and materials used in this research are available in Medline/PubMed. References have been provided.

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82. Coplan PM, Nikas A, Japour A, et al. Incidence of myocardial infarction in randomized clinical trials of protease inhibitor-based antiretroviral therapy: an analysis of four different protease inhibitors. *AIDS research and human retroviruses* 2003;19(6):449-55. doi: 10.1089/088922203766774487

83. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis *Psychological Methods* 1998;3(4):486-504.

Figure Titles and Legends

Figure 1. Flow diagram of study selection

Legend: *, Includes several conference abstract records captured through the database search; **, Includes one study involving a 'general population' comparison group

ART, Combination antiretroviral therapy; CVD, Cardiovascular disease

Figure 2. Forest plot of the meta-analysis of the risk of MI associated with HIV infection

Legend: ART, Antiretroviral therapy; CI, Confidence interval

Figure 3. Forest plot of the meta-analysis of the risk of MI associated with CD4 cell count and plasma viral load levels

Legend: CI, Confidence interval

Figure 4. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NRTI class

Legend: CI, Confidence interval

Figure 5. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NNRTI class

Legend: CI, Confidence interval

Figure 6. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the protease inhibitor class

Legend: CI, Confidence interval

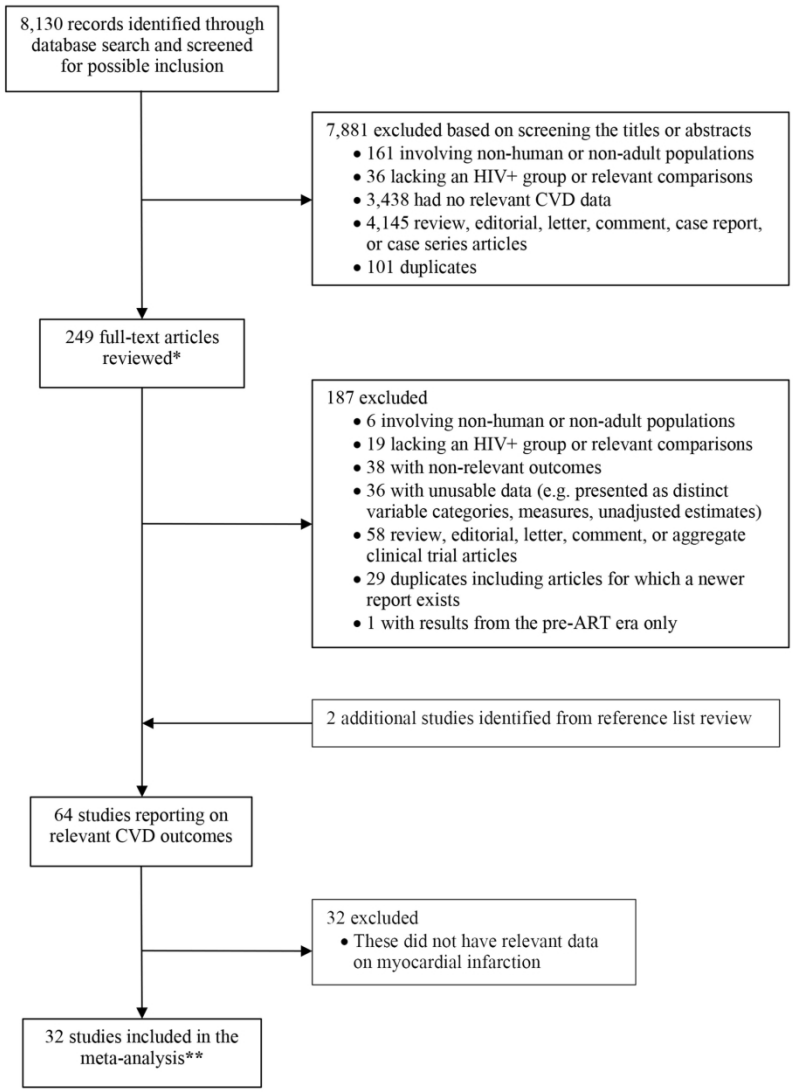

Figure 1. Flow diagram of study selection
Legend: *, Includes several conference abstract records captured through the database search; **, Includes one study involving a 'general population' comparison group
ART, Combination antiretroviral therapy; CVD, Cardiovascular disease

Figure 1. Flow diagram of study selection

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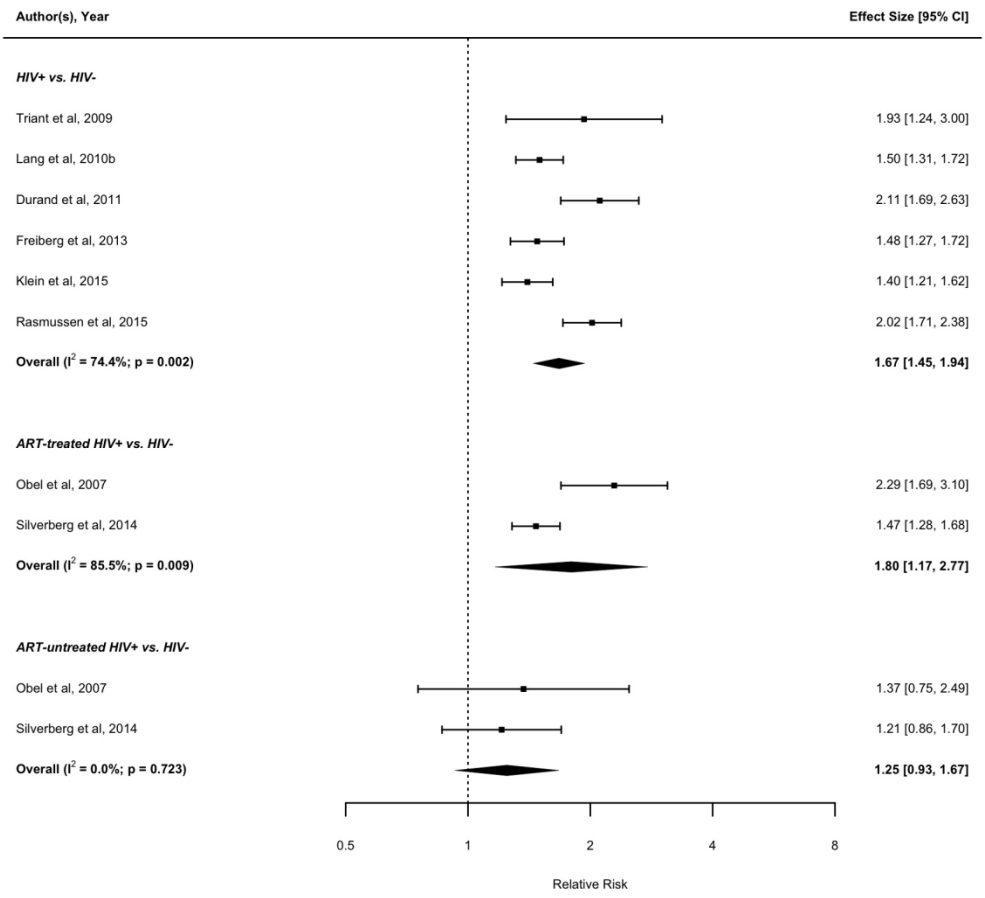

Figure 2. Forest plot of the meta-analysis of the risk of MI associated with HIV infection

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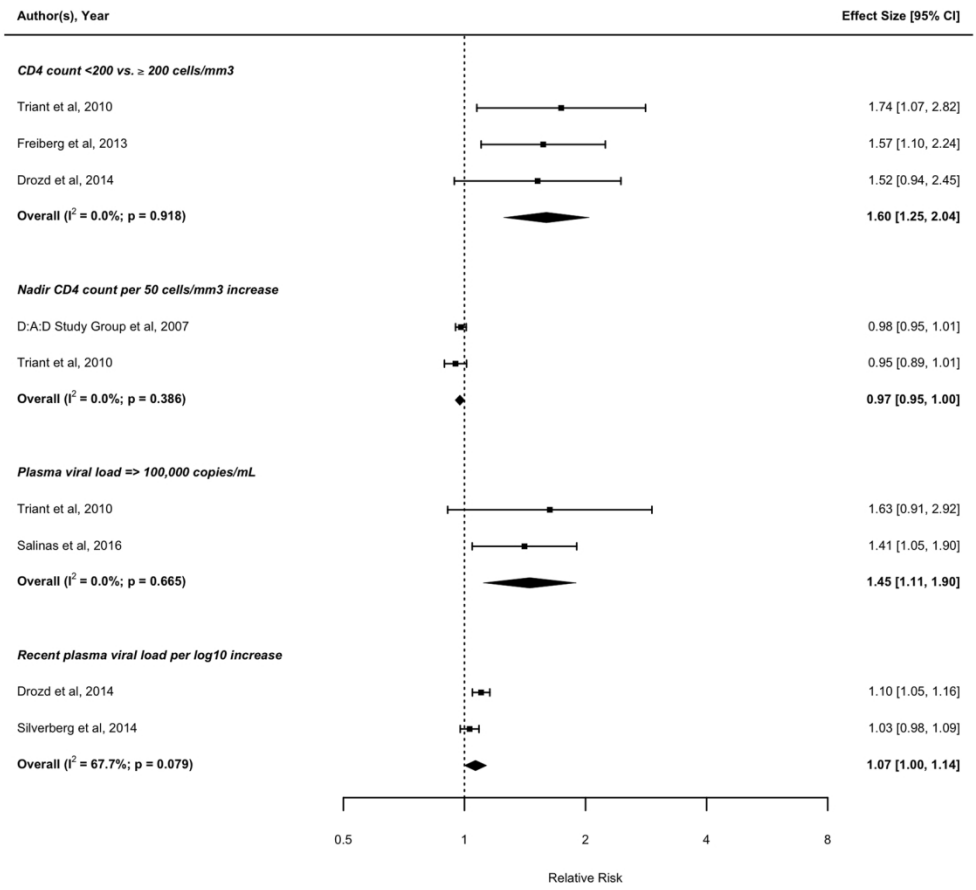

Figure 3. Forest plot of the meta-analysis of the risk of MI associated with CD4 cell count and plasma viral load levels

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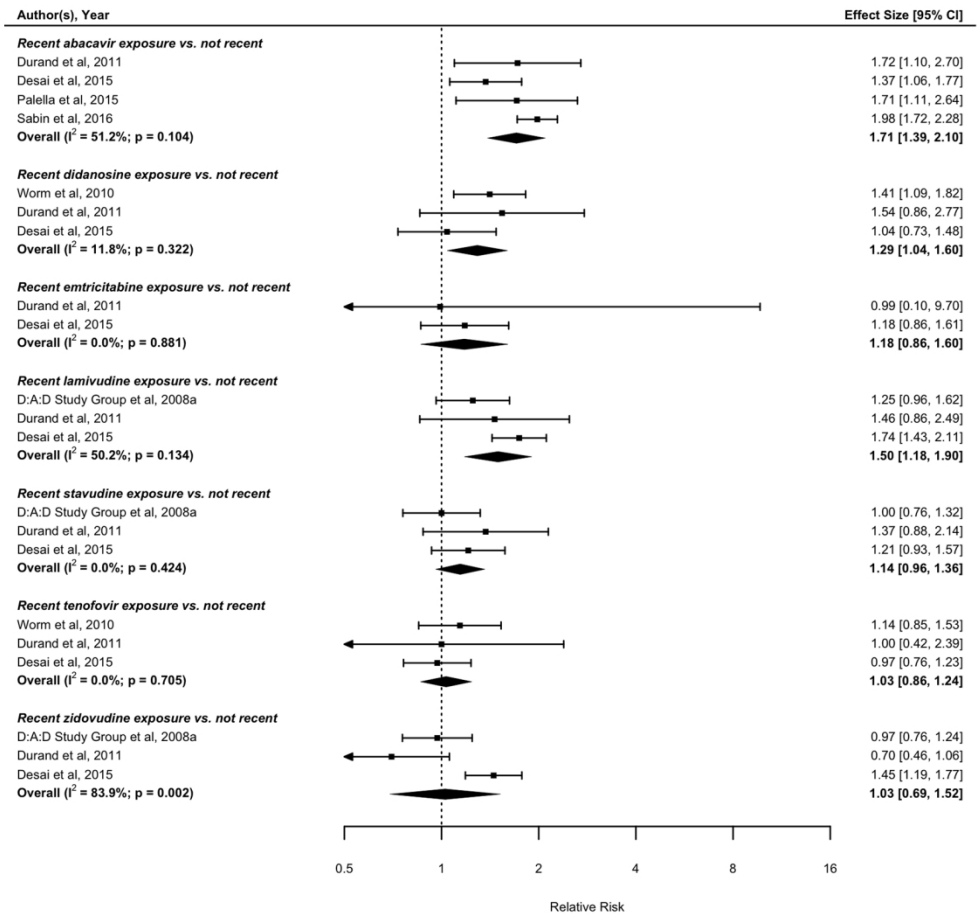

Figure 4. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NRTI class

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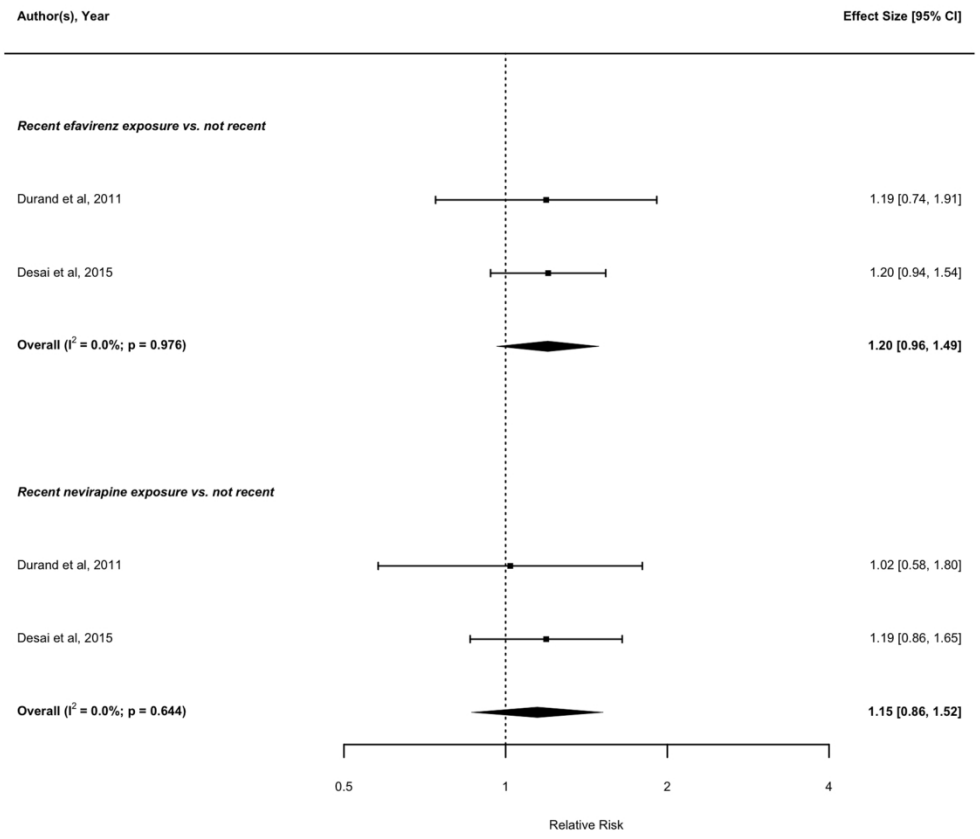

Figure 5. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NNRTI class

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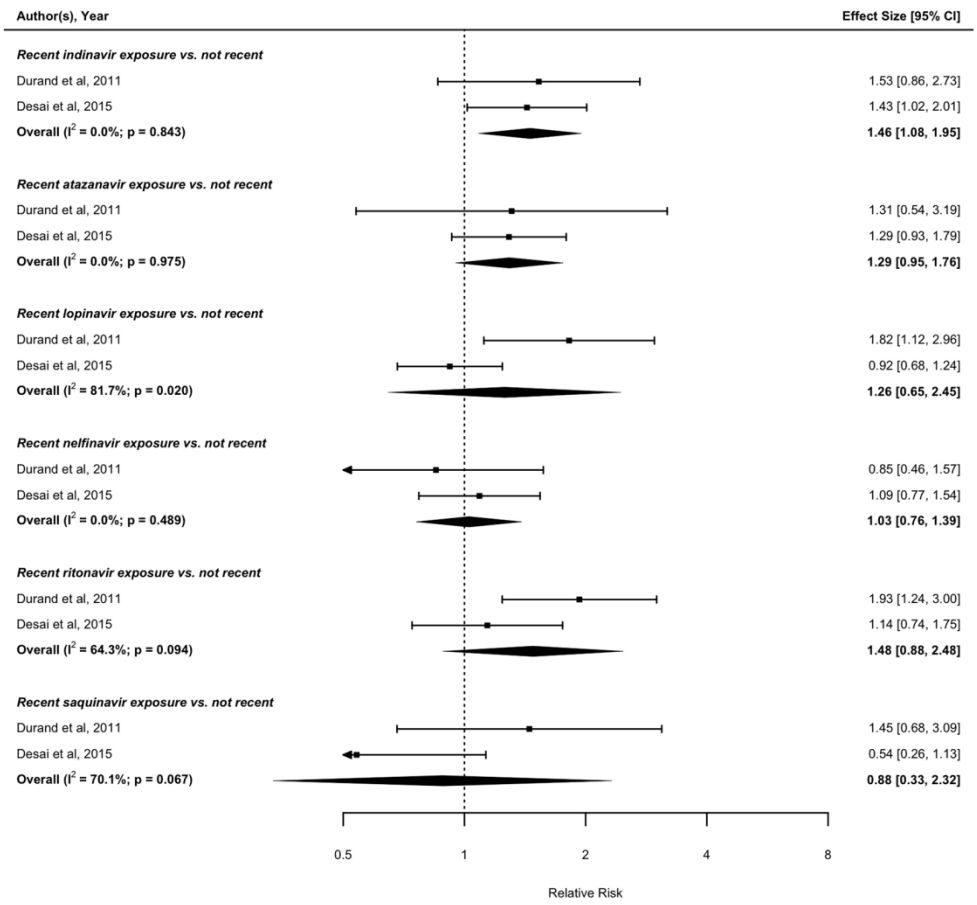


Figure 6. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the protease inhibitor class

152x138mm (300 x 300 DPI)

Appendix

Appendix Table 1. Search strategy

1	hiv.af.
2	human immunodeficiency virus.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
3	acquired immunodeficiency syndrome.af.
4	hiv aids.af.
5	1 or 2 or 3 or 4
6	stroke.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
7	(myocardial infarction or heart attack).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
8	cardiac death.af.
9	cerebrovascular disease.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
10	(ischemic heart disease or Ischaemic heart disease).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
11	(cardiovascular disease or cvd).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
12	6 or 7 or 8 or 9 or 10 or 11
13	5 and 12
14	limit 13 to human
15	limit 14 to english language
16	Limit 15 to yr= "2000 – Current"
17	remove duplicates from 16

Note: The searches were executed in the following four databases: (1) EBM Reviews - Cochrane Central Register of Controlled Trials <June 2018>, (2) EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 11, 2018>, (3) Embase <1974 to 2018 July 17>, (4) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily <1946 to July 17, 2018>

Study selection

The excluded studies included several key CVD review articles,[1–8] and aggregate clinical trial studies,[9–12] whose bibliographies were screened for identification of additional relevant studies. We also excluded a number of potentially eligible records when more comprehensive or updated results for the same participants and risk comparison were published in another report;[13–16] risk associations were reported in a way that would not allow for pairwise grouping with other studies reporting similar associations to facilitate pooling of results;[17–21] or results were reported as number of events or unadjusted risk estimates only.[22–25]

Note: the references cited in the paragraph above are listed at the end of the appendix

Appendix Table 2. Characteristics of included studies

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
LaFleur *et al* 2017[55]	Cohort	USA	ATV-cohort: 12 months Non-ATV: 13 months	HIV+	ATV-cohort: 1,529 (96) Non-ATV: 7,971 (92)	50 years	MI	ATV exposure vs. not exposed	HRᵝ
Drozd *et al* 2017[43]	Cohort	North America	HIV+: 4.5 years HIV-: 19.7 years	HIV+/HIV- (NA-ACCORD / ARIC)	HIV+: 28,912 (81) HIV-: 14,308 (44)	HIV+: 80% were < 50 years HIV-: 27% were < 50 years	Type 1 MI	HIV+ vs. HIV-**	IRRᵝ
Rosenblatt *et al* 2016a[56]	Cohort	USA	EFV-cohort: 23.2 months EFV-free: 19.3 months	HIV+	EFV-cohort: 11,978 (86) EFV-free: 10,234 (79)	EFV-cohort: 40.2 years EFV-free: 40.7 years	MI	EFV exposure vs. not exposed	HRᵝ
Rosenblatt *et al* 2016b[57]	Cohort	USA	ATV-cohort: 24 months ATV-free: 21 months	HIV+	ATV-cohort: 2,437 (76) ATV-free: 19,774 (84)	ATV-cohort: 41.0 years ATV-free: 40.4 years	MI	ATV exposure vs. not exposed	HRᵝ
Sabin *et al* 2016[44]	Cohort	Multi-national	7.0 (4.4-11.1) yearsᵅ	HIV+	49,717 (74)	38 (32-44) yearsᵅ	MI	Current ABC exposure vs. not current (1999-2013)	IRRᵝ
Salinas *et al* 2016[45]	Cohort	USA	1996-2012 (follow-up)	HIV+	8,168 (97)	46 (40-53) yearsᵅ	AMI	VL at ART initiation ≥ 100,000 copies/mL vs. < 100,000	HRᵝ
Desai *et al* 2015[58]	Cohort	USA	~6.7 years	HIV+	24,510 (98)	46.5	MI	Current exposure to ABC vs. not currently exposed Current exposure to DDI vs. not currently exposed Current exposure to ATV vs. not currently exposed Current exposure to TDF vs. not currently exposed Current exposure to LPV vs. not currently exposed Current exposure to FTC vs. not currently exposed Current exposure to 3TC vs. not currently exposed Current exposure to d4T vs. not currently exposed Current exposure to ZDV vs. not currently exposed Current exposure to IDV vs. not currently exposed	ORᵝ / HRᵝ

