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ORIGINAL RESEARCH

Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis

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Objectives
The aim of this study was to estimate the relative risk of cardiovascular disease (CVD) among people living with HIV (PLHIV) compared with the HIV-uninfected population.

Methods
We conducted a systematic review and meta-analysis of studies from the peer-reviewed literature. We searched the Medline database for relevant journal articles published before August 2010. Eligible studies were observational and randomized controlled trials, reporting CVD, defined as myocardial infarction (MI), ischaemic heart disease, cardiovascular and cerebrovascular events or coronary heart disease among HIV-positive adults. Pooled relative risks were calculated for various groupings, including different classes of antiretroviral therapy (ART).

Results
The relative risk of CVD was 1.61 [95% confidence interval (CI) 1.43–1.81] among PLHIV without ART compared with HIV-uninfected people. The relative risk of CVD was 2.00 (95% CI 1.70–2.37) among PLHIV on ART compared with HIV-uninfected people and 1.52 (95% CI 1.35–1.70) compared with treatment-naïve PLHIV. We estimate the relative risk of CVD associated with protease inhibitor (PI)-, nucleoside reverse transcriptase inhibitor- and nonnucleoside reverse transcriptase inhibitor-based ART to be 1.11 (95% CI 1.05–1.17), 1.05 (95% CI 1.01–1.10) and 1.04 (95% CI 0.99–1.09) per year of exposure, respectively. Not all ART was associated with increased risk; specifically, lopinavir/ritonavir and abacavir were associated with the greater risk and the relative risk of MI for PI-based versus non-PI-based ART was 1.41 (95% CI 1.20–1.65).

Conclusion
PLHIV are at increased risk of cardiovascular disease. Although effective in prolonging survival, ART (in particular PI-based regimens) is related to further increased risk of CVD events among people at highest initial absolute risk of cardiovascular disease.

Keywords: cardiovascular disease, HIV, meta-analysis, relative risk, review

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Introduction

Cardiovascular disease (CVD), a commonly used term for diseases of the heart and blood vessels, is the number one cause of death world-wide [1]. It is projected that annual global cardiovascular deaths will increase from 16.7 million in 2002 to 23.9 million by 2030 [1]. The HIV pandemic has contributed significantly to mortality rates in many countries over the past three decades. However, the introduction of effective antiretroviral therapy (ART) has substantially reduced AIDS-related mortality [2,3] and thus non-HIV-related mortality, such as that attributable to CVD, has become increasingly important for the estimated 33.3 million people living with HIV (PLHIV) [4,5]. There is no consensus on the risk of CVD associated with HIV infection and the use of ART [6,7]. Therefore, in this study we conducted a systematic review and meta-analysis of the published literature to assess the relative risk (RR) of CVD

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among PLHIV compared with the HIV-uninfected population. We also investigated the RR of CVD associated with the use and duration of ART, including different classes of ART drugs administered.

Methods

Search strategy

We conducted a comprehensive literature search of the peer-reviewed publications through Medline, during July–November 2010, and conference proceedings of the Conference on Retroviruses and Opportunistic Infections (CROI) and International AIDS Society with the following search keywords: 'HIV or human immunodeficiency virus or AIDS or acquired immunodeficiency syndrome' AND 'cardiovascular or CVD or myocardial infarction or heart disease or vascular disease or coronary artery disease or coronary heart disease or myocarditis or cardiomyopathy or cardiac disease or cardiac arrhythmias' AND 'relative risk or risk ratio or RR or odds ratio or OR or hazard ratio or HR or incidence'. We included cohort studies and randomized controlled trials that reported HIV-infected adults in at least one study arm. We categorized studies that reported on ART according to the three major drug classes [protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitor (NRTI)] compared with the outcome among PLHIV not on ART.

Outcome measures

The primary outcome for our analysis was the incidence of CVD. For the purpose of this review, CVD includes myocardial infarction (MI), ischaemic heart disease (IHD), cardiovascular and cerebrovascular disease (CVD) and coronary heart disease (CHD). Studies that estimated the risks using incidence rate ratio (IRR), relative risk (RR), odds ratio (OR) or hazard ratios (HR) were included.

Selection of studies

We screened the titles of all articles for appropriateness, followed by the abstract, before retrieval of the full text. Studies that reported HIV and/or AIDS and CVD, and provided estimates of risk factors or estimates of RR, were included in the analysis. Studies that did not report risk estimates were excluded from further review. Non-English publications and review articles were also excluded from further analysis. The selection process, arriving at a final set of studies for formal analysis [7–29], is presented in Figure 1.

Data extraction

The data were extracted using a standardized form. The following information was extracted from each study: author, study design, study period, publication year, follow-up period, sample sizes, disease, comparator groups, outcome measures, estimates, age and geographical location. Details of the selected studies are given in Table 1.

Quality assessment of included studies

Two reviewers independently rated study quality using the Downs and Black checklist [30]. The checklist comprises 27 criteria including subsection of reporting (10), external validity (three) (generalizability of study population), assessment of bias (seven), confounding factors (six) and power (one) of detecting an important clinical effect. We estimated the average quality index score using the checklist based on our 23 observational (21) and randomized (two) studies [13,26], which resulted in an average score of 15.6 and 19.5 for nonrandomized and randomized studies, respectively, with a range of 12.5 to 20.

Statistical analysis

We conducted a series of meta-analyses based on similar comparator groups among the studies. The RR of CVD estimated includes: (1) PLHIV who were not on ART compared with HIV-uninfected people; (2) PLHIV who were treated with ART compared with HIV-uninfected people; (3) PLHIV who were treated with ART compared with treatment-naïve PLHIV; and (4) different classes of ART and the duration of treatment.

The risk estimates extracted from the selected studies were from either logistic regression or proportional hazards models with reported confidence intervals. This analysis used estimates where risk was already adjusted for common risk factors such as age, sex, race, smoking, diabetes and hypertension. The rationale to pool RRs from regression and proportional hazards models was based on the investigation of D'Agostino *et al.* [31]. D'Agostino *et al.* demonstrated the asymptotic equivalence of estimating RRs from logistic regression and proportional hazards models. Pooling of RR estimates in this manner has been applied in other analyses (e.g. Lollgen *et al.* [32]). We calculated the pooled estimates of risks for groups in which there were at least two individual studies.

We applied the DerSimonian–Laired (DSL) random effects model [33] to measure the outcome of interest that encounters a heterogeneity effect. We quantified the degree of heterogeneity using the *I*-squared (I^2) statistic, which can be interpreted as the percentage of total variation across the studies attributable to heterogeneity, and a value of