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Current exposure to NFV vs. not currently exposed Current exposure to SQV vs. not currently exposed Current exposure to RTV vs. not currently exposed Current exposure to EFV vs. not currently exposed Current exposure to NVP vs. not currently exposed	
Klein *et al* 2015[63]	Cohort	USA	HIV+: 4.8years HIV-: 5.8 years	HIV+/HIV-	282,368 (91)	HIV+: 41 years HIV-: 40 years	MI	HIV+ vs HIV-	IRR[β]
Palella *et al* 2015[46]	Cohort	USA	~3.9 years	HIV+	16,733 (81)	Reported proportion of individuals by age categories	MI	Recent ABC use vs. non-recent use	HR[β]
Rasmussen *et al* 2015[47]	Cohort	Denmark	HIV+: 55,050–57,631 PYs HIV-: 638,204–659,237 PYss	HIV+/HIV-	HIV+: 5,897 (76) HIV-: 53,073 (76)	HIV+: 36.8 years[α] HIV-: 36.8 years[α]	MI	HIV+ vs. HIV-	IRR[β]
Drozd *et al* 2014[48]	Cohort	USA	1996-2012 (follow-up) NR	HIV+ HIV+	18,155 (NR) 17,626 (79)	NR Reported proportion of individuals by age categories	MI Primary MI	Current HIV RNA (log (copies/mL)+1) CD4 < 200 vs ≥ 200	OR[β] HR[β]
Silverberg *et al* 2014[65]	Cohort	USA	HIV+: 4.5 years HIV-: 5.4 years	HIV+/HIV-	HIV+: 22,081 (90.6) HIV-: 230,069 (90.5)	Reported proportion of individuals by age categories	MI	ART-treated HIV+ vs. HIV- ART-untreated HIV+ vs. HIV- Recent HIV RNA (per 1 log increase) Prior ART (yes vs no) Duration of PI use per year increase Duration of NNRTI use per year increase	IRR[β]
Freiberg *et al* 2013 [3]	Cohort	USA	5.9 years[α]	HIV+/HIV-	HIV+: 27,350 (97.3) HIV-: 55,109 (97.2)	HIV+: 48.2 years HIV-: 48.8 years	AMI	HIV+ vs. HIV- Recent CD4 < 200 (yes/no) Recent PI use (yes/no)	HR[β]
Lang *et al* 2012[41]	Nested case control	France	4.0 years	HIV+	Cases: 289 (88.9) Controls: 884 (89.1)	Cases: 47 (41-54) years[α] Controls: 46 (40-54) years[α]	MI	Current ABC vs not current HIV RNA per log10 increase	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
Bedimo *et al* 2011[12]	Cohort	USA	3.9 years [α]	HIV+	19,424 (98)	46 years [α]	AMI	Cumulative ABC HAART per year of exposure Current ABC HAART vs. neither ABC/TDF Cumulative ARV per year of exposure	HR[β]
Choi *et al* 2011[59]	Cohort	USA	4.5 years[α]	HIV+	10,931 (98)	46 to 49 years (within subgroups by ART use)	MI	Recent ABC vs. not recent ABC or TDF	HR[β]
Durand *et al* 2011[42]	Cohort	Canada	4.0 years	HIV+/HIV-	HIV+: 7,053 (78); HIV-: 27,681 (78)	HIV+: 39.5 years HIV-: 39.7 years	AMI	HIV+ vs. HIV-	HR[β]
	Nested case control			HIV+	Cases: 125 (91.2); Controls: 1,084 (92.2)	Cases: 49.0 years Controls: 47.5 years	AMI	ABC exposure vs. no exposure Recent ABC vs. not recent DDI exposure vs. no exposure Recent DDI vs. not recent TDF exposure vs. no exposure Recent TDF vs. not recent ATV exposure vs. no exposure Recent ATV vs. not recent Recent LPV vs. not recent Recent RTV vs. not recent Recent EFV vs. not recent NVP exposure vs. no exposure Recent NVP vs. not recent FTC exposure vs. no exposure Recent FTC vs. not recent Recent 3TC vs. not recent d4T exposure vs. no exposure Recent d4T vs. not recent ZDV exposure vs. no exposure Recent ZDV vs. not recent Recent IDV vs. not recent NFV exposure vs. no exposure Recent NFV vs. not recent SQV exposure vs. no exposure	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent SQV vs. not recent	
Carman *et al* 2011[54]	Cohort	USA	1998-2007 (follow-up)	HIV+	66,286 (NR)	NR	AMI	Recent ABC use vs. no use Recent PI use vs. no use	IRR[β]
Lang *et al* 2010b[64]	Cohort	France	2000-2006 (follow-up)	HIV+/ general population	HIV+: ~ 74,958 General population: unclear	35 to 64 years	MI	HIV+ vs general population	SMR
Lang *et al* 2010a[11]	Nested case control	France	2000-2006 (follow-up)	HIV+	Cases: 289 (89) Controls: 884 (89)	Cases: 47 (41-54) years[α] Controls: 46 (40-54) years[α]	MI	Recent ABC exposure vs. no exposure Cumulative ABC exposure vs. no exposure Cumulative DDI per year of exposure Cumulative TDF per year of exposure Cumulative ZVD per year of exposure Cumulative EFV per year of exposure Cumulative NVP per year of exposure Cumulative LPV + RTV per year of exposure Cumulative NFV per year of exposure Cumulative 3TC exposure per year Cumulative d4T exposure per year	OR[β]
Obel *et al* 2010[8]	Cohort	Denmark	~ 6.5 years	HIV+	2,952 (76.4)	39.1 (33.0-46.6) years[α]	MI	ABC exposure vs. no exposure	IRR[β]
Worm *et al* 2010[49]	Cohort	Multi-national	5.8 (3.9-7.5) years[α]	HIV+	33,308 (74)	With MI: 49 (43-65) years[α] Without MI: 44 (38-50) years[α]	MI	Cumulative ABC exposure per year Recent TDF exposure vs. not recent Cumulative TDF exposure per year Recent DDI exposure vs. not recent Cumulative LPV-RTV exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Cumulative NFV exposure per year Cumulative NVP exposure per year Cumulative EFV exposure per year	
Triant *et al* 2010[60]	Cohort	USA	5.1 years[α]	HIV+	6,517 (69)	46 years	AMI	CD4 count < 200/mm^3 vs ≥ 200 Nadir CD4 per 50/mm^3 increase VL > 100,000 copies/mL vs. ≤ 100,000 HIV RNA per log 10 increase ART per year since first ART use TDF use vs. none ABC use vs. none DDI use vs. none FTC use vs. none d4T use vs. none NVP use vs. none ATV use vs. none NFV use vs. none SQV use vs. none	OR[β]
Triant *et al* 2009[61]	Cohort	USA	HIV+: 6.0 years HIV-: 5.8 years	HIV+/HIV-	HIV+: 487 (62.8) HIV-: 69,870 (45.6)	HIV+/HIV-: Reported proportion by age categories	AMI	HIV+ vs. HIV-	OR[β]
D:A:D Study Group *et al* 2008a[13]	Cohort	Multi-national	5.1 years[α]	HIV+	33,347 (74)	With MI: 49 (range: 24-92) years[α] Without MI: 44 (range: 12-95) years[α]	MI	Recent ABC exposure vs. never exposed to ABC Recent DDI exposure vs. never exposed Cumulative DDI exposure per year Recent ZDV exposure vs. never exposed Recent ZDV exposure vs. not recent Cumulative ZDV exposure per year Recent 3TC exposure vs. not recent Cumulative 3TC exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent d4T exposure vs. not recent Recent d4T exposure vs. never exposed Cumulative d4T exposure per year	
D:A:D Study Group *et al* 2008b[50]	Cohort	Multi-national	4.5 years[α]	HIV+	28,985 (NR)	Reported by calendar period	MI	Cumulative exposure to PIs per year Cumulative exposure to NNRTIs per year	Relative rate[β]
D:A:D Study Group *et al* 2007[7]	Cohort	Multi-national	4.5 years[α]	HIV+	23,437 (76)	39 (34-45) years[α]	MI	Nadir CD4 per 50 cells/mm^3 increase	Relative rate[β]
Obel *et al* 2007[51]	Cohort	Denmark	HIV+: 6.9years[α] HIV-: 8.1 years[α]	HIV+/ HIV-	HIV+: 3,953 (76.8) HIV-: 373,856 (76.3)	HIV+: 36.8 (30.8-44.6) years[α] HIV-: 36.4 (30.6-44.0) years[α]	MI	HIV+, on HAART+ vs. HIV- HIV+ not on HAART- vs. HIV-	IRR[β]
Kwong *et al* 2006[62]	Cohort	USA and Netherlands	3.49 (range: 0.02-18.46) years[α]	HIV+	18,603 (82.63)	36 (range: 18-92) years[α]	MI	PI per year of exposure NNRTI per year of exposure HAART per year of exposure	RR[β]
Mary-Krause *et al* 2003[6]	Cohort	France	With MI: 28 (18-39) months[α] Without MI: 33 (15-48) months[α]	HIV+ men	34,976 (100)	With MI: 41.9 years Without MI: 37.7 years	MI	Exposure to PI	Relative hazard[β]
Holmberg *et al* 2002[52]	Cohort	USA	~ 3.1 years	HIV+	5,672 (82)	42.6 years	MI	PI use (yes vs no)	HR[β]
Rickerts *et al* 2000*[53]	Cohort	Germany	24.6 ± 18.1 months	HIV+	2,861 (78)	36.6 ± 9.5 years	MI	Prior HAART (yes vs. no)	OR[β]

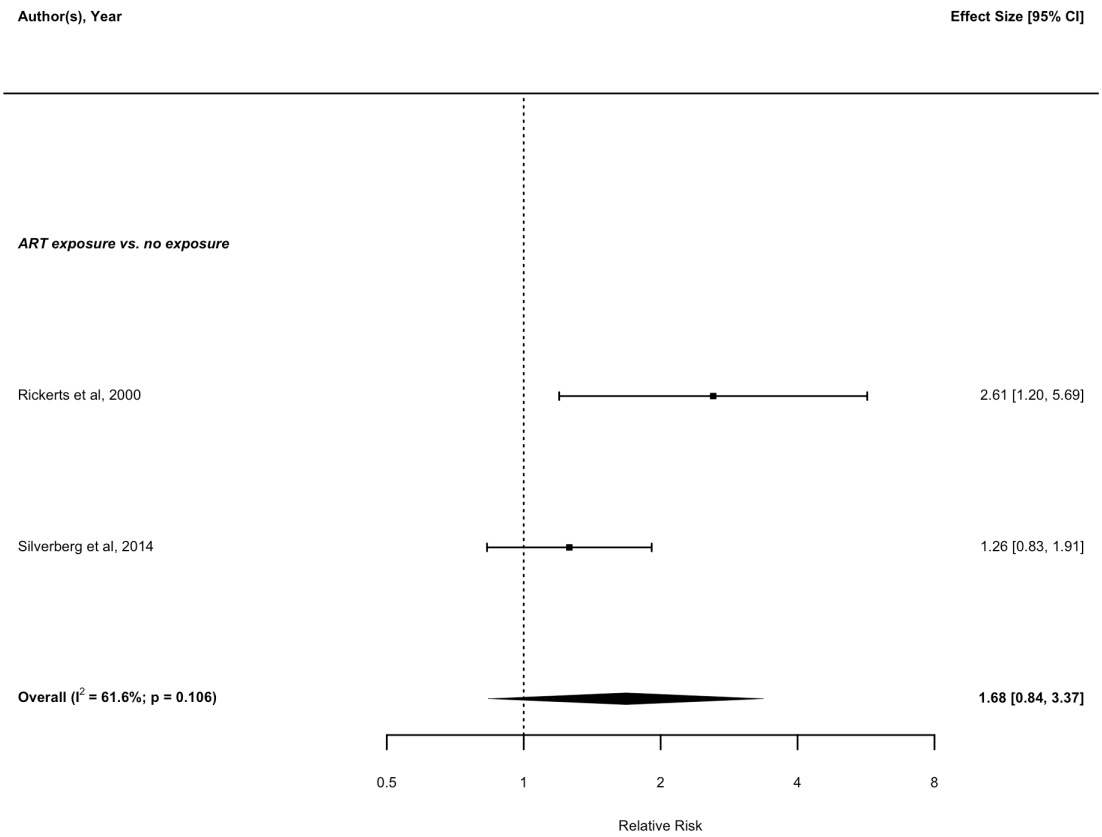
Legend: [α], median (including lower and upper quartiles, where reported); [β], adjusted estimate; *, extracted data from the ART era only; **, this was a general population comparison group and may not have consisted of HIV- individuals only; Note: a superscript alongside the author name/year is used to denote the reference number of the study; **ABC**, abacavir; **AMI**, acute myocardial infarction; **ARIC**, Atherosclerosis Risk in Communities; **ART**, antiretroviral therapy; **ATV**, atazanavir; **DDI**, didanosine; **d4T**, stavudine; **EFV**, efavirenz; **FTC**, emtricitabine; **HAART**, highly active antiretroviral therapy; **HR**, Hazard ratio; **IDV**, indinavir; **IRR**, incidence rate ratio; **LPV**, lopinavir; **LPV-RTV**, lopinavir-ritonavir; **MI**, myocardial infarction; **NA-ACCORD/ARIC**, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)/Atherosclerosis Risk in Communities (ARIC) cohorts; **NFV**, nelfinavir; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **NR**, not reported; **NRTI**, nucleoside reverse transcriptase inhibitor; **NVP**, nevirapine; **OR**, Odds ratio; **PI**, protease inhibitor; **RR**, relative risk; **RTV**, ritonavir; **SMR**, standardized morbidity ratio; **SQV**, saquinavir; **TDF**, tenofovir; **VL**, viral load; **ZDV**, zidovudine; **3TC**, lamivudine

Appendix Table 3. Risk of bias in the included studies

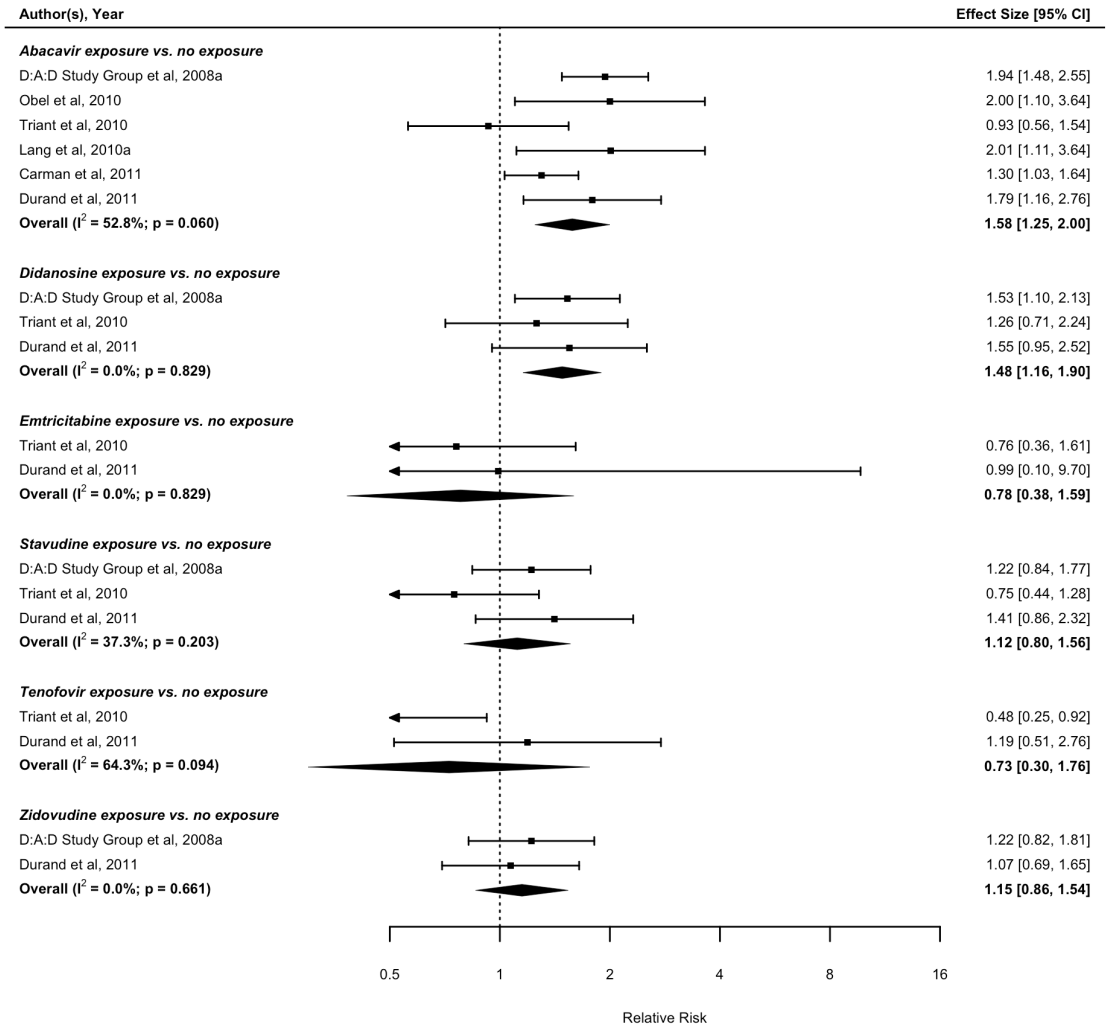
Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
LaFleur *et al* 2017[55]	Journal	Cohort (R)	+	+	No	+	-	-	Public. industry
Drozd *et al* 2017[43]	Journal	Cohort (P & R)	+	+	Yes*	-	+	+	Public
Rosenblatt *et al* 2016a[56]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Rosenblatt *et al* 2016b[57]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Sabin *et al* 2016[44]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Salinas *et al* 2016[45]	Journal	Cohort (P)	+	+	No	+	-	+	Public
Desai *et al* 2015[58]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Klein *et al* 2015[63]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Palella *et al* 2015[46]	Abstract	Cohort (P & R)	+	+	No	-	+	+	-
Rasmussen *et al* 2015[47]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Drozd *et al* 2014[48]	Abstract	Cohort (P)	-	+	No	-	+	-	Public
Silverberg *et al* 2014[65]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Freiberg *et al* 2013[3]	Journal	Cohort (P)	+	+	No	+	+	+	Public
Lang *et al* 2012[41]	Journal	Nested case-control	+	+	No	+	+	+	Public
Bedimo *et al* 2011[12]	Journal	Cohort (R)	+	+	No	+	-	+	-
Choi *et al* 2011[59]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Durand *et al* 2011[42]	Journal	Cohort (R), & nested case-control	+	+	No	+	-	+	Industry
Carman *et al* 2011[54]	Abstract	Cohort (R)	-	+	-	-	-	+	-

Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
Lang *et al* 2010a[64]	Journal	Nested case-control	+	+	No	+	+	+	Public
Lang *et al* 2010b[11]	Journal	Cohort (R)	+	+	No	-	+	+	Public
Obel *et al* 2010[8]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Worm *et al* 2010[49]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Triant *et al* 2010[60]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Triant *et al* 2009[61]	Journal	Cohort (R)	+	+	No	+	-	+	Public
D:A:D Study Group *et al* 2008a[13]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2008b[50]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2007[7]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Obel *et al* 2007[51]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Kwong *et al* 2006[62]	Journal	Cohort (R)	+	+	No	+	-	+	Public, industry
Mary-Krause *et al* 2003[6]	Journal	Cohort (R)	+	+	No	+	+	+	Public
Holmberg *et al* 2002[52]	Journal	Cohort (P)	+	+	No	-	+	+	Public
Rickerts *et al* 2000[53]	Journal	Cohort (P)	+	+	No	+	+	+	-

Legend: + means this is clearly described and adequate; - means this is unclear, inadequate or not reported; *, The HIV+ cohort (NA-ACCORD study) was compared to a general population cohort from a different study (Atherosclerosis Risk in Communities [ARIC] study); Note: a superscript alongside the author name/year is used to denote the reference number of the study; **NA**, Not applicable; **P**, Prospective; **R**, Retrospective

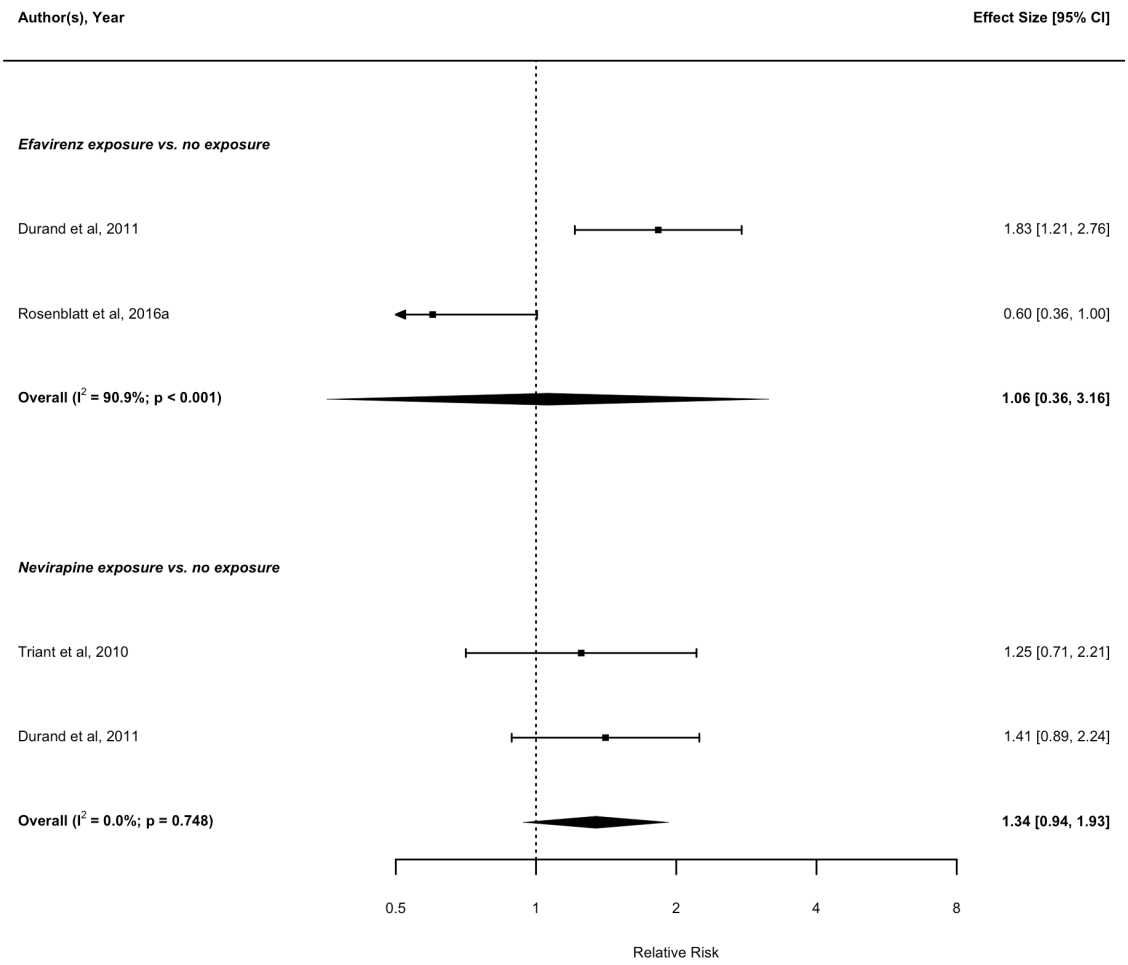


Appendix Figure A1. Forest plot of the meta-analysis of the risk of MI associated with any exposure to antiretroviral therapy
Legend: CI, Confidence interval