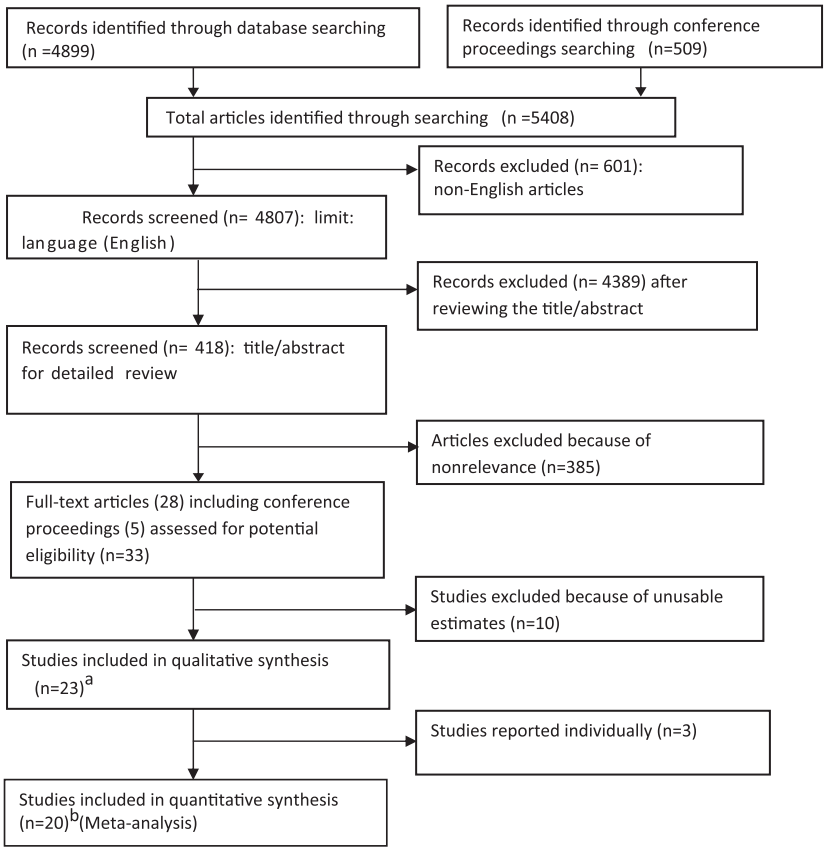


Fig. 1 Information flow diagram for the systematic review. [a]Qualitative synthesis: results of primary studies are summarized but not statistically combined. [b]Quantitative synthesis: statistical methods were applied to combine the results of two or more studies [35,42].

zero indicates no observed heterogeneity [34]. The methodology and reporting of this review conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [35,36]. Secondary analyses were conducted using meta-regression and subgroup analysis. All statistical tests were performed using two-tailed p-values ($P < 0.05$) except for meta-regression where we considered $P < 0.10$ to detect potential heterogeneity among variables. Publication bias was assessed using Egger's method [37]. Analyses were conducted in STATA (version 10; STATA Corporation, College Station, Texas, USA).

Results

Study selection

The search strategy initially resulted in 5408 articles. We identified 418 for detailed review. After reviewing the titles and abstracts in detail, we excluded 385 studies that were not relevant to CVD with HIV. Of 33 articles selected for potential eligibility, 10 were excluded as they were unrelated to our study question. We also searched conference proceedings of the Conference on Retroviruses and Opportunistic Infections (CROI) and International AIDS Society until 2010, and five out of 509 abstracts were selected [10,11,14,15,17]. A total of 23 studies were included, of which 21 were observational studies and two were randomized trials. Details of the search strategies and exclusion process are provided in Figure 1.

Study characteristics

Of the 23 studies included in our analysis, three were cross-sectional studies, two were case–control studies, 16 were cohort studies and two were randomized controlled trials. These studies recruited PLHIV and HIV-uninfected people with an average follow-up of 5 years. The studies varied greatly with respect to various ART combinations used as comparator.

Three studies recruited PLHIV who were not ART-experienced and HIV-uninfected people and compared the RR of CVD events. Three studies compared PLHIV treated