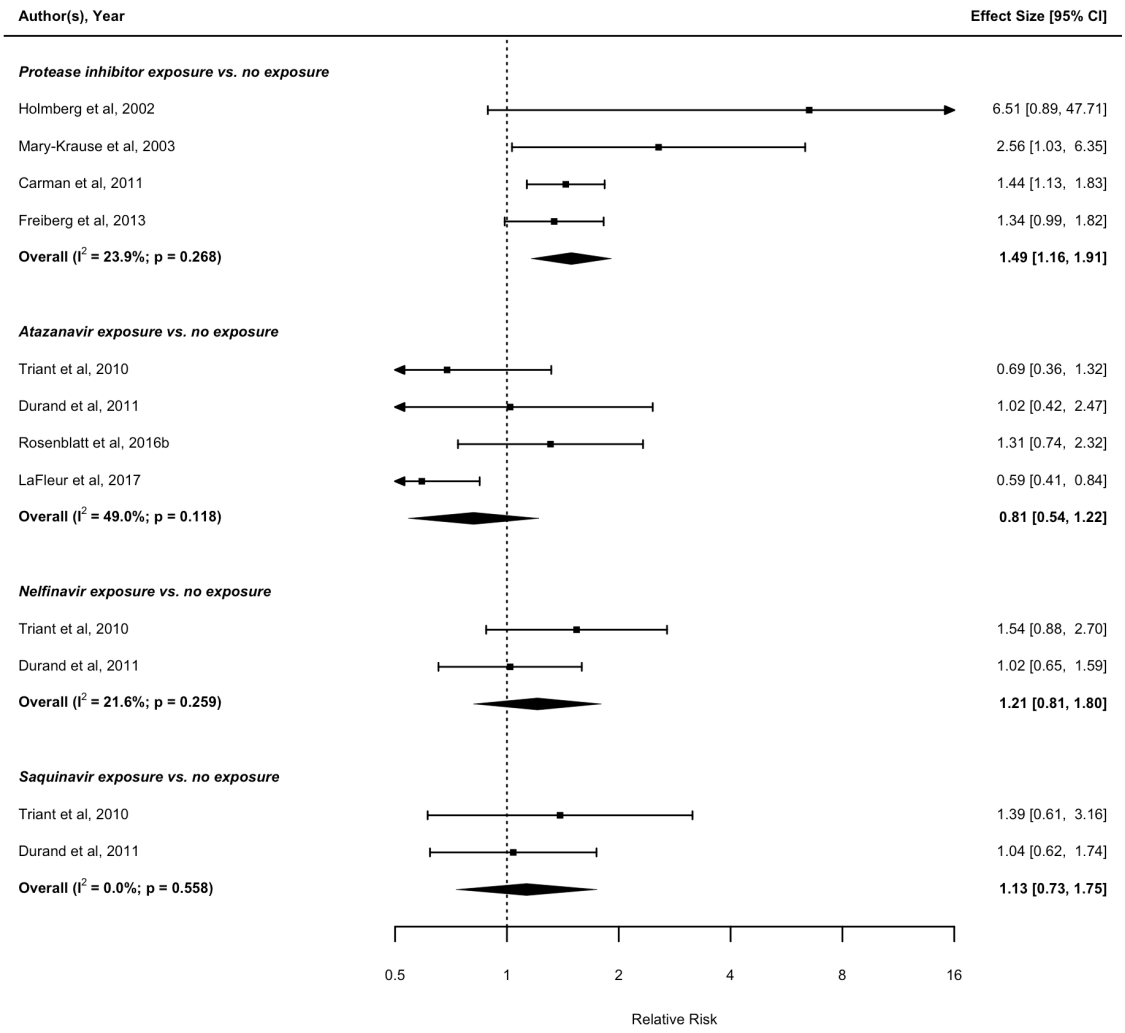


Appendix Figure A2. Forest plot of the meta-analysis of the risk of MI associated with any exposure to drugs of the NRTI class

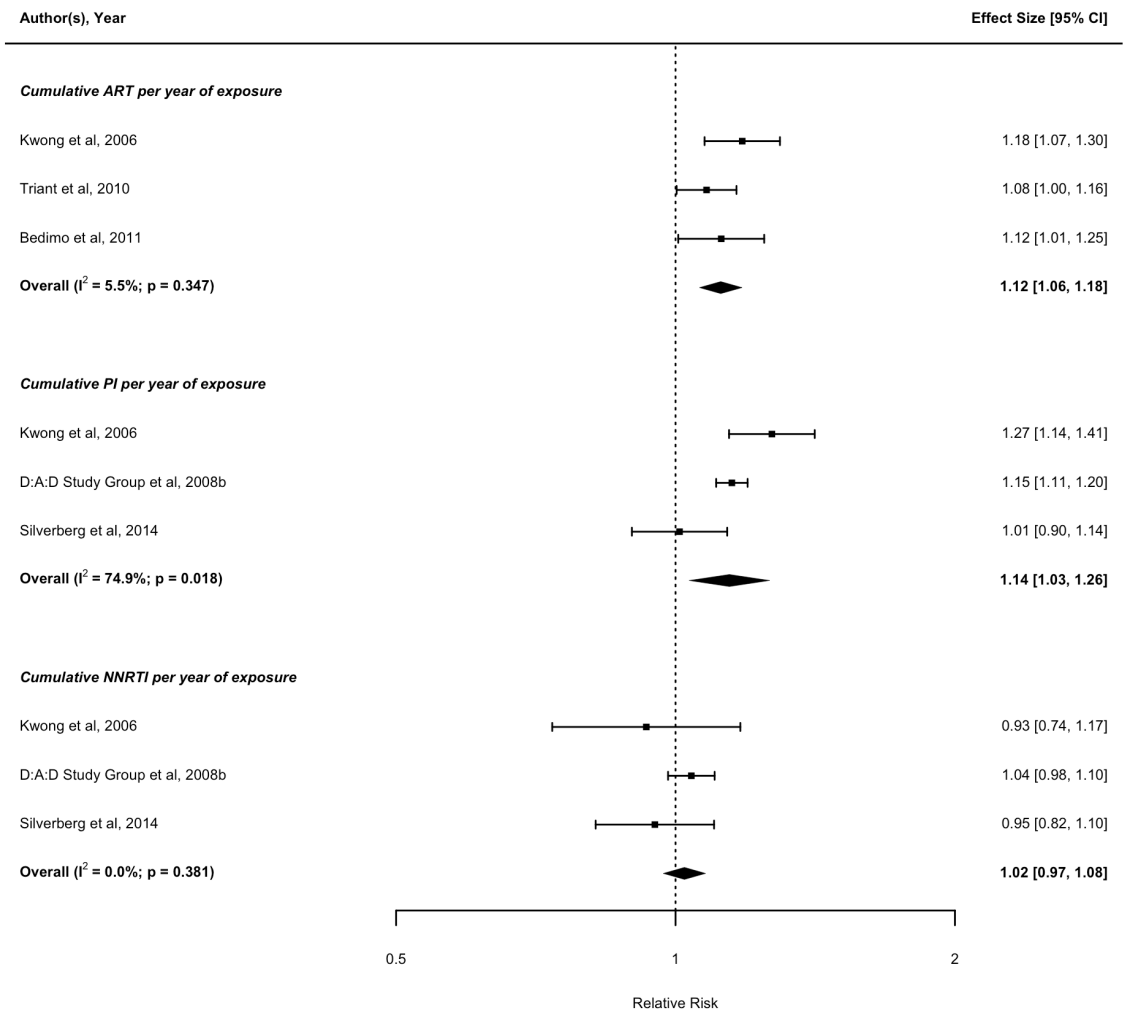
Legend: CI, Confidence interval



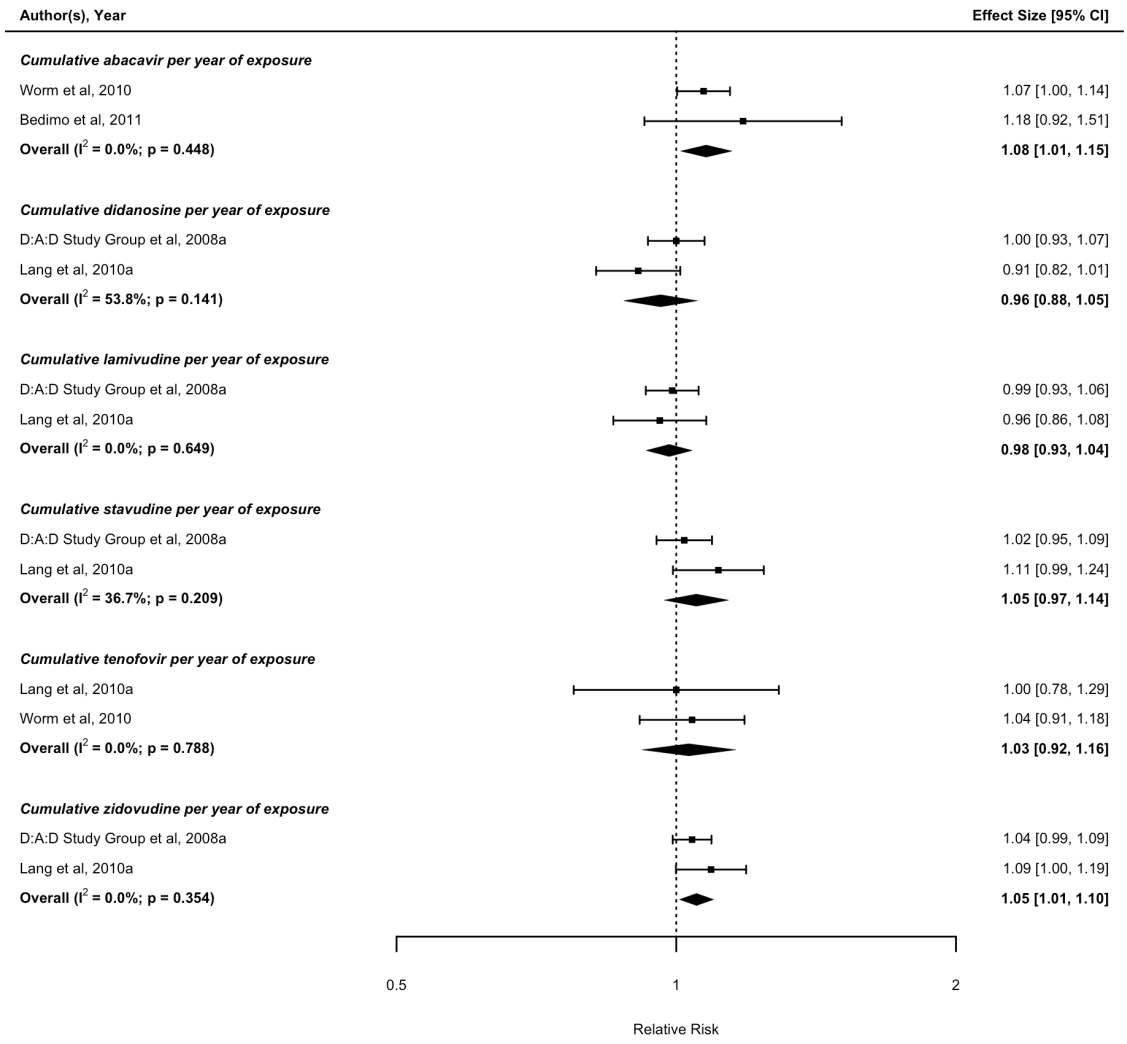
Appendix Figure A3. Forest plot of the meta-analysis of the risk of MI associated with any exposure to drugs of the NNRTI class
Legend: CI, Confidence interval



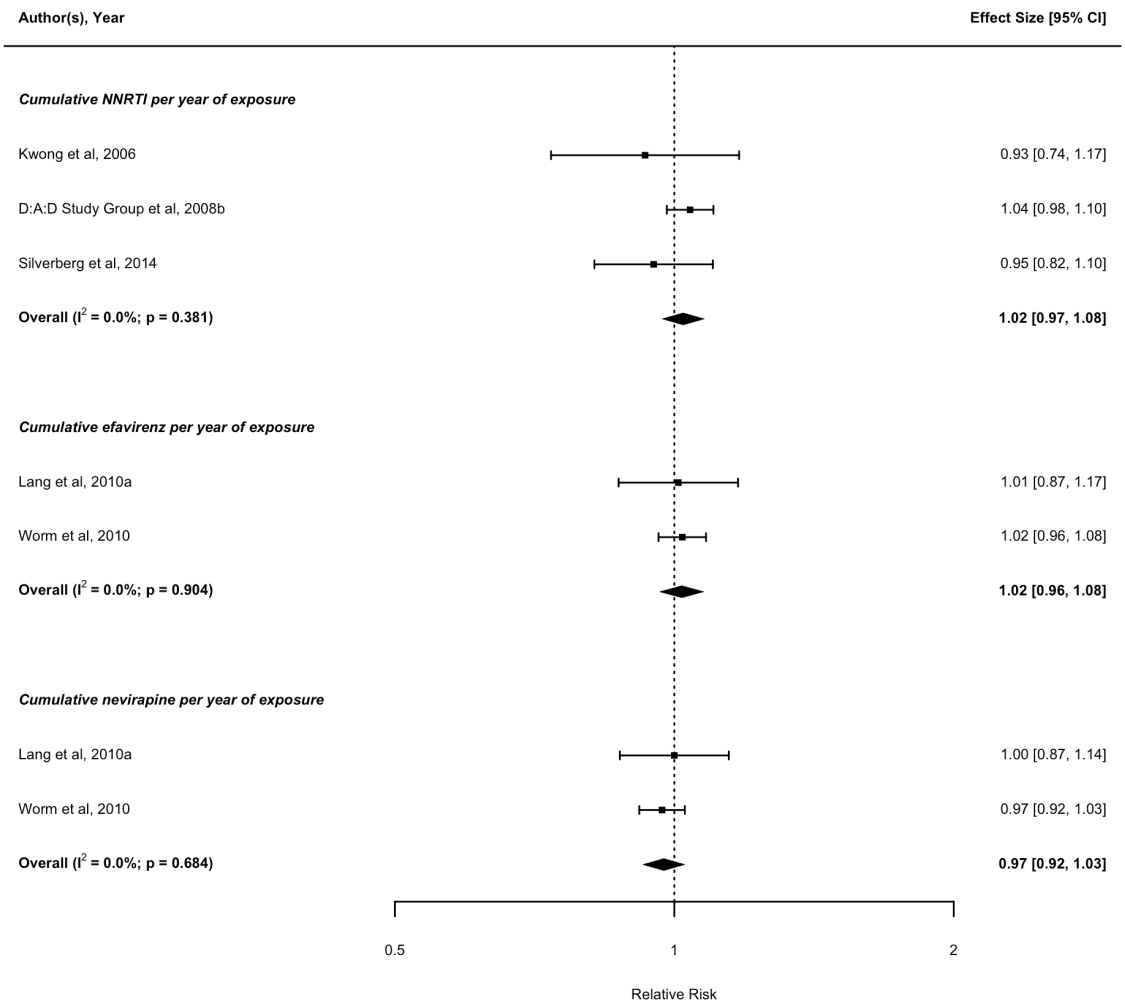
Appendix Figure A4. Forest plot of the meta-analysis of the risk of MI associated with any exposure to protease inhibitors (both as a class and individually)
Legend: CI, Confidence interval



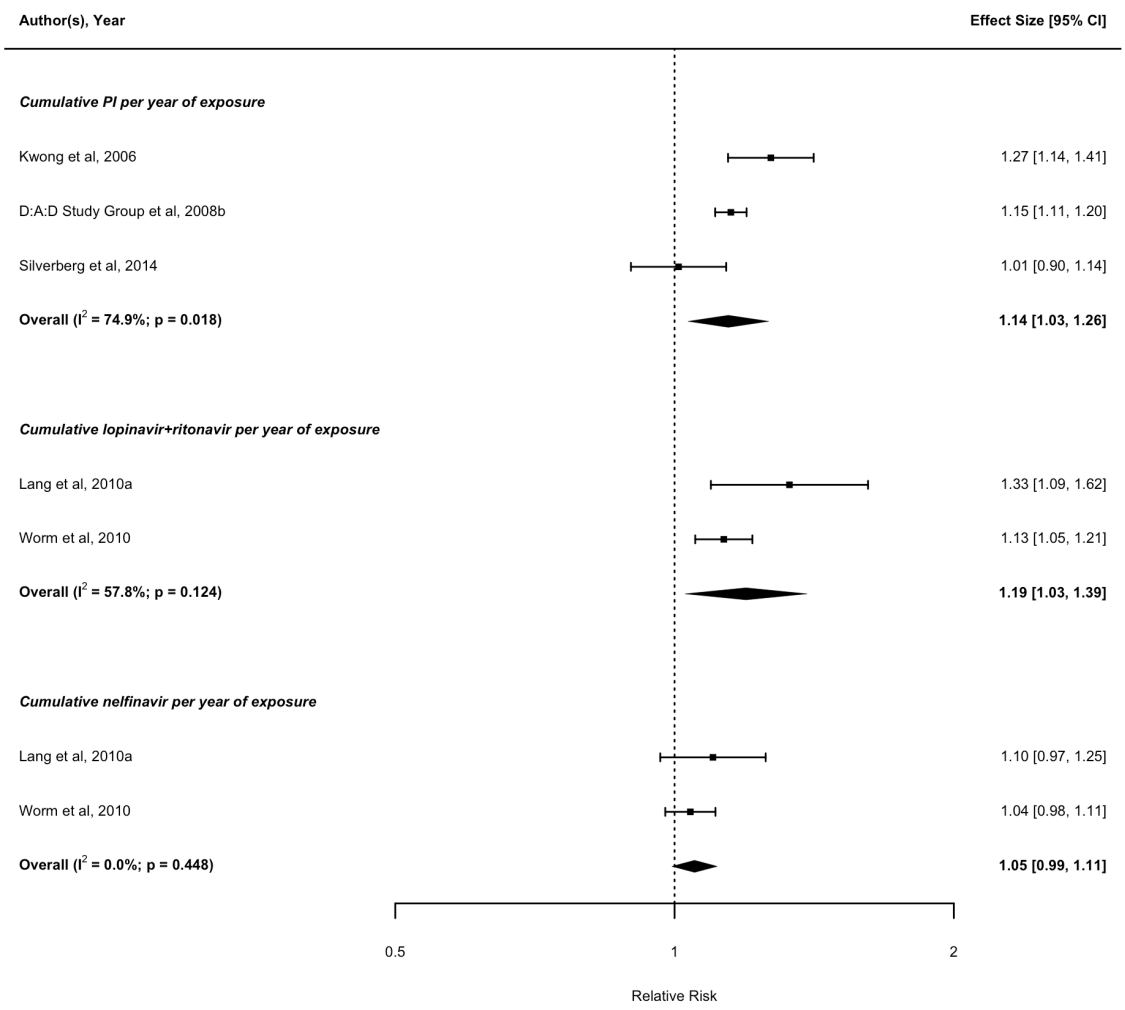
Appendix Figure A5. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to antiretroviral therapy (ART) including class of ART
Legend: ART, Antiretroviral therapy; CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease inhibitors



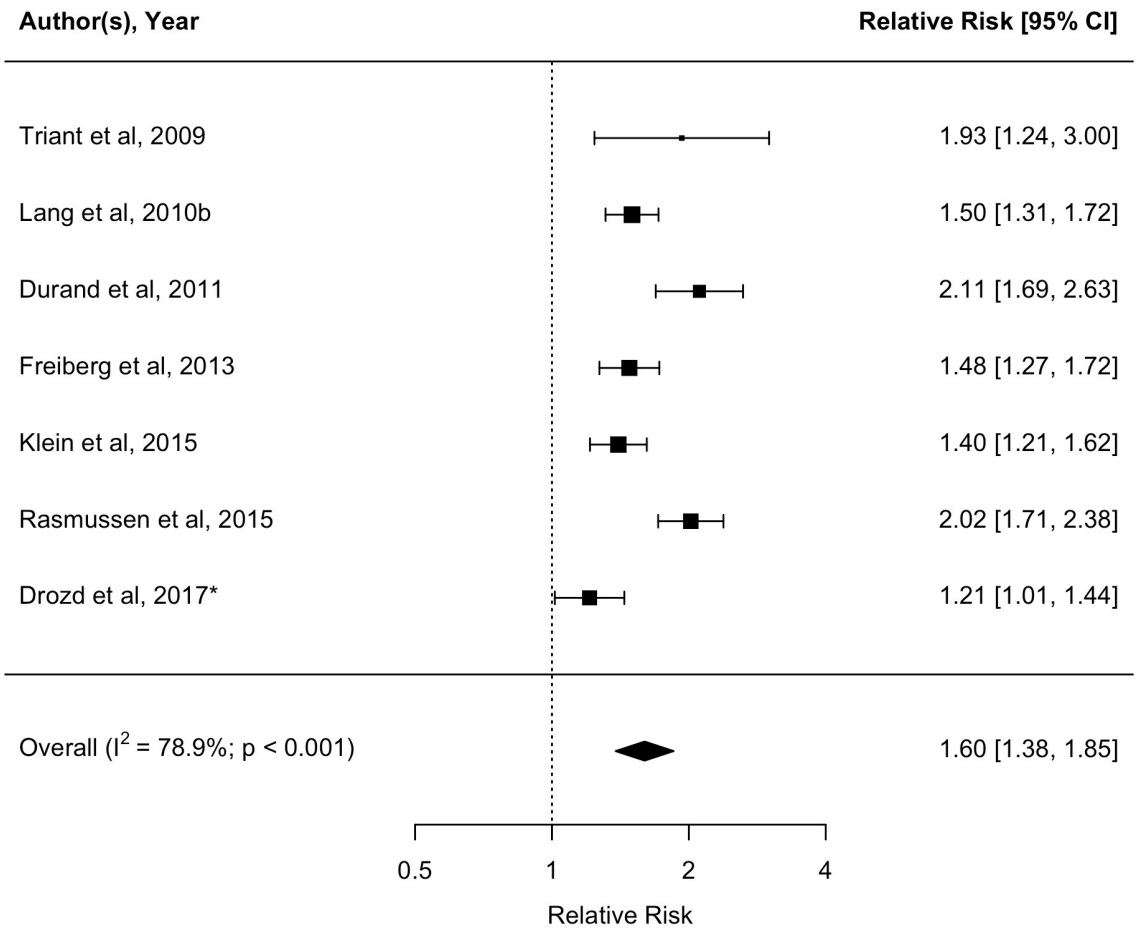
Appendix Figure A6. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to drugs of the NRTI class
Legend: CI, Confidence interval



Appendix Figure A7. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to NNRTI (both as a class and individually)
Legend: CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors

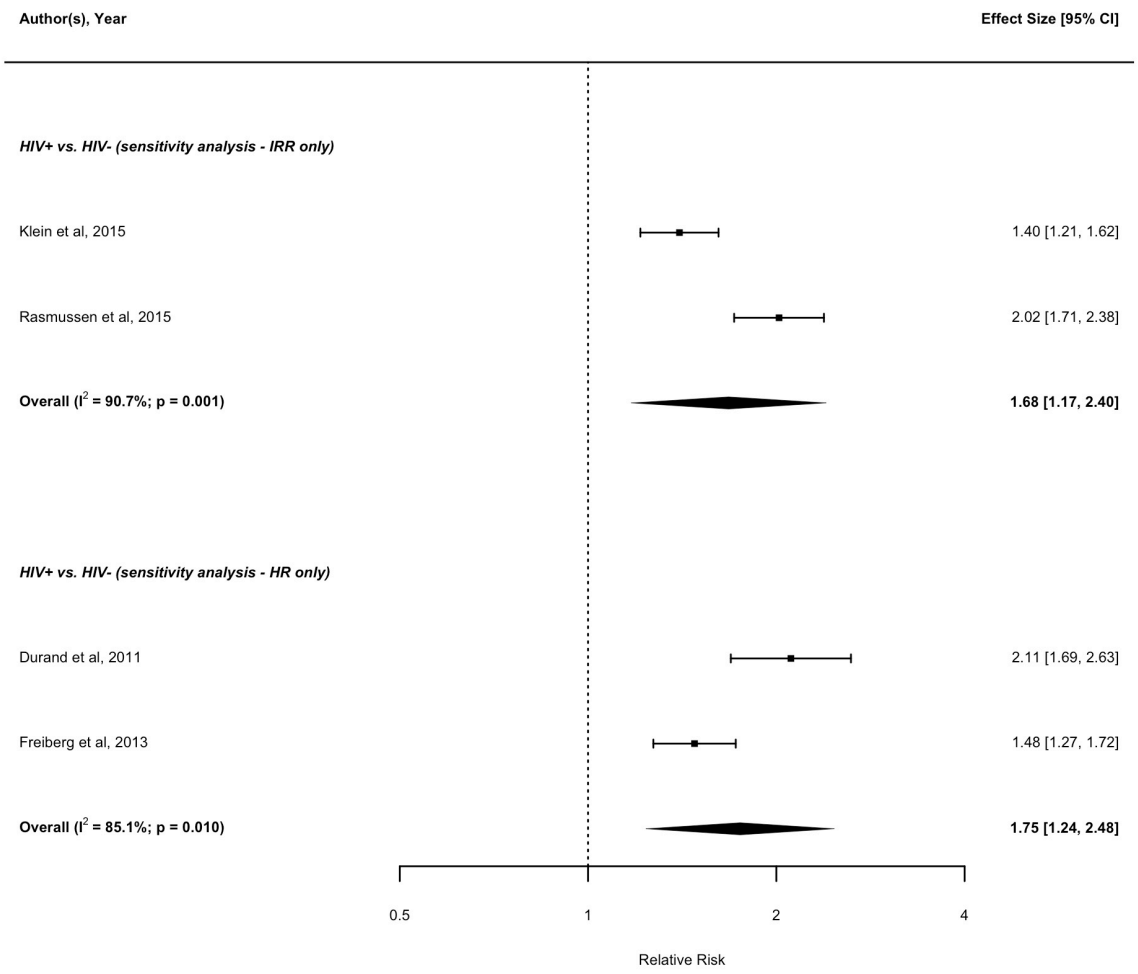


Appendix Figure A8. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to protease inhibitors (both as a class and individually)
Legend: CI, Confidence interval; PI, Protease inhibitors



Appendix Figure S1. Forest plot of the sensitivity analysis for the meta-analysis of the risk of MI associated with HIV infection, where one additional study involving a general population comparison group was included

Legend: *, This study had a 'general population' comparison group and may not have consisted of HIV-negative individuals only; CI, Confidence interval



Appendix Figure S2. Forest plot of the sensitivity analyses for the meta-analysis of the risk of MI associated with HIV infection, where estimates reported using similar relative effect measures were pooled

Legend: CI, Confidence interval; HR, Hazard ratio; IRR, Incidence rate ratio

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Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the MOOSE reporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

	Reporting Item	Page Number
#1	Identify the study as a meta-analysis of observational research	1
#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2
#3a	Problem definition	5
#3b	Hypothesis statement	6
#3c	Description of study outcomes	5
#3d	Type of exposure or intervention used	5, 6

	#3e	Type of study designs used	6
	#3f	Study population	7
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	6
	#4b	Search strategy, including time period included in the synthesis and keywords	6
	#4c	Effort to include all available studies, including contact with authors	7
	#4d	Databases and registries searched	7
	#4e	Search software used, name and version, including special features used (eg, explosion)	7
	#4f	Use of hand searching (eg, reference lists of obtained articles)	7
	#4g	List of citations located and those excluded, including justification	See note 1
	#4h	Method of addressing articles published in languages other than English	6
	#4i	Method of handling abstracts and unpublished studies	7
	#4j	Description of any contact with authors	8
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	6-8
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5-8
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	7,8
	#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	n/a
	#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	8,9
	#5f	Assessment of heterogeneity	9
	#5g	Description of statistical methods (eg, complete description of fixed or	8, 9

	random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
#5h	Provision of appropriate tables and graphics	9, 10
#6a	Graphic summarizing individual study estimates and overall estimate	10-14
#6b	Table giving descriptive information for each study included	36
#6c	Results of sensitivity testing (eg, subgroup analysis)	32
#6d	Indication of statistical uncertainty of findings	32
#7a	Quantitative assessment of bias (eg. publication bias)	9
#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	10
#7c	Assessment of quality of included studies	8, 10
#8a	Consideration of alternative explanations for observed results	18
#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	18
#8c	Guidelines for future research	18
#8d	Disclosure of funding source	19

Author notes

1. 10, Appendix

BMJ Open

Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis

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Primary Subject Heading:	HIV/AIDS
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Keywords:	Myocardial infarction < CARDIOLOGY, Cardiovascular disease, HIV & AIDS < INFECTIOUS DISEASES, Combination antiretroviral therapy, Relative risk, systematic review and meta-analysis

Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis

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Abstract

Objective: Cardiovascular disease is one of the leading non-AIDS-defining causes of death among HIV-positive (HIV+) individuals. However, the evidence surrounding specific components of cardiovascular disease risk remains inconclusive. We conducted a systematic review and meta-analysis to synthesize the available evidence and establish the risk of myocardial infarction (MI) among HIV+ compared with uninfected individuals. We also examined MI risk within subgroups of HIV+ individuals according to exposure to combination antiretroviral therapy (ART), ART class/regimen, CD4 cell count and plasma viral load levels.

Design: Systematic review and meta-analysis

Data sources: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews until July 18, 2018. Furthermore, we scanned recent HIV conference abstracts (CROI, IAS/AIDS) and bibliographies of relevant articles.

Eligibility criteria: Original studies published after December 1999 and reporting comparative data relating to the rate of MI among HIV+ individuals were included.

Data extraction and synthesis: Two reviewers working in duplicate, independently extracted data. Data were pooled using random-effects meta-analysis and reported as relative risk (RR) with 95% confidence intervals (CI).

Results: Thirty-two of the 8,130 identified records were included in the review. The pooled RR suggests that HIV+ individuals have a greater risk of MI compared to uninfected individuals (RR: 1.73, 95%CI: 1.44, 2.08). Depending on risk stratification, there was moderate variation according to ART uptake (RR, ART-treated = 1.80; 95%CI: 1.17, 2.77; ART-untreated HIV+ individuals: 1.25; 95%CI: 0.93, 1.67, both relative to uninfected individuals). We found low CD4 count, high

plasma viral load, and certain ART characteristics including cumulative ART exposure, any/cumulative use of protease inhibitors as a class, and exposure to specific ART drugs (e.g. abacavir) to be importantly associated with a greater MI risk.

Conclusions: Our results indicate that HIV infection, low CD4, high plasma viral load, cumulative ART use in general including certain exposure to specific ART class/regimen are associated with increased risk of MI. The association with cumulative ART may be an index of the duration of HIV infection with its attendant inflammation, and not entirely the effect of cumulative exposure to ART per se.

PROSPERO registration number: CRD42014012977

Keywords: Myocardial infarction, Cardiovascular disease, HIV, Combination antiretroviral therapy (ART), Relative risk, Systematic review, Meta-analysis

Word count: 4,997

Article Summary

Strengths and limitations of this study

- We used explicit eligibility criteria and a comprehensive search strategy for this systematic review and meta-analysis
- Adjudication of studies for eligibility and the data extraction were performed by two independent reviewers working in duplicate
- This systematic review and meta-analysis analyzed several additional drug exposure comparisons and clinical measures (e.g. CD4 cell count, plasma viral load) that had not been previously examined in relation to MI risk among HIV-positive individuals
- Some of the meta-analyses were based on a small number of studies which is a limitation
- Variability in the quality of the included studies may have influenced the results and thus the conclusions drawn.

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading non-AIDS causes of death and disability among people living with HIV in the combination antiretroviral therapy (ART) era.[1 2] Although HIV-positive (HIV+) individuals are believed to be at higher risk of CVD compared to uninfected individuals,[3 4] the results and conclusions from the studies that have examined the nature of the risk of CVD, in particular myocardial infarction (MI) among HIV+ individuals have been conflicting. While some cohort studies have suggested a positive association between ART including specific drug (e.g. abacavir) or drug class (e.g. protease inhibitors [PI]) use and MI, or CVD risk,[5-9] others have not.[10-12] Furthermore, there has been a lack of agreement between observational studies,[8 11 13] and randomized controlled trials (RCT).[14 15] Clearly, the evidence regarding the nature of, and extent of the risk of MI and other CVD events among HIV+ individuals is far from uniform.

Five meta-analyses have been conducted in an attempt to synthesize the data on CVD risk among HIV+ individuals.[16-20] These have either been limited in scope by assessing only the association between ART use and risk of CVD;[16] included trials that lacked MI event adjudication;[17] included trials where CVD events were not among the pre-specified outcomes of interest;[18] provided incomplete results on MI risk;[19] or amalgamated all CVD events (e.g. MI, stroke) as a single outcome.[20] In addition, this latter meta-analysis was fraught with a number of methodological ambiguities.[21]

Given these limitations, coupled with the publication of several new and updated study reports on the topic, we sought to undertake an updated systematic review and meta-analysis of studies

assessing the risk of CVD among persons living with HIV. Considering the scope, diversity and differences in the definition,[22-25] etiology and clinical picture of different CVD events,[26] coupled with the strong body of literature related to HIV and MI and the ongoing debate around potential MI risk associated with use of specific ART medications such as abacavir, we have elected to focus primarily on MI as the outcome of interest for this meta-analysis, as it is the most widely researched CVD outcome among HIV+ individuals. The objective of our study was to estimate the risk of MI among HIV+ individuals relative to uninfected individuals. Additionally, we examined MI risk within subgroups of HIV+ individuals according to exposure to ART, ART class, specific ART regimen, CD4 cell count and plasma viral load levels.

METHODS

Search strategy and selection criteria

The systematic review and meta-analysis was performed in accordance with the PRISMA Statement.[27] A protocol describing the inclusion criteria and analysis methods for this systematic review was specified in advance, registered and published at the international prospective register of systematic reviews (PROSPERO, registration number CRD42014012977).[28]

The search strategy (see Appendix Table 1) was developed in consultation with a medical librarian at Simon Fraser University, BC, Canada. The search terms were based on a combination of indexed and free-text terms reflecting clinical outcomes of interest to the review, and included the following keywords: 'HIV, human immunodeficiency virus, acquired immunodeficiency syndrome, HIV/AIDS, stroke, myocardial infarction, cardiac death, cerebrovascular disease, ischemic heart disease, cardiovascular disease and CVD'. These terms were used in combination

to execute the searches, which were up to July 18, 2018. Using the Ovid platform, we searched the following electronic databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews. In addition, we screened the abstracts of the International AIDS Society conferences (AIDS 2012, 2014, 2016; IAS 2013) and the Conference on Retroviruses and Opportunistic Infections (CROI 2014, 2015, and 2016). We also searched the reference lists of relevant articles and previous systematic reviews for additional eligible publications. Finally, we set up automatic PubMed literature alerts to identify any new relevant article published while the manuscript was under development.

We included original research published in English where at least one of the participant groups were individuals living with HIV, and presenting comparative data on the incidence of MI. We included studies in which results were stratified according to HIV status; CD4 cell count; plasma viral load (pVL) levels; ART use; or exposure to particular ART class or regimen. Studies involving non-human populations; children; as well as those reporting only unadjusted estimates, intermediate, surrogate or CVD biomarker outcomes were excluded (for additional information, see 'study selection' in the Appendix, p1). To reflect the current context of HIV treatment and disease management, we selected studies published from the year 2000 onwards. Although both observational studies and RCTs were eligible for inclusion, we did not include RCTs that were not designed to assess CVD events as a pre-specified outcome to avoid bias.

Working independently and in duplicate, two reviewers (OE and GB) scanned the titles and abstracts of the retrieved records for eligibility. The full-text articles of potentially eligible studies were obtained and reviewed in greater details. Disagreements in study selection were resolved

through discussion, and where necessary, a third investigator (RSH) was invited to facilitate consensus.

Data extraction and quality assessment

The same two reviewers (OE and GB) conducted data extraction independently using a pre-designed data abstraction sheet. We extracted data on study descriptors, sample characteristics, outcome assessment, risk estimate for relevant comparisons, and study quality features. Where necessary, we sought clarification directly from study authors through email contact. In cases where data from the same study described the same event risk in multiple publications, we extracted data from the most comprehensive report while supplementing missing study-level information from the others. In keeping with characterizations in the included studies, exposure to ART was categorized as any (or prior/some *compared to none*), recent (or within the preceding six months *compared to not recent*) and cumulative ART exposure per year of exposure.

The quality of the included studies was assessed according to risk of bias criteria based on the type of study design. As only observational studies were eventually included in the meta-analysis since eligible RCTs were not identified, we made this assessment by evaluating study design features of the eligible observational studies. Following guidelines in the Newcastle-Ottawa Scale (NOS) for assessing the quality of observational studies in meta-analyses[29] and with slight modification of the scoring system to simplify reporting, the risk of bias assessment was performed based on the adequacy of three key domains of the study design features namely: the group/participant selection; comparability of groups; and the exposure and outcome assessments in the individual studies. For each of these key features, we assigned a "+" (plus) sign when this was clearly and

adequately described in the study, and a "–" (minus) sign when it was not clearly described or was missing. A detailed description of the results of the quality assessment is available in the appendix.

Patient and public involvement

No patients were involved in this study. We used data from published materials only.

Data analysis

We calculated the kappa statistic as a measure of the inter-reviewer agreement for the selection of articles meeting the inclusion/exclusion criteria. For interpretation, we defined *a priori* the interval for the kappa result using Landis and Koch criteria.[30] For effect measure, we assumed the incidence rate ratio (IRR), odds ratio (OR) and hazard ratio (HR) with corresponding sampling variance to be numerical approximate measures of the relative risk (RR) for a given association of interest with the underlying assumption of a generally low event risk (< 20%),[31-36] and thus combined them as previously described.[19 37-40] We tested this assumption in sensitivity analyses by performing separate meta-analyses where studies presenting results reported using a similar effect measure type were pooled. Given the expected variability among eligible studies, we pooled studies using the DerSimonian-Laird random-effects model.[41] To minimize bias in our pooled estimates, adjusted risk estimates were not combined with unadjusted estimates. The final set of studies that adjusted for confounders did not consistently adjust for the same set of confounders but were deemed to have sufficient internal validity to permit pooling. For the analysis that quantified the overall RR of MI associated with HIV infection, we performed a sensitivity analysis where we examined the appropriateness of the comparison group by repeating the meta-analysis and including two additional studies that involved a general population comparison group,[42 43] as

opposed to an HIV-uninfected comparison group. Given the limitations of the I^2 statistics with observational studies and Cochran Q test when the number of studies is small,[44 45] we assessed heterogeneity by visual inspection of the forest plots for overlap in the confidence intervals of the individual studies, although the I^2 as a measure of the degree of heterogeneity across studies is reported in the forest plots for completeness. We were unable to perform meta-regression analyses to assess the potential effect of study-level covariates on the pooled estimate due to insufficient studies (< 10),[46] in each of the meta-analyses. Although we assessed publication bias by visually inspecting and testing for funnel plot asymmetry,[47] its interpretation was limited by a lack of sufficient number of studies per meta-analysis.[48 49] A p-value < 0.05 was considered statistically significant. The meta-analysis was conducted using the *metafor* package of the R statistical program (version 3.3.1) [50].

RESULTS

Of 8,130 records identified through the database search, the final screening process yielded 64 potentially eligible publications on CVD outcomes, 32 of which had relevant data on MI and were included in this meta-analysis (Figure 1). Overall, there was near perfect agreement between reviewers on the inclusion of studies (kappa statistic = 0.94; 95% confidence interval (95%CI): 0.89, 0.99). The included studies, most of which were conducted in the United States and Europe, were published between 2000 and 2017 and involved approximately 383,471 HIV+ and > 798, 424 HIV- individuals (Appendix Table 2: characteristics of the included studies; *note: the number of individuals in cohorts with multiple publications was accessed only from one of the publication*s). The mean duration of follow-up varied across studies from approximately one to twenty years. All 32 publications were non-randomized studies and included two nested case-

control studies,[11 51] one cohort/nested case-control study,[52] and 29 cohort studies; 15 of which were prospective studies, by design.[3 7 8 13 42 53-62] Twenty-nine studies were published as full-text journal articles, while three were available as conference abstracts.

In general, the reporting and quality of the methodological aspects of the included studies were variable. Three studies did not provide sufficient information necessary to assess the study quality, as they were reported and available as conference abstract/poster.[55 57 63] The eligibility criteria were clearly defined in the majority of studies (94%), description of study participants/ groups was sufficient (100%); however, the exposure or outcome was not adequately ascertained in 15 studies (47%);[8 12 24 52 54 56 60 63-70] one (7%) of which was published as an abstract [63] (see Appendix Table 3: risk of bias in the included studies).

Meta-analysis of the risk of MI

Below, we summarize the results of the meta-analyses of MI risk according to the various risk stratifications assessed. To avoid duplication of reporting, only statistically important RR are stated in text; although both statistically significant and insignificant results are presented in the figures (forest plots).

Risk of MI associated with HIV infection

The pooled RR from the five studies that met eligibility for this assessment of MI risk according to HIV serostatus suggests that HIV+ individuals are more likely to have an MI event compared to uninfected individuals (RR: 1.73; 95%CI: 1.44, 2.08).[3 52 56 69 71] In sensitivity analysis (Appendix Figure S1) where we repeated the meta-analysis and included two additional studies that involved

a general population comparison group,[42 43] the overall pooled RR was 1.60; 95%CI: 1.38, 1.85. Figure 2 shows the forest plots for the association between HIV infection and MI risk. Two studies assessed the risk of MI by HIV serostatus according to whether ART treatment was received.[60 72] Compared to uninfected individuals, the pooled RR of MI was significantly higher among HIV+ individuals on ART (RR: 1.80; 95%CI: 1.17, 2.77), but not the ART-untreated HIV+ individuals (RR: 1.25; 95%CI: 0.93, 1.67).

Risk of MI associated with CD4 cell count and plasma viral load levels

The pooled RR based on combining data from three studies suggests that low CD4 cell count (< 200 cells/mm^3) is associated with higher MI risk compared to CD4 ≥ 200 (RR: 1.60; 95%CI: 1.25, 2.04).[3 57 68] Conversely, a high pVL (≥ 100,000 copies/mL) was found to be associated with increased MI risk compared to pVL < 100,000 (RR: 1.45; 95%CI: 1.11, 1.90), based on the pooled results from two studies (Figure 3).[54 68]

Risk of MI associated with recent ART exposure

With regards to *recent treatment exposure* (i.e. within the preceding six months), four eligible studies with data on nucleoside reverse transcriptase inhibitors (NRTI) exposure assessed the risk of MI associated with recent compared to not recent abacavir exposure.[52 53 55 67] The pooled result from these four studies suggests that recent abacavir exposure is associated with increased risk of MI compared to not recent exposure (RR: 1.71; 95%CI: 1.39, 2.10). Similarly, recent didanosine (RR: 1.29; 95%CI: 1.04, 1.60),[52 58 67] and lamivudine (RR: 1.50; 95%CI: 1.18, 1.90),[13 52 67] exposure is associated with increased risk of MI compared to not recent exposures. In contrast, there was no detectable association between recent tenofovir,[52 58 67] zidovudine,[13 52 67] stavudine,[13

[52 67] emtricitabine,[52 67] and MI risk compared to not recent exposure (Figure 4). Based on pooling data from two studies with data on non-nucleoside reverse transcriptase inhibitors (NNRTI) exposure,[52 67] no association was found between recent efavirenz or nevirapine exposure and MI risk compared to not recent exposure (Figure 5). Based on pooled results from the studies assessing the MI risk of individual PIs, recent indinavir was associated with increased MI risk compared to not recent exposure (RR: 1.46; 95%CI: 1.08, 1.95).[52 67] Recent exposure to other PI regimens including atazanavir,[52 67] lopinavir,[52 67] ritonavir,[52 67] nelfinavir,[52 67] and saquinavir,[52 67] were not found to be significantly associated with MI risk compared to not recent exposure (Figure 6).

Risk of MI associated with any ART exposure

In terms of *any treatment exposure*, our meta-analysis did not find an association between exposure to ART and risk of MI compared to no exposure (Appendix Figure A1).[62 72] Based on the pooled results from six studies with data on NRTI exposure,[8 11 13 52 63 68] individuals receiving abacavir were more likely to have an MI compared to those who did not (RR: 1.58; 95%CI: 1.25, 2.00). We found a similar association between didanosine exposure and MI risk (RR: 1.48; 1.16, 1.90).[13 52 68] No detectable association was found between exposure to tenofovir,[52 68] zidovudine,[13 52] stavudine,[13 52 68] emtricitabine,[52 68] and MI risk, based on our pooled results (Appendix Figure A2). The meta-analysis of studies with data on NNRTI exposure did not find any evidence of an association between either efavirenz,[52 65] or nevirapine exposure,[52 68] and MI risk compared to no exposure (Appendix Figure A3). The pooled RR from four studies demonstrates that PI exposure is associated with an increase in the risk of MI events compared to no exposure to PI (RR: 1.49; 95%CI: 1.16, 1.91).[3 6 61 63] When the analysis was limited to two studies comparing recent PI exposure to no exposure,[3 63] similar results were found (RR: 1.40; 95%CI: 1.16, 1.69 [data not

shown]). For the individual PIs, there was no association between either atazanavir,[52 64 66 68] saquinavir,[52 68] or nelfinavir exposure,[52 68] and MI risk, compared to no exposure (Appendix Figure A4).

Risk of MI associated with cumulative ART exposure

With regards to *cumulative treatment exposure*, three eligible studies provided relevant data regarding the risk of MI and cumulative ART exposure.[12 68 70] We found that cumulative exposure to ART was associated with an increase in the risk of MI per year of exposure (RR: 1.12; 95%CI: 1.06, 1.18) (Appendix Figure A5). For exposure to NRTI regimens, we estimated an increase in MI risk per year of exposure to abacavir (RR: 1.08; 95%CI: 1.01, 1.15) based on pooling data from two eligible studies.[12 58] Similar to abacavir, cumulative zidovudine exposure was associated with an increase in MI risk per year of exposure (RR: 1.05; 95%CI: 1.01, 1.10).[11 13] We found no association between cumulative exposure to either didanosine,[11 13] tenofovir,[11 58] lamivudine,[11 13] or stavudine,[11 13] and MI risk per year of exposure (Appendix Figure A6). The overall RR suggests that cumulative NNRTI exposure as a class (RR: 1.02; 95%CI: 0.97, 1.08),[59 70 72] or as individual drugs (nevirapine, and efavirenz),[11 58] is not significantly associated with increased risk of MI events per year of exposure (Appendix Figure A7). Three eligible studies reported data assessing the risk of MI associated with cumulative exposure to PIs as a class.[59 70 72] There was an increase in risk of MI per year of exposure to PIs (RR: 1.14; 95%CI: 1.03, 1.26). For individual drugs, cumulative exposure to lopinavir with ritonavir (RR: 1.19; 95%CI: 1.03, 1.39),[11 58] but not nelfinavir,[11 58] was found to be associated with increase in the risk of MI events per year of exposure (Appendix Figure A8).

Sensitivity analyses

The strength and direction of the overall RR from the various meta-analyses remained robust in sensitivity analyses where estimates reported using similar effect measures were pooled. For example, HIV+ individuals continued to have higher risk of MI events compared to uninfected individuals when pooled using either IRRs (overall effect: 1.68; 95%CI: 1.17, 2.40) or HRs (overall effect: 1.75; 95%CI: 1.24, 2.48) effect measures, compared to a RR of 1.73; 95%CI: 1.44, 2.08, obtained from pooling results reported using multiple relative effect measures (Appendix Figure S2).

DISCUSSION

This updated systematic review and meta-analysis assessing the risk of MI among people living with HIV reflects contemporary ART era and found the following: (1) HIV+ individuals have a greater risk of MI compared to uninfected individuals; and among HIV+ individuals, (2) low CD4 cell count (< 200 cells/mm^3) and high pVL (> 100,000 copies/mL) are associated with increases in MI risk compared to higher CD4 or lower pVL respectively; (3) cumulative ART exposure is associated with a greater risk of MI per year of exposure; (4) among NRTIs, any type of exposure to abacavir; cumulative exposure to zidovudine; and recent exposure to either didanosine or lamivudine are significantly associated with higher risk of MI; (5) compared to no exposure, any or cumulative exposure to PIs as a class; cumulative exposure to lopinavir with ritonavir; and recent indinavir exposure were associated with higher risk of MI; (6) NNRTIs assessed either as a class or individually were not associated with increased MI risk.

Previous meta-analyses comparing CVD risk among HIV+ and uninfected individuals reported estimates for the association between HIV-seropositivity and MI (RR: 1.79, 95%CI: 1.54, 2.08)[19] or CVD (RR: 1.61, 95%CI: 1.43, 1.81);[20] risk that are similar to our findings for MI (RR: 1.73; 95%CI: 1.44, 2.08). As has been previously hypothesized,[3 23 73-75] the probable mechanistic pathway through which HIV infection can induce MI may include a cascade of events involving chronic inflammation, immunodeficiency/CD4 cell depletion, endothelial dysfunction, increased thrombosis and accelerated atherosclerosis that typically accompany both controlled and uncontrolled HIV disease. Relative to uninfected individuals and similar to what we found (RR: 1.80, 95%CI: 1.17, 2.77), one of the previous meta-analysis also reported a higher risk of CVD among ART-treated individuals (RR: 2.00, 95%CI: 1.70, 2.37).[20] We suspect that the higher MI risk among ART-treated HIV+ individuals may not necessarily be attributable to ART alone but rather to the combined effect from a host of factors including HIV itself, ART, and other comorbid risk factors which have been individually shown to contribute to MI risk.[3 5 76 77] Furthermore, the risk associated with cumulative ART exposure may be an index of the duration of HIV infection with its attendant inflammation, and not entirely the effect of cumulative exposure to ART per se.

Specific to abacavir and MI risk, our findings were similar to reports from a previous meta-analysis of observational studies of MI,[16] but different from those of the meta-analysis of RCTs,[17 18] or reports from aggregate clinical trial studies,[14 15] that suggested no risk associated with abacavir exposure. Although observational studies and RCT results regarding MI and CVD risk due to abacavir exposure among people living with HIV are largely at odds, the Simplification with Tenofovir-Emtricitabine or Abacavir-Lamivudine (STEAL) trial is the first RCT to support observational studies finding of increased risk of CVD with exposure to abacavir.[78] Based on the

available evidence to date, the controversy regarding the potential association between abacavir use and risk of MI will likely continue to plague the field of HIV therapeutics until such a time when definitive evidence describing the underlying mechanism can be produced.[79 80] A sufficiently powered RCT with long follow-up and including real-world populations reflective of those typically seen clinically may be needed to fully resolve this clinical controversy.

Unlike our results where a class-level effect was evident for PIs, pooled aggregate clinical trial data after one year of treatment with four different PI-based regimens did not find evidence of an increased risk associated with PI compared to NRTI regimen (RR: 1.69; 95%CI: 0.54, 7.48).[81] When we pooled data of individual PIs separately, we did not observe the same 'class-level' results. In our analysis, different PI regimens carried different risks. For example, while recent indinavir and cumulative lopinavir-ritonavir exposure were associated with increased MI risk, nelfinavir or atazanavir did not appear to contribute to MI risk irrespective of the type of exposure data that were pooled.

In terms of the scope and design, our study differs from previous meta-analyses on this topic in several ways. First, we used an expanded search strategy that included more data sources and search of conference archives compared to prior meta-analyses.[16-20] Second, as the association of HIV and ART may affect the risk of MI and other CVD events differently, we did not assess the risk of CVD in general, as was done in previous meta-analysis.[20] Third, we have used more recent risk estimates from studies with longer follow-up such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Fourth, we have included studies published between 2000 and 2017 with reported data from the post-ART era. The historical nature of some of the studies

included in previous meta-analysis may have limited their relevance in contemporary times. Finally, this systematic review analyzed several additional drug exposure comparisons and clinical measures (e.g. CD4 cell count, plasma viral load) in relation to MI risk that had not been previously examined.

There are several important considerations that should be taken into account in the interpretation of the results of this study. Accurate characterization of the risk of MI and CVD outcomes in general may be confounded by a number of factors that may have affected our conclusions. The first concern has to do with the differences in the risk factors, drug exposure, HIV-related variables, or population considered in the included studies. Indeed, no two studies of HIV+ individuals from different underlying populations can have participants with the same exact demographic, clinical and drug exposure profile – all of which play a role in overall health outcomes. Given that studies typically included in a global meta-analysis such as ours do not come from the same underlying source population, we acknowledge that there may be some differences in the population distribution in the included studies (e.g., in the distribution by age, sex, disease stage, medication profile/history) that we were unable to account for. A second concern relates to the variability in the quality and design features of the included studies, which may have influenced the results of the meta-analyses and thus the conclusions drawn. Although the majority of included studies were cohort-based (90%), almost one half (47%) were retrospective in nature and did not adequately report how the exposure or outcome was ascertained including whether an adjudication protocol was applied in the ascertainment of MIs. It has been shown that the application of an adjudication protocol in the study of MI and other CVD events is important to ensuring accurate identification of events as relying only on administrative diagnostic codes could result in misclassification.[82]

While some studies retrospectively assessed MI and relied on International Classification of Diseases (ICD) codes alone – something that is quite common in large epidemiological studies of MI,[76] others followed participants over time and prospectively assessed and validated the MI events. It is unclear how differences in MI definition across studies may have affected our results although in two studies from the same underlying population (Veterans Aging Cohort Study (VACS)) that used similar but not the same definitions for MI,[3 83] the RR differed slightly: 1.48 (95%CI: 1.27, 1.72)[3] vs. 1.76 (95%CI: 1.49, 2.07).[83] Regarding studies that quantified the risk of MI associated with HIV infection, the available evidence based on the included studies all point in the same direction suggesting an increase in MI risk. However, we noted some variability in the design and quality of the studies, something that may have contributed in part to the observed heterogeneity. For example, three studies did not provide sufficient information on the exposure or outcome ascertainment in the studies.[52 56 69] Furthermore, the appropriateness of the HIV-uninfected group used for comparison purposes is critical in the assessment of MI risk associated with HIV infection; an issue that has been extensively reviewed elsewhere.[84] While some studies made this comparison using an HIV-uninfected group, other studies used the general population group for comparison. In sensitivity analysis, the overall RR of MI associated with HIV infection was reduced when we included in the meta-analysis two additional studies involving a 'general population' comparison group,[42 43] therefore highlighting the importance of using an appropriate control group.

Another potential concern relates to differences in the extent to which key confounding factors were adjusted for in the individual analysis contributing to the meta-analysis. For example, some studies lacked data on smoking – an important risk factor for CVD in general, and therefore did not account for it in the analyses.[52 60 65] In this regard, we noted that the included studies did

not consistently control for the exact same set of confounders which may have undermined their internal validity and explained some of the differences in the effect measures from the individual studies. There is also the potential for residual, unmeasured confounding given the observational nature of the included studies. Therefore, heterogeneity arising from differences in study design or other quality features may have influenced the results and thus the overall conclusions drawn. Although we observed heterogeneity across results of studies included in some of the meta-analyses, this is a common limitation in meta-analysis especially those involving observational studies.[44] Our *a priori* choice of employing the random-effects modeling strategy was driven in part by this expected variability among studies.[85] Furthermore, our study combined results presented using several different relative effect measures with the assumption that these represent approximately the same numerical value.[31-36] In sensitivity analyses, we did not find any evidence of bias in our pooled estimates, as these did not differ importantly from the pooled estimates we obtained when we combined studies reporting results using the same effect measure. Moreover, we reached comparable conclusions with previous meta-analyses that combined,[19] or did not combine HR estimates with OR, and RR.[16]

Also, some of the meta-analyses in our study such as those examining the risk of MI in relation to CD4, pVL, or use of specific ARV regimens were based on a small number of studies (only 2-3 studies), which is a serious limitation. It is important to also consider this point in the interpretation of these specific findings. We acknowledge that the results from such meta-analyses could have been strengthened with the inclusion of additional eligible studies. Nevertheless, in the absence of sufficient number of studies examining these relationships, our results could be viewed as the best available evidence summarizing the risk of MI associated with CD4, pVL, or use of specific ARV regimens among people living with HIV.

Given the foregoing discussion in relation to the design and quality aspects of the included studies as well as issues of sufficiency of available studies examining several potential associations with MI risk, additional rigorously conducted studies with extensive confounding factor stratification/adjustment are needed to further confirm our findings. Furthermore, considering that the majority of the studies on this topic are carried out in North America and Europe, our study highlights the need for more research to be conducted in resource limited settings where most people living with HIV reside.

CONCLUSIONS

In summary, this updated systematic review and meta-analysis suggests that HIV infection, ART use in general including exposure to specific ART class (e.g. PIs) and regimen (e.g. abacavir) are associated with increased risk of MI. These findings should be interpreted in light of the key considerations that we have highlighted in this review. We found the totality of the evidence for an association between HIV infection and MI to be compelling. With respect to ART and MI risk, HIV treatment strategies should certainly consider cardiovascular risk factors including exposure to particular ART drugs as part of patient-tailored care. However, given what we currently know about ART's effectiveness, the benefits of ART for the treatment of HIV infection in terms of viral suppression and immune reconstitution should be balanced against its potential unfavorable impact on MI. Specific to abacavir and MI risk where there is conflicting evidence between observational studies and RCTS, additional rigorously conducted studies in real-world populations are needed to definitively substantiate our findings and strengthen the existing evidence on this topic. Given the multiple potential contributory and mechanistic pathways to developing MI among HIV+

individuals and the complexity/feasibility of designing a large enough study to completely tease apart the potential contributions of each of the factors believed to increase the risk of MI, managing known modifiable risk factors for CVD outcomes (e.g. smoking) through behavioural/lifestyle interventions, would be an excellent first step in reducing the incidence and risk of MI among people living with HIV.

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Author contributions

OE, MWH, SAL, JSGM and RSH conceived and designed the study. OE, GB, and RSH acquired the data. OE performed the statistical analysis with input from CHG, CF-V, and EM. OE, GB, CHG, MWH, SAL, MB, SG, CF-V, AA, EM, JSGM, and RSH contributed to the interpretation of the data. OE drafted the manuscript. OE, GB, CHG, MWH, SAL, MB, SG, CF-V, AA, EM, JSGM, and RSH reviewed the manuscript critically for important intellectual content and approved the final version submitted for publication.

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Competing interests

We declare no competing interests

Patient consent

None required

Data sharing statement

All data and materials used in this research are available in Medline/PubMed. References have been provided.

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Figure Titles and Legends

Figure 1. Flow diagram of study selection

Legend: *, Includes several conference abstract records captured through the database search; **, Includes two studies involving a 'general population' comparison group

ART, Combination antiretroviral therapy; CVD, Cardiovascular disease

Figure 2. Forest plot of the meta-analysis of the risk of MI associated with HIV infection

Legend: ART, Antiretroviral therapy; CI, Confidence interval

Figure 3. Forest plot of the meta-analysis of the risk of MI associated with CD4 cell count and plasma viral load levels

Legend: CI, Confidence interval

Figure 4. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NRTI class

Legend: CI, Confidence interval

Figure 5. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NNRTI class

Legend: CI, Confidence interval

Figure 6. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the protease inhibitor class

Legend: CI, Confidence interval

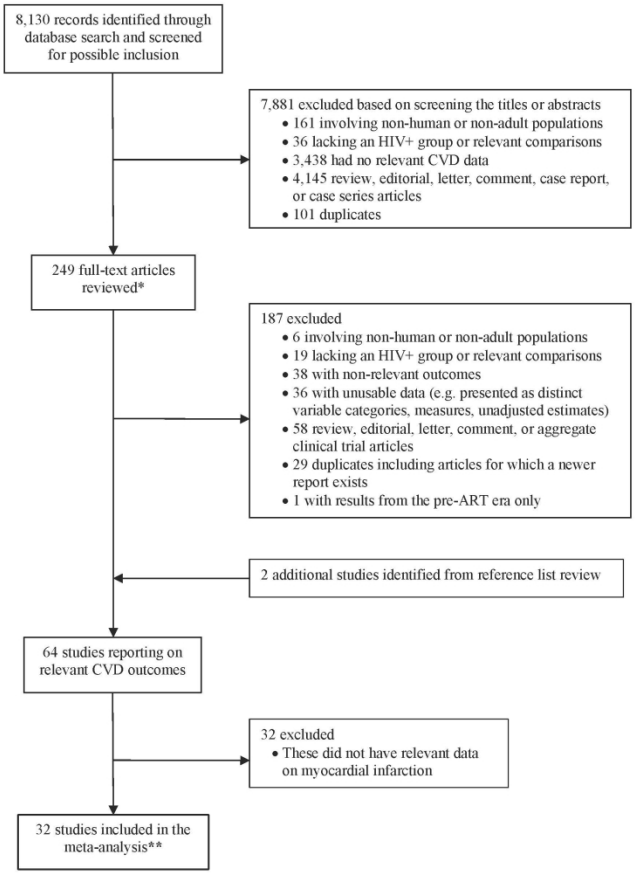

Figure 1. Flow diagram of study selection
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Figure 1. Flow diagram of study selection

215x279mm (300 x 300 DPI)

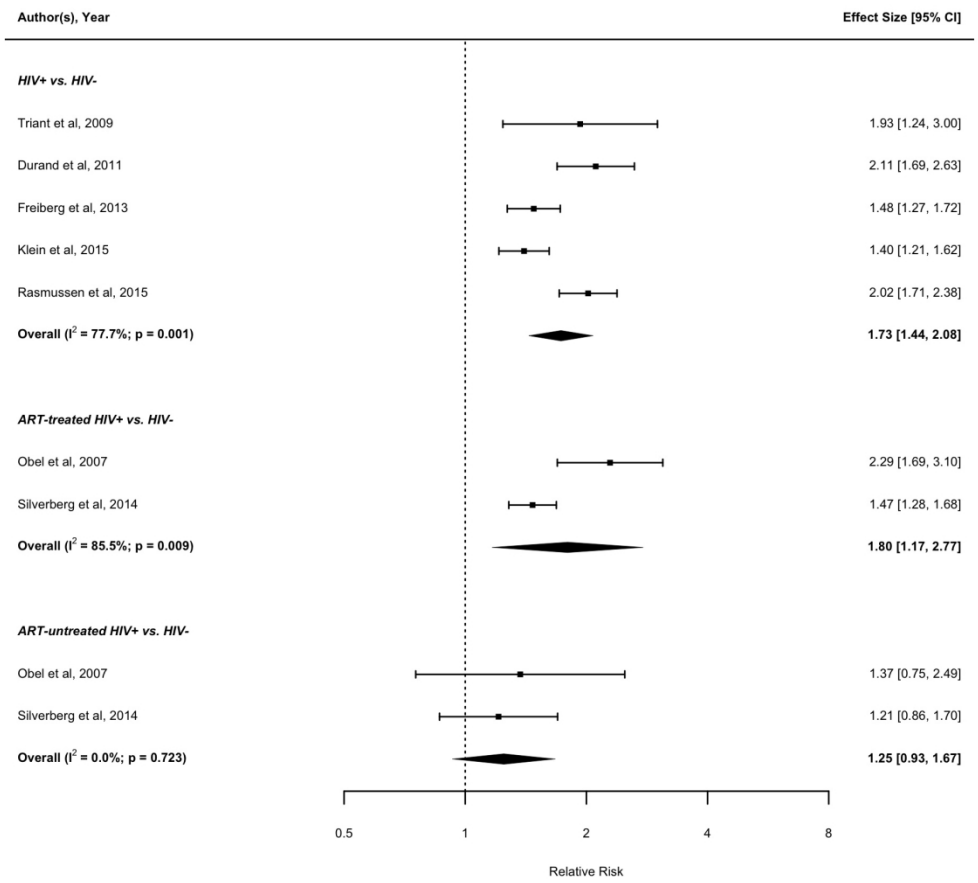

Figure 2. Forest plot of the meta-analysis of the risk of MI associated with HIV infection

662x585mm (72 x 72 DPI)

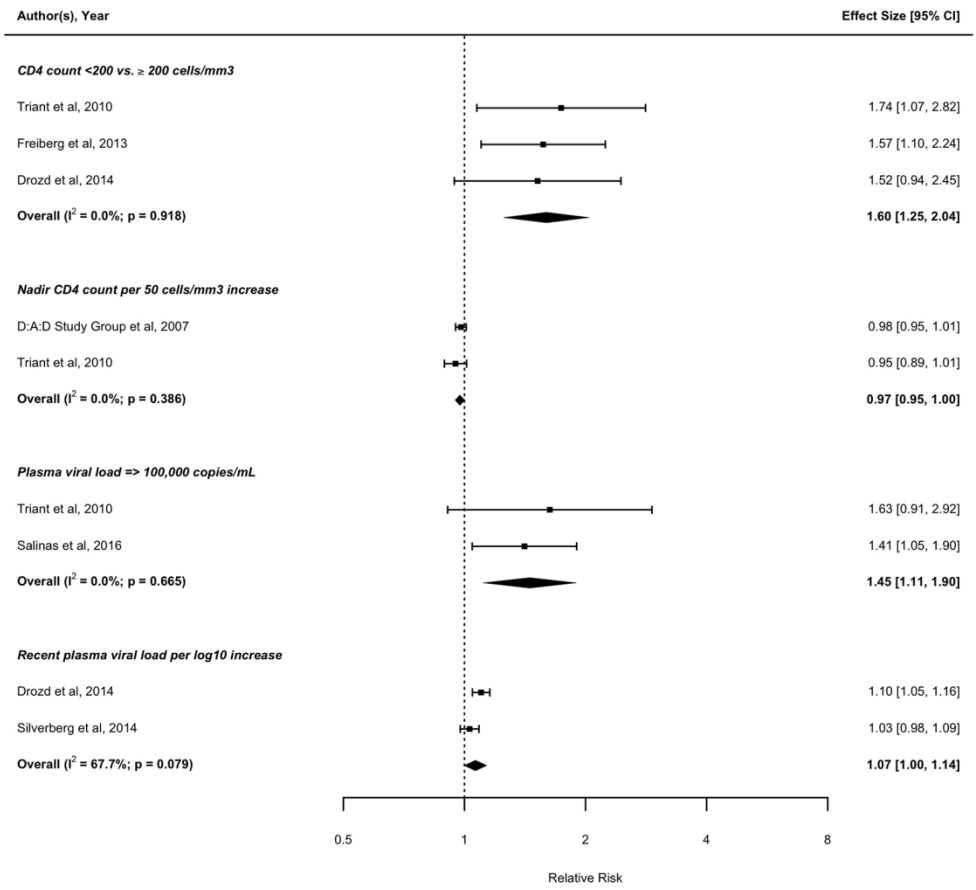

Figure 3. Forest plot of the meta-analysis of the risk of MI associated with CD4 cell count and plasma viral load levels

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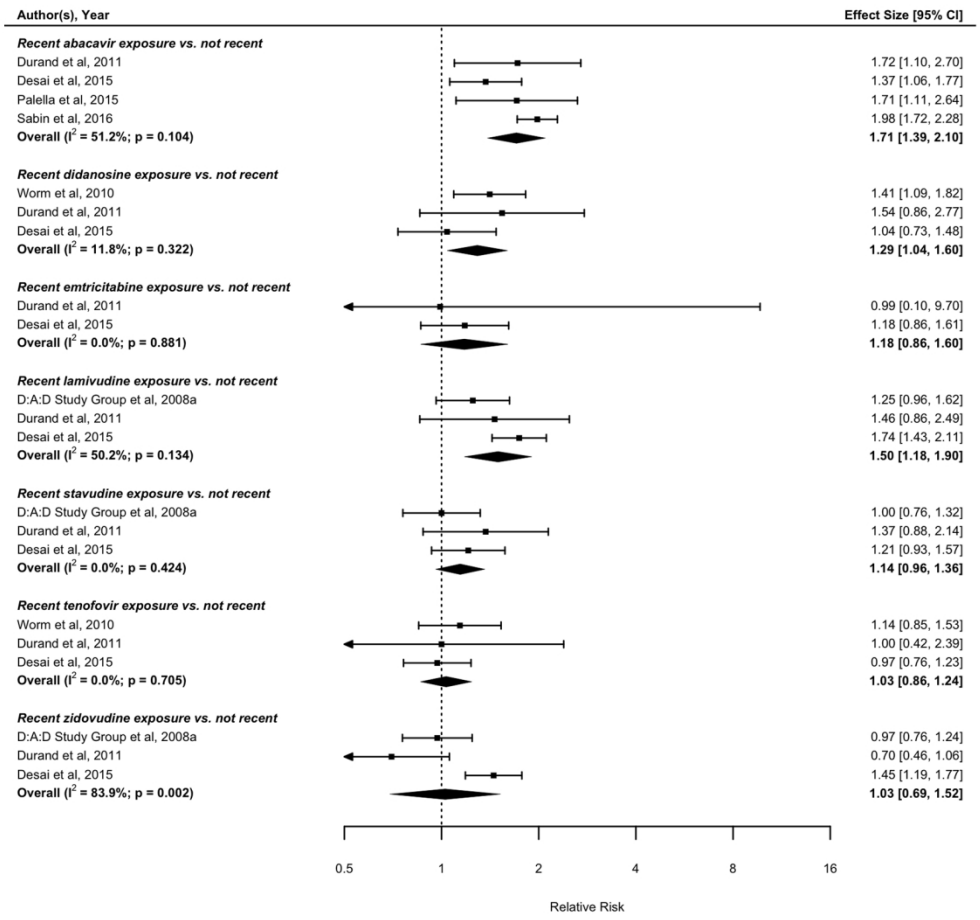


Figure 4. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NRTI class

152x140mm (300 x 300 DPI)

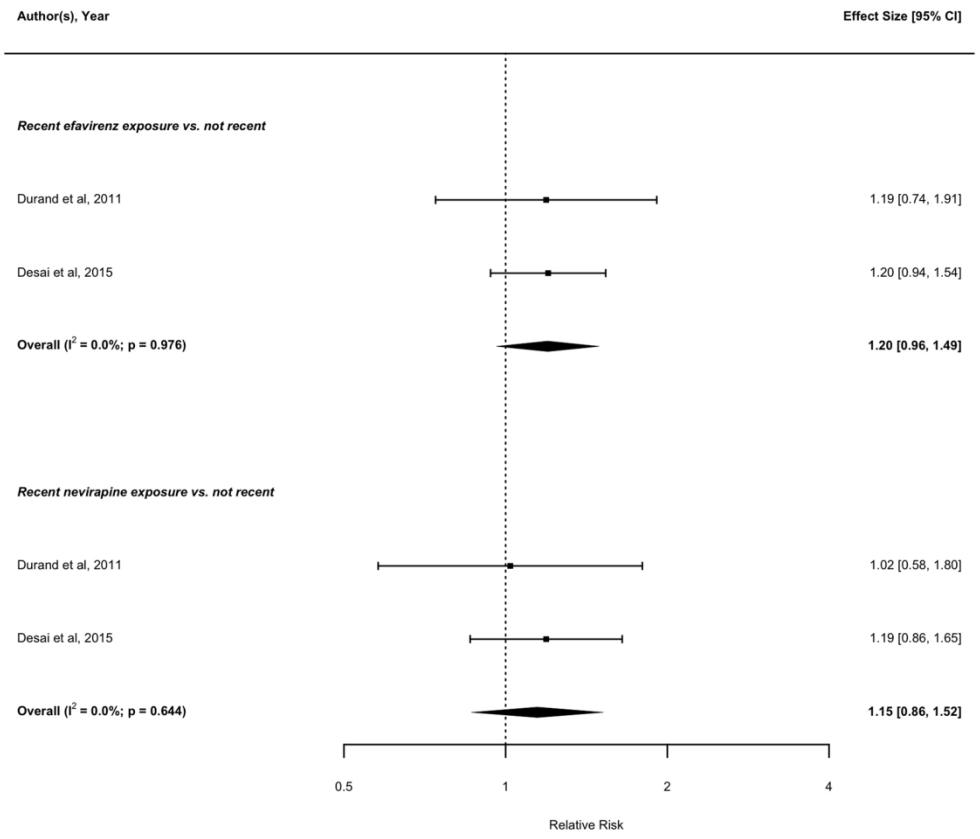


Figure 5. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the NNRTI class

152x128mm (300 x 300 DPI)

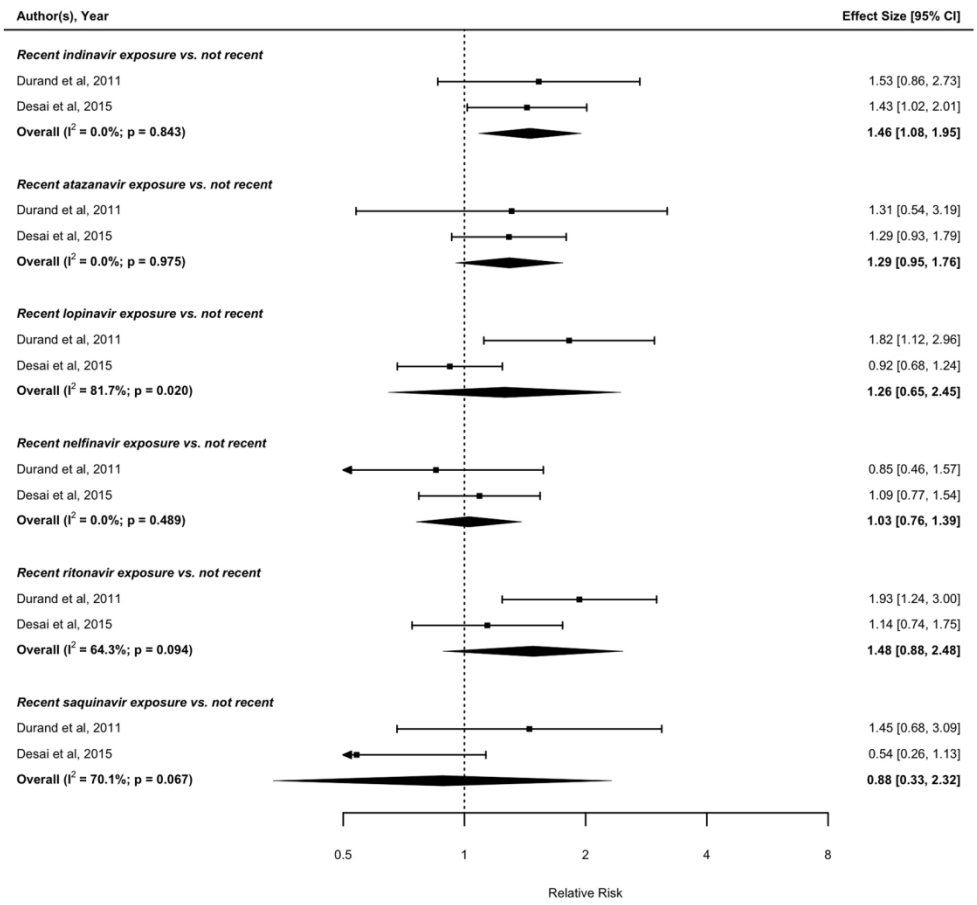


Figure 6. Forest plot of the meta-analysis of the risk of MI associated with recent exposure to drugs of the protease inhibitor class

152x138mm (300 x 300 DPI)

Appendix

Appendix Table 1. Search strategy

1	hiv.af.
2	human immunodeficiency virus.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
3	acquired immunodeficiency syndrome.af.
4	hiv aids.af.
5	1 or 2 or 3 or 4
6	stroke.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
7	(myocardial infarction or heart attack).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
8	cardiac death.af.
9	cerebrovascular disease.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
10	(ischemic heart disease or Ischaemic heart disease).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
11	(cardiovascular disease or cvd).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
12	6 or 7 or 8 or 9 or 10 or 11
13	5 and 12
14	limit 13 to human
15	limit 14 to english language
16	Limit 15 to yr= "2000 – Current"
17	remove duplicates from 16

Note: The searches were executed in the following four databases: (1) EBM Reviews - Cochrane Central Register of Controlled Trials <June 2018>, (2) EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 11, 2018>, (3) Embase <1974 to 2018 July 17>, (4) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily <1946 to July 17, 2018>

Study selection

The excluded studies included several key CVD review articles,[1–8] and aggregate clinical trial studies,[9–12] whose bibliographies were screened for identification of additional relevant studies. We also excluded a number of potentially eligible records when more comprehensive or updated results for the same participants and risk comparison were published in another report;[13–16] risk associations were reported in a way that would not allow for pairwise grouping with other studies reporting similar associations to facilitate pooling of results;[17–21] or results were reported as number of events or unadjusted risk estimates only.[22–25]

Note: the references cited in the paragraph above are listed at the end of the appendix

Appendix Table 2. Characteristics of included studies

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
LaFleur *et al* 2017[64]	Cohort	USA	ATV-cohort: 12 months Non-ATV: 13 months	HIV+	ATV-cohort: 1,529 (96) Non-ATV: 7,971 (92)	50 years	MI	ATV exposure vs. not exposed	HR[β]
Drozd *et al* 2017[42]	Cohort	North America	HIV+: 4.5 years HIV-: 19.7 years	HIV+/HIV- (NA-ACCORD / ARIC)	HIV+: 28,912 (81) HIV-: 14,308 (44)	HIV+: 80% were < 50 years HIV-: 27% were < 50 years	Type 1 MI	HIV+ vs. HIV-**	IRR[β]
Rosenblatt *et al* 2016a[65]	Cohort	USA	EFV-cohort: 23.2 months EFV-free: 19.3 months	HIV+	EFV-cohort: 11,978 (86) EFV-free: 10,234 (79)	EFV-cohort: 40.2 years EFV-free: 40.7 years	MI	EFV exposure vs. not exposed	HR[β]
Rosenblatt *et al* 2016b[66]	Cohort	USA	ATV-cohort: 24 months ATV-free: 21 months	HIV+	ATV-cohort: 2,437 (76) ATV-free: 19,774 (84)	ATV-cohort: 41.0 years ATV-free: 40.4 years	MI	ATV exposure vs. not exposed	HR[β]
Sabin *et al* 2016[53]	Cohort	Multi-national	7.0 (4.4-11.1) years[α]	HIV+	49,717 (74)	38 (32-44) years[α]	MI	Current ABC exposure vs. not current (1999-2013)	IRR[β]
Salinas *et al* 2016[54]	Cohort	USA	1996-2012 (follow-up)	HIV+	8,168 (97)	46 (40-53) years[α]	AMI	VL at ART initiation ≥ 100,000 copies/mL vs. < 100,000	HR[β]
Desai *et al* 2015[67]	Cohort	USA	~6.7 years	HIV+	24,510 (98)	46.5	MI	Current exposure to ABC vs. not currently exposed Current exposure to DDI vs. not currently exposed Current exposure to ATV vs. not currently exposed Current exposure to TDF vs. not currently exposed Current exposure to LPV vs. not currently exposed Current exposure to FTC vs. not currently exposed Current exposure to 3TC vs. not currently exposed Current exposure to d4T vs. not currently exposed Current exposure to ZDV vs. not currently exposed Current exposure to IDV vs. not currently exposed	OR[β] / HR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Current exposure to NFV vs. not currently exposed Current exposure to SQV vs. not currently exposed Current exposure to RTV vs. not currently exposed Current exposure to EFV vs. not currently exposed Current exposure to NVP vs. not currently exposed	
Klein *et al* 2015[71]	Cohort	USA	HIV+: 4.8years HIV-: 5.8 years	HIV+/HIV-	282,368 (91)	HIV+: 41 years HIV-: 40 years	MI	HIV+ vs HIV-	IRR[β]
Palella *et al* 2015[55]	Cohort	USA	~3.9 years	HIV+	16,733 (81)	Reported proportion of individuals by age categories	MI	Recent ABC use vs. non-recent use	HR[β]
Rasmussen *et al* 2015[56]	Cohort	Denmark	HIV+: 55,050–57,631 PYs HIV-: 638,204–659,237 PYss	HIV+/HIV-	HIV+: 5,897 (76) HIV-: 53,073 (76)	HIV+: 36.8 years[α] HIV-: 36.8 years[α]	MI	HIV+ vs. HIV-	IRR[β]
Drozd *et al* 2014[57]	Cohort	USA	1996-2012 (follow-up) NR	HIV+ HIV+	18,155 (NR) 17,626 (79)	NR Reported proportion of individuals by age categories	MI Primary MI	Current HIV RNA (log (copies/mL)+1) CD4 < 200 vs ≥ 200	OR[β] HR[β]
Silverberg *et al* 2014[72]	Cohort	USA	HIV+: 4.5 years HIV-: 5.4 years	HIV+/HIV-	HIV+: 22,081 (90.6) HIV-: 230,069 (90.5)	Reported proportion of individuals by age categories	MI	ART-treated HIV+ vs. HIV- ART-untreated HIV+ vs. HIV- Recent HIV RNA (per 1 log increase) Prior ART (yes vs no) Duration of PI use per year increase Duration of NNRTI use per year increase	IRR[β]
Freiberg *et al* 2013 [3]	Cohort	USA	5.9 years[α]	HIV+/HIV-	HIV+: 27,350 (97.3) HIV-: 55,109 (97.2)	HIV+: 48.2 years HIV-: 48.8 years	AMI	HIV+ vs. HIV- Recent CD4 < 200 (yes/no) Recent PI use (yes/no)	HR[β]
Lang *et al* 2012[51]	Nested case control	France	4.0 years	HIV+	Cases: 289 (88.9) Controls: 884 (89.1)	Cases: 47 (41-54) years[α]	MI	Current ABC vs not current HIV RNA per log10 increase	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
						Controls: 46 (40-54) years[α]			
Bedimo *et al* 2011[12]	Cohort	USA	3.9 years [α]	HIV+	19,424 (98)	46 years [α]	AMI	Cumulative ABC HAART per year of exposure Current ABC HAART vs. neither ABC/TDF Cumulative ARV per year of exposure	HR[β]
Choi *et al* 2011[24]	Cohort	USA	4.5 years[α]	HIV+	10,931 (98)	46 to 49 years (within subgroups by ART use)	MI	Recent ABC vs. not recent ABC or TDF	HR[β]
Durand *et al* 2011[52]	Cohort	Canada	4.0 years	HIV+/HIV-	HIV+: 7,053 (78); HIV-: 27,681 (78)	HIV+: 39.5 years HIV-: 39.7 years	AMI	HIV+ vs. HIV-	HR[β]
	Nested case control			HIV+	Cases: 125 (91.2); Controls: 1,084 (92.2)	Cases: 49.0 years Controls: 47.5 years	AMI	ABC exposure vs. no exposure Recent ABC vs. not recent DDI exposure vs. no exposure Recent DDI vs. not recent TDF exposure vs. no exposure Recent TDF vs. not recent ATV exposure vs. no exposure Recent ATV vs. not recent Recent LPV vs. not recent Recent RTV vs. not recent Recent EFV vs. not recent NVP exposure vs. no exposure Recent NVP vs. not recent FTC exposure vs. no exposure Recent FTC vs. not recent Recent 3TC vs. not recent d4T exposure vs. no exposure Recent d4T vs. not recent ZDV exposure vs. no exposure Recent ZDV vs. not recent Recent IDV vs. not recent	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								NFV exposure vs. no exposure Recent NFV vs. not recent SQV exposure vs. no exposure Recent SQV vs. not recent	
Carman *et al* 2011[63]	Cohort	USA	1998-2007 (follow-up)	HIV+	66,286 (NR)	NR	AMI	Recent ABC use vs. no use Recent PI use vs. no use	IRR[β]
Lang *et al* 2010b[43]	Cohort	France	2000-2006 (follow-up)	HIV+/ general population	HIV+: ~ 74,958 General population: unclear	35 to 64 years	MI	HIV+ vs general population	SMR
Lang *et al* 2010a[11]	Nested case control	France	2000-2006 (follow-up)	HIV+	Cases: 289 (89) Controls: 884 (89)	Cases: 47 (41-54) years[α] Controls: 46 (40-54) years[α]	MI	Recent ABC exposure vs. no exposure Cumulative ABC exposure vs. no exposure Cumulative DDI per year of exposure Cumulative TDF per year of exposure Cumulative ZVD per year of exposure Cumulative EFV per year of exposure Cumulative NVP per year of exposure Cumulative LPV + RTV per year of exposure Cumulative NFV per year of exposure Cumulative 3TC exposure per year Cumulative d4T exposure per year	OR[β]
Obel *et al* 2010[8]	Cohort	Denmark	~ 6.5 years	HIV+	2,952 (76.4)	39.1 (33.0-46.6) years[α]	MI	ABC exposure vs. no exposure	IRR[β]
Worm *et al* 2010[58]	Cohort	Multi-national	5.8 (3.9-7.5) years[α]	HIV+	33,308 (74)	With MI: 49 (43-65) years[α] Without MI: 44 (38-50) years[α]	MI	Cumulative ABC exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent TDF exposure vs. not recent Cumulative TDF exposure per year Recent DDI exposure vs. not recent Cumulative LPV-RTV exposure per year Cumulative NFV exposure per year Cumulative NVP exposure per year Cumulative EFV exposure per year	
Triant *et al* 2010[68]	Cohort	USA	5.1 years[α]	HIV+	6,517 (69)	46 years	AMI	CD4 count < 200/mm^3 vs ≥ 200 Nadir CD4 per 50/mm^3 increase VL > 100,000 copies/mL vs. ≤ 100,000 HIV RNA per log 10 increase ART per year since first ART use TDF use vs. none ABC use vs. none DDI use vs. none FTC use vs. none d4T use vs. none NVP use vs. none ATV use vs. none NFV use vs. none SQV use vs. none	OR[β]
Triant *et al* 2009[69]	Cohort	USA	HIV+: 6.0 years HIV-: 5.8 years	HIV+/HIV-	HIV+: 487 (62.8) HIV-: 69,870 (45.6)	HIV+/HIV-: Reported proportion by age categories	AMI	HIV+ vs. HIV-	OR[β]
D:A:D Study Group *et al* 2008a[13]	Cohort	Multi-national	5.1 years[α]	HIV+	33,347 (74)	With MI: 49 (range: 24-92) years[α] Without MI: 44 (range: 12-95) years[α]	MI	Recent ABC exposure vs. never exposed to ABC Recent DDI exposure vs. never exposed Cumulative DDI exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent ZDV exposure vs. never exposed Recent ZDV exposure vs. not recent Cumulative ZDV exposure per year Recent 3TC exposure vs. not recent Cumulative 3TC exposure per year Recent d4T exposure vs. not recent Recent d4T exposure vs. never exposed Cumulative d4T exposure per year	
D:A:D Study Group *et al* 2008b[59]	Cohort	Multi-national	4.5 years[α]	HIV+	28,985 (NR)	Reported by calendar period	MI	Cumulative exposure to PIs per year Cumulative exposure to NNRTIs per year	Relative rate[β]
D:A:D Study Group *et al* 2007[7]	Cohort	Multi-national	4.5 years[α]	HIV+	23,437 (76)	39 (34-45) years[α]	MI	Nadir CD4 per 50 cells/mm^3 increase	Relative rate[β]
Obel *et al* 2007[60]	Cohort	Denmark	HIV+: 6.9years[α] HIV-: 8.1 years[α]	HIV+/ HIV-	HIV+: 3,953 (76.8) HIV-: 373,856 (76.3)	HIV+: 36.8 (30.8-44.6) years[α] HIV-: 36.4 (30.6-44.0) years[α]	MI	HIV+, on HAART+ vs. HIV- HIV+ not on HAART- vs. HIV-	IRR[β]
Kwong *et al* 2006[70]	Cohort	USA and Netherlands	3.49 (range: 0.02-18.46) years[α]	HIV+	18,603 (82.63)	36 (range: 18-92) years[α]	MI	PI per year of exposure NNRTI per year of exposure HAART per year of exposure	RR[β]
Mary-Krause *et al* 2003[6]	Cohort	France	With MI: 28 (18-39) months[α] Without MI: 33 (15-48) months[α]	HIV+ men	34,976 (100)	With MI: 41.9 years Without MI: 37.7 years	MI	Exposure to PI	Relative hazard[β]
Holmberg *et al* 2002[61]	Cohort	USA	~ 3.1 years	HIV+	5,672 (82)	42.6 years	MI	PI use (yes vs no)	HR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
Rickerts *et al* 2000*[62]	Cohort	Germany	24.6 ± 18.1 months	HIV+	2,861 (78)	36.6 ± 9.5 years	MI	Prior HAART (yes vs. no)	OR[β]

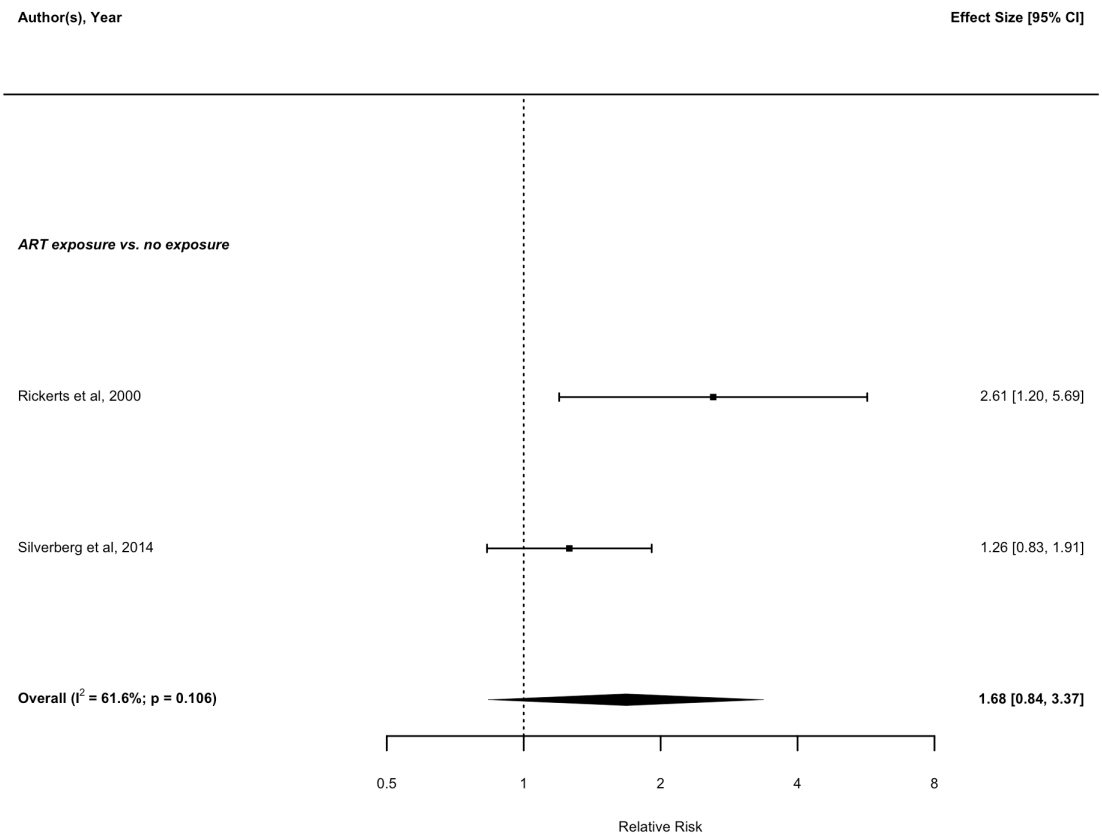
Legend: [α], median (including lower and upper quartiles, where reported); [β], adjusted estimate; *, extracted data from the ART era only; **, this was a general population comparison group and may not have consisted of HIV- individuals only; Note: a superscript alongside the author name/year is used to denote the reference number of the study; **ABC**, abacavir; **AMI**, acute myocardial infarction; **ARIC**, Atherosclerosis Risk in Communities; **ART**, antiretroviral therapy; **ATV**, atazanavir; **DDI**, didanosine; **d4T**, stavudine; **EFV**, efavirenz; **FTC**, emtricitabine; **HAART**, highly active antiretroviral therapy; **HR**, Hazard ratio; **IDV**, indinavir; **IRR**, incidence rate ratio; **LPV**, lopinavir; **LPV-RTV**, lopinavir-ritonavir; **MI**, myocardial infarction; **NA-ACCORD/ARIC**, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)/Atherosclerosis Risk in Communities (ARIC) cohorts; **NFV**, nelfinavir; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **NR**, not reported; **NRTI**, nucleoside reverse transcriptase inhibitor; **NVP**, nevirapine; **OR**, Odds ratio; **PI**, protease inhibitor; **RR**, relative risk; **RTV**, ritonavir; **SMR**, standardized morbidity ratio; **SQV**, saquinavir; **TDF**, tenofovir; **VL**, viral load; **ZDV**, zidovudine; **3TC**, lamivudine

Appendix Table 3. Risk of bias in the included studies

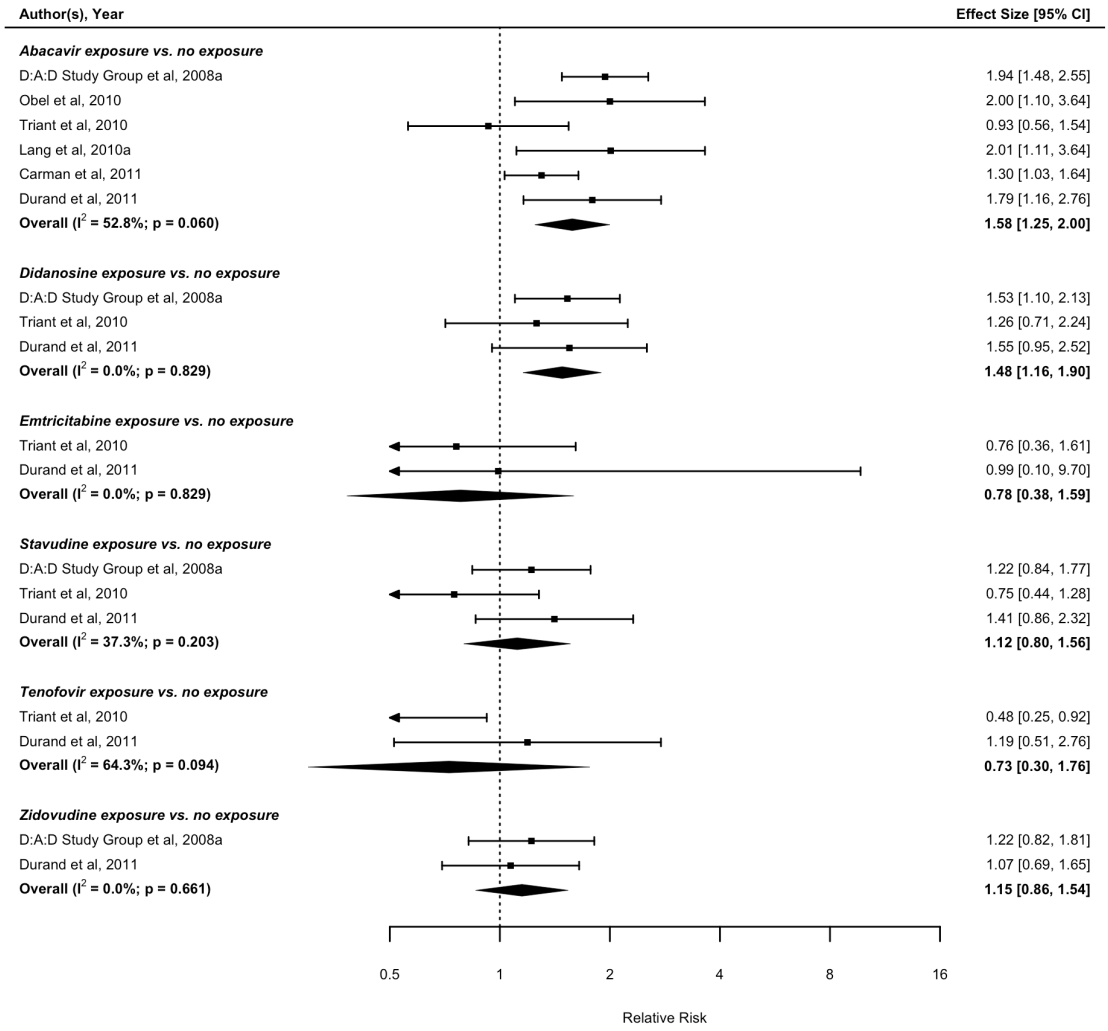
Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
LaFleur *et al* 2017[64]	Journal	Cohort (R)	+	+	No	+	-	-	Public. industry
Drozd *et al* 2017[42]	Journal	Cohort (P & R)	+	+	Yes*	-	+	+	Public
Rosenblatt *et al* 2016a[65]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Rosenblatt *et al* 2016b[66]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Sabin *et al* 2016[53]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Salinas *et al* 2016[54]	Journal	Cohort (P)	+	+	No	+	-	+	Public
Desai *et al* 2015[67]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Klein *et al* 2015[71]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Palella *et al* 2015[55]	Abstract	Cohort (P & R)	+	+	No	-	+	+	-
Rasmussen *et al* 2015[56]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Drozd *et al* 2014[57]	Abstract	Cohort (P)	-	+	No	-	+	-	Public
Silverberg *et al* 2014[72]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Freiberg *et al* 2013[3]	Journal	Cohort (P)	+	+	No	+	+	+	Public
Lang *et al* 2012[51]	Journal	Nested case-control	+	+	No	+	+	+	Public
Bedimo *et al* 2011[12]	Journal	Cohort (R)	+	+	No	+	-	+	-
Choi *et al* 2011[24]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Durand *et al* 2011[52]	Journal	Cohort (R), & nested case-control	+	+	No	+	-	+	Industry
Carman *et al* 2011[63]	Abstract	Cohort (R)	-	+	-	-	-	+	-

Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
Lang *et al* 2010a[11]	Journal	Nested case-control	+	+	No	+	+	+	Public
Lang *et al* 2010b[43]	Journal	Cohort (R)	+	+	No	-	+	+	Public
Obel *et al* 2010[8]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Worm *et al* 2010[58]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Triant *et al* 2010[68]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Triant *et al* 2009[69]	Journal	Cohort (R)	+	+	No	+	-	+	Public
D:A:D Study Group *et al* 2008a[13]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2008b[59]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2007[7]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Obel *et al* 2007[60]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Kwong *et al* 2006[70]	Journal	Cohort (R)	+	+	No	+	-	+	Public, industry
Mary-Krause *et al* 2003[6]	Journal	Cohort (R)	+	+	No	+	+	+	Public
Holmberg *et al* 2002[61]	Journal	Cohort (P)	+	+	No	-	+	+	Public
Rickerts *et al* 2000[62]	Journal	Cohort (P)	+	+	No	+	+	+	-

Legend: + means this is clearly described and adequate; - means this is unclear, inadequate or not reported; *, The HIV+ cohort (NA-ACCORD study) was compared to a general population cohort from a different study (Atherosclerosis Risk in Communities [ARIC] study); Note: a superscript alongside the author name/year is used to denote the reference number of the study; **NA**, Not applicable; **P**, Prospective; **R**, Retrospective

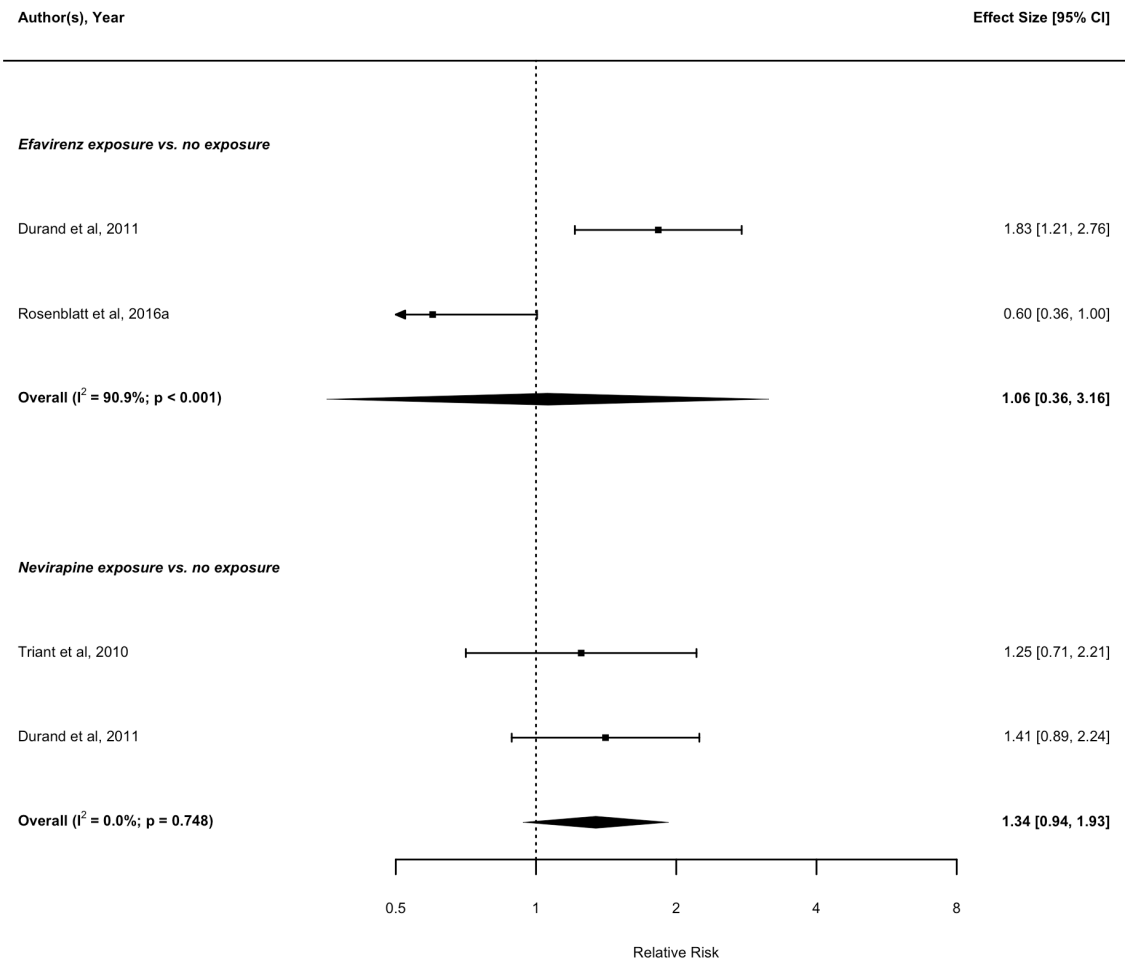


Appendix Figure A1. Forest plot of the meta-analysis of the risk of MI associated with any exposure to antiretroviral therapy
Legend: CI, Confidence interval

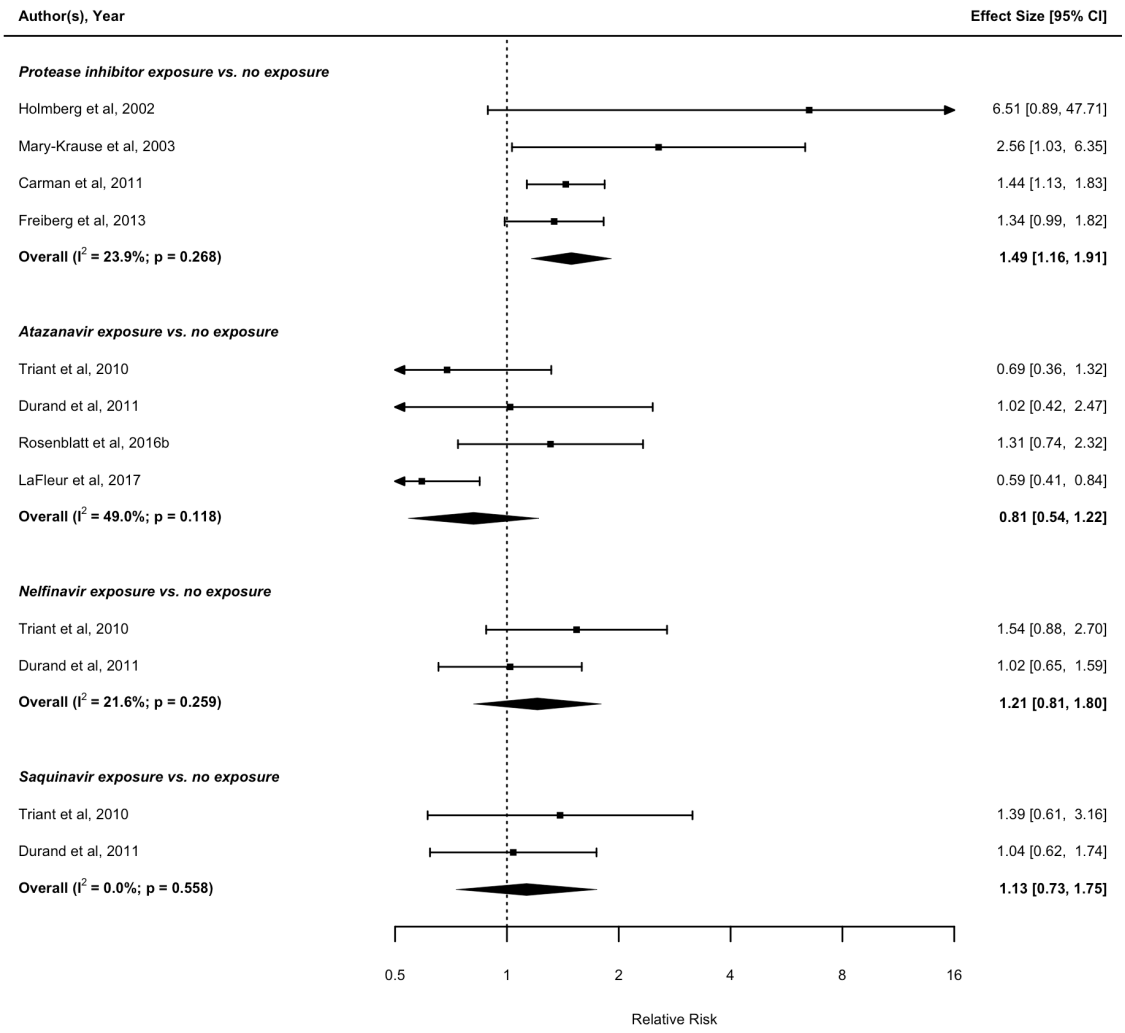


Appendix Figure A2. Forest plot of the meta-analysis of the risk of MI associated with any exposure to drugs of the NRTI class

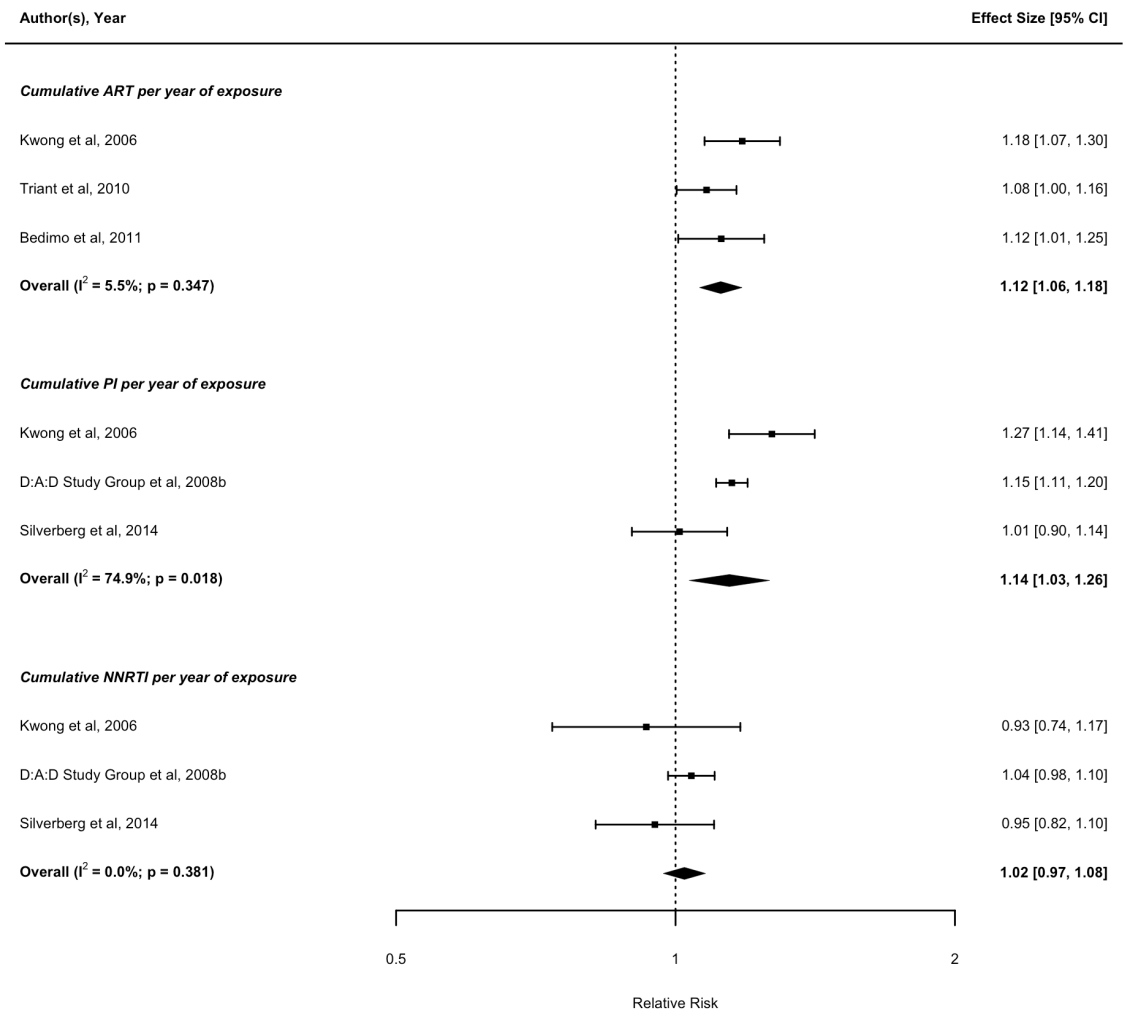
Legend: CI, Confidence interval



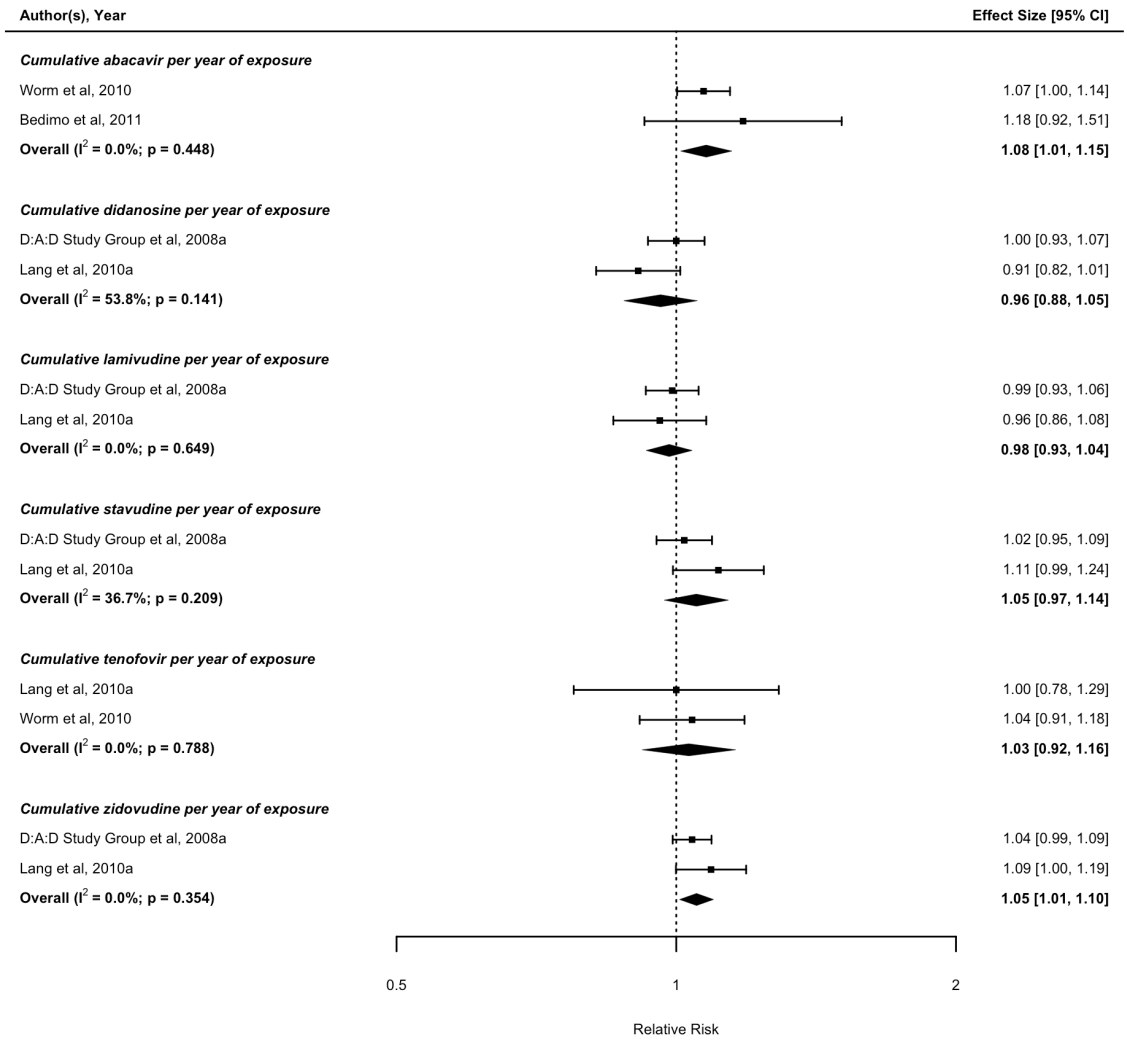
Appendix Figure A3. Forest plot of the meta-analysis of the risk of MI associated with any exposure to drugs of the NNRTI class
Legend: CI, Confidence interval



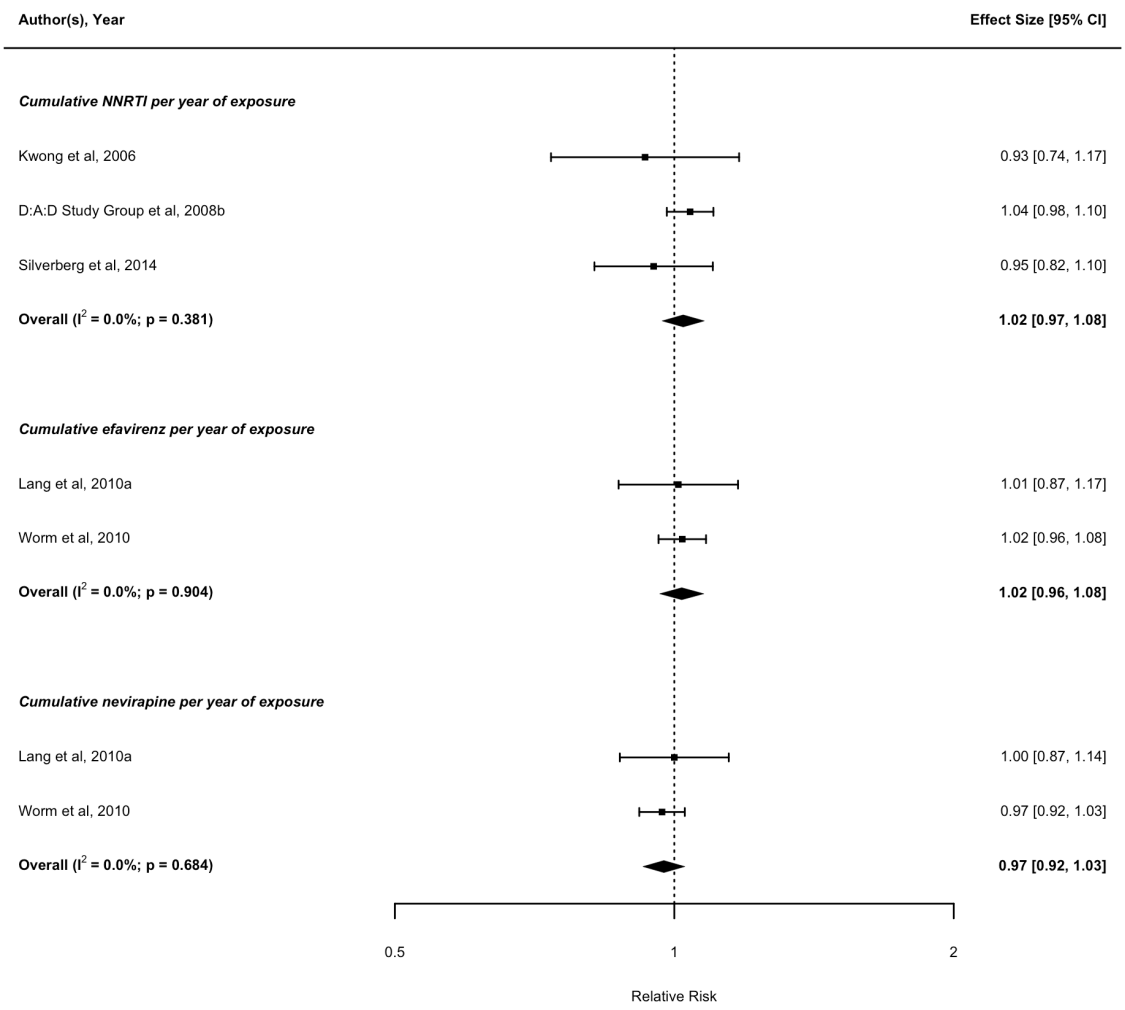
Appendix Figure A4. Forest plot of the meta-analysis of the risk of MI associated with any exposure to protease inhibitors (both as a class and individually)
Legend: CI, Confidence interval



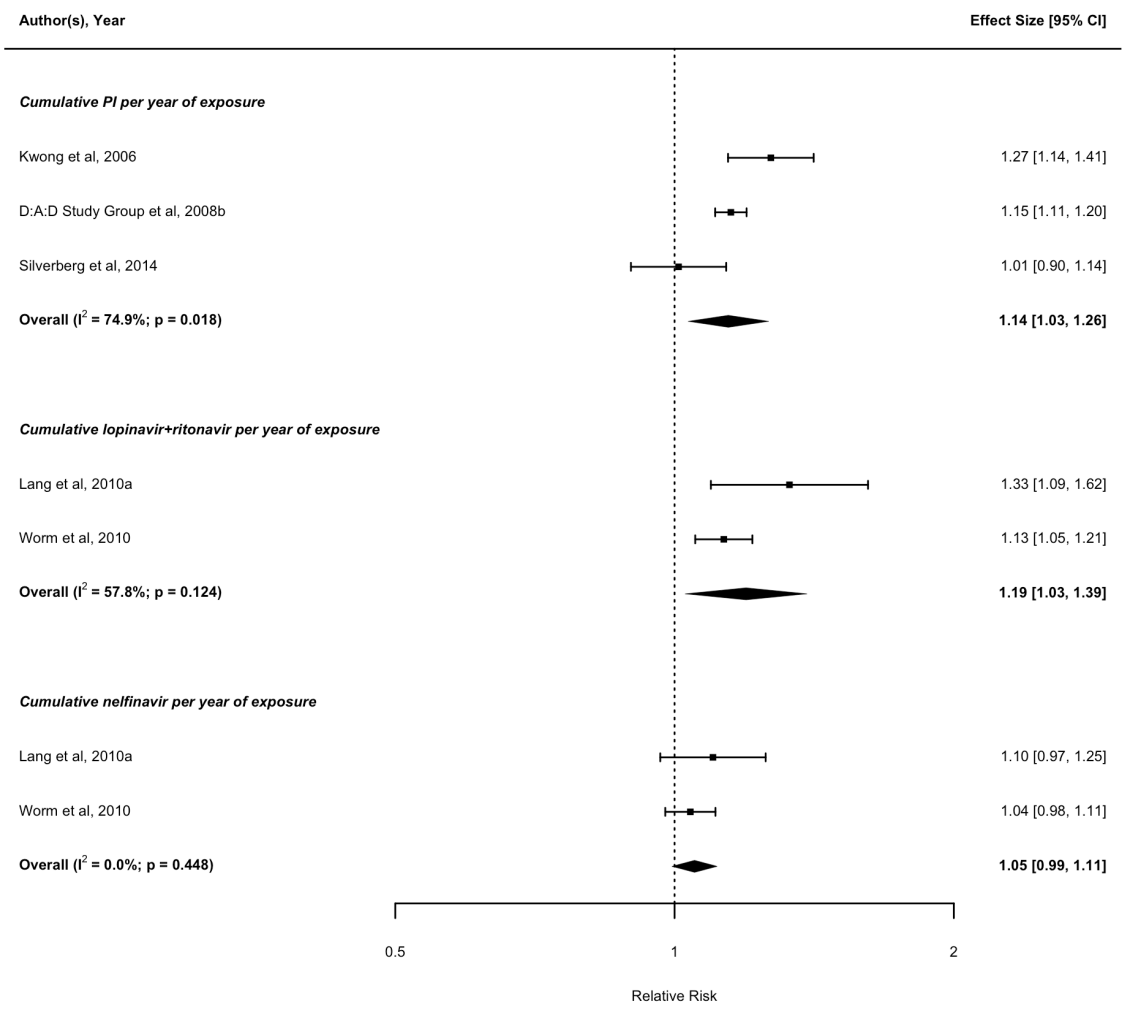
Appendix Figure A5. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to antiretroviral therapy (ART) including class of ART
Legend: ART, Antiretroviral therapy; CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease inhibitors



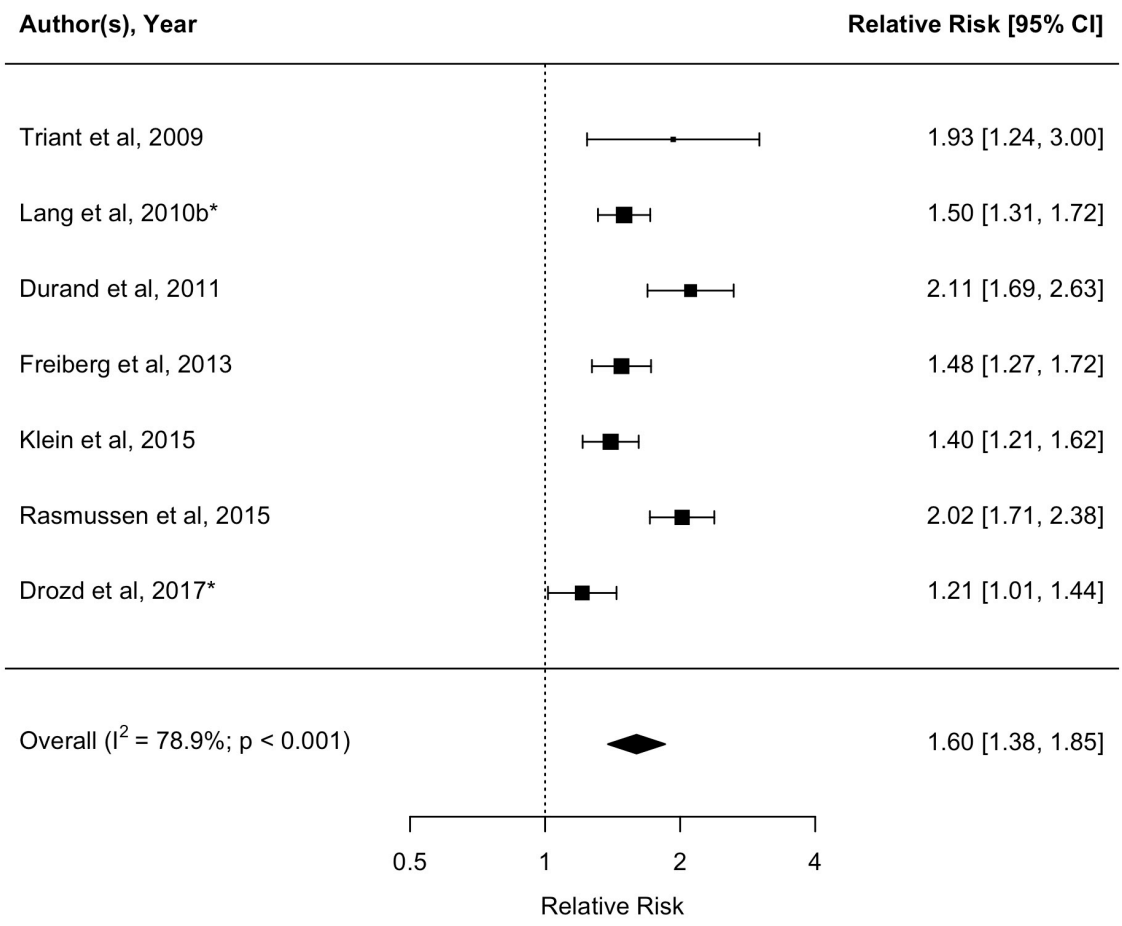
Appendix Figure A6. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to drugs of the NRTI class
Legend: CI, Confidence interval



Appendix Figure A7. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to NNRTI (both as a class and individually)
Legend: CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors

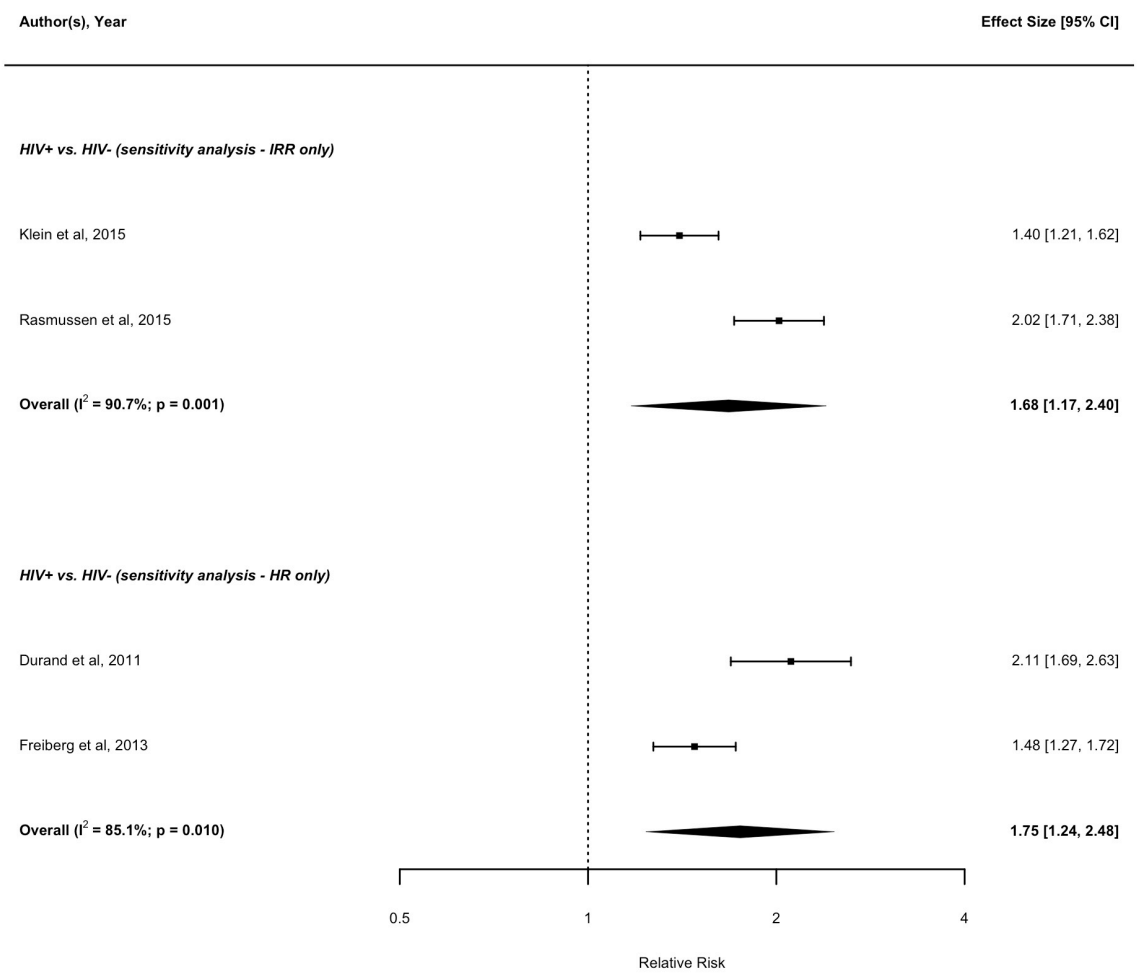


Appendix Figure A8. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to protease inhibitors (both as a class and individually)
Legend: CI, Confidence interval; PI, Protease inhibitors



Appendix Figure S1. Forest plot of the sensitivity analysis for the meta-analysis of the risk of MI associated with HIV infection, where two additional studies involving a general population comparison group were included

Legend: *, This study had a 'general population' comparison group and may not have consisted of HIV-negative individuals only; CI, Confidence interval



Appendix Figure S2. Forest plot of the sensitivity analyses for the meta-analysis of the risk of MI associated with HIV infection, where estimates reported using similar relative effect measures were pooled

Legend: CI, Confidence interval; HR, Hazard ratio; IRR, Incidence rate ratio

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Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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	Reporting Item	Page Number
#1	Identify the study as a meta-analysis of observational research	1
#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2
#3a	Problem definition	5
#3b	Hypothesis statement	6
#3c	Description of study outcomes	5
#3d	Type of exposure or intervention used	5, 6

	#3e	Type of study designs used	6
	#3f	Study population	7
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	6
	#4b	Search strategy, including time period included in the synthesis and keywords	6
	#4c	Effort to include all available studies, including contact with authors	7
	#4d	Databases and registries searched	7
	#4e	Search software used, name and version, including special features used (eg, explosion)	7
	#4f	Use of hand searching (eg, reference lists of obtained articles)	7
	#4g	List of citations located and those excluded, including justification	See note 1
	#4h	Method of addressing articles published in languages other than English	6
	#4i	Method of handling abstracts and unpublished studies	7
	#4j	Description of any contact with authors	8
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	6-8
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5-8
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	7,8
	#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	n/a
	#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	8,9
	#5f	Assessment of heterogeneity	9
	#5g	Description of statistical methods (eg, complete description of fixed or	8, 9

	random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
#5h	Provision of appropriate tables and graphics	9, 10
#6a	Graphic summarizing individual study estimates and overall estimate	10-14
#6b	Table giving descriptive information for each study included	36
#6c	Results of sensitivity testing (eg, subgroup analysis)	32
#6d	Indication of statistical uncertainty of findings	32
#7a	Quantitative assessment of bias (eg. publication bias)	9
#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	10
#7c	Assessment of quality of included studies	8, 10
#8a	Consideration of alternative explanations for observed results	18
#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	18
#8c	Guidelines for future research	18
#8d	Disclosure of funding source	19

Author notes

1. 10, Appendix