Table 1 Details of study populations

								Study group 1				Study group 2						
Study name	Study type	Study period	Median age (years)	Disease	Location	Study size (N)	Average follow-up (years)	Study description	Sample size (n1)	Event 1	Incidence (per 1000 py)	Study description	Sample size (n2)	Event 2	Incidence (per 1000 py)	Relative rate	HR/RR/ OR	95% CI
Aboud et al, 2010 [8]	Cross-sectional	2005–2006	41	CVD	UK	1021		ART				ART-naïve					1.13	0.72, 1.80
				CHD				ART				ART-naïve					1.02	0.57, 1.85
Bedimo et al, 2009 [10]	Cohort	1996–2004	–	AMI	South Africa	19424	3.88	Abacavir/year		278							1.18	0.92, 1.50
				CVA				Abacavir/year		868							1.16	0.98, 1.37
Benito et al, 2002 [11]	Cross-sectional		34	CVD		80		HIV (ART)		33	Non-HIV	256	43			2.4	1.69, 3.46	
Bozzette et al, 2008 [12]	Cohort	1993–2003	45	CVD	USA	41213	4	ART				ART-naïve					1.22	0.77, 1.92
								PI				ART-naïve					1.28	0.71, 2.30
								NNRTI				ART-naïve					1.02	0.51, 2.06
Coplan et al, 2003 [13]	RCT	1999	37	MI	USA	10986	1	PI	7951	7	1.38	NRTI	3035	3	1.17	1.18	1.18	0.32, 4.41
Currier et al, 2003 [7]	Cohort	1994–2000	26	CHD	USA	28513		ART				ART-naïve					2.06	1.42, 2.99
Durand et al, 2009 [14]	Case–control		52.1	MI	Canada	6168	4.6	Abacavir				ART-naïve					1.74	1.18, 2.56
								didanosine				ART-naïve					1.6	1.06, 2.43
								Stavudine				ART-naïve					1.5	1.07, 2.12
Holmberg et al, 2002 [15]	Cohort	1993–2002	50	MI	USA	5,672	3.1	PI	3247	19	1.4	Non-PI	2425	2	0.5	3.1	6.5	0.89, 47.8
Iloeje et al, 2005 [16]	Cohort	1996–2003	39.4	CVD	USA	7542	3.5	PI	5787	112	9.8	Non-PI	1755	15	6.5	1.5	1.71	1.08, 2.74
Klein et al, 2007 [17]	Cohort	1994–2006	43	MI	USA	6702	11	HIV (ART)	6702			Non-HIV	72840				1.78	1.43, 2.21
								PI/year									1.16	0.97, 1.4
Kwong et al, 2006 [18]	Cohort	1983–2004	36	MI	USA	18377	4.2	ART				NRTI					1.26	1.07, 1.48
								PI				NRTI					1.37	1.15, 1.62
								NNRTI				NRTI					1.02	0.78, 1.33
								NNRTI+PI				NRTI					0.8	0.54, 1.19
Lang et al, 2010 [19]	Cohort	2000–2006	49.5	MI	France	74958	4	HIV				Non-HIV					1.5	1.3, 1.7
Lang et al, 2010 [20]	Case–control	2000–2006	47	MI	France	74958		Abacavir		289		ART-naïve		884			2.01	1.11, 3.64
								NNRTI/year									1.01	0.87, 1.17
								Didanosine/year									0.91	0.82, 1.01
								Lamivudine/year									0.96	0.85, 1.07
								Stavudine/year									1.11	0.99, 1.24
								Tenovir/year									1	0.77, 1.28
								Zalcitabine/year									0.98	0.81, 1.20
								Zidovudine/year									1.09	1.00, 1.19
								Efavirenz/year									1.01	0.87, 1.17
								Nevirapine/year									1	0.87, 1.14
								Amprenavir/fosamprenavir+/-ritonavir/year									1.53	1.21, 1.94
								Indinavir+/-ritonavir/year									1.07	0.94, 1.20
								Lopinavir+ritonavir/year									1.33	1.09, 1.61
								Nelfinavir/year									1.1	0.97, 1.26
								Saquinavir+/-ritonavir/year									0.93	0.80, 1.09

Table 1 (Contd.)

Study name	Study type	Study period	Median age (years)	Disease	Location	Study size (N)	Average follow-up (years)	Study group 1				Study group 2				Relative rate	HR/RR/OR	95% CI
								Study description	Sample size (n1)	Event 1	Incidence (per 1000 py)	Study description	Sample size (n2)	Event 2	Incidence (per 1000 py)			
Lichtenstein et al, 2010 [21]	Cohort	2002–2009	42	CVD	USA	2005	5.5	CD4<350 cells/μL	–	–	–	CD4≥500 cells/μL	–	–	–	–	1.58	1.09, 2.30
								CD4350-499 cells/μL	–	–	–	CD4≥ 500 cells/μL	–	–	–	–	1.28	0.81, 2.02
Mary-Krause et al, 2003 [22]	Cohort	1996–1999	37.7	MI	France	34976	2.5	NRTI				ART-naïve					0.93	0.19, 4.65
								NNRTI				ART-naïve					1.38	0.67, 2.83
								PI				ART-naïve					2.56	1.03, 6.34
Obel et al, 2010 [23]	Cohort	1995–2005	39.1	MI	Denmark	2952	6.5	Abacavir	1191	36	5.7	ART-naïve	1751	31	2.4	2.4	2	1.10, 3.64
Obel et al, 2007 [24]	Cohort	1995–2004	38.9	IHD	Denmark	3953	5.8	HIV	3953	48	3.5	Non-HIV	373856	11	1.2	3	1.39	0.81, 2.33
								HIV (ART)				Non-HIV					2.12	1.62, 2.76
Pere et al, 2008 [25]	Cross-sectional		40	CVD	Spanish	2358		NNRTI				NRTI					0.63	0.28, 1.42
								PI				NRTI					1.13	0.52, 2.46
								NNRTI+PI				NRTI					1.19	0.48, 7.57
								ART/year									1.07	1.02, 1.12
								NRTI/year									1.07	1.03, 1.11
								NNRTI/year									1.05	0.99, 1.11
								PI/year									1.04	1.00, 1.08
Phillips et al, 2008 [26]	RCT	2006	44	CVD	USA	5472		DC (ART)	2720	48	13.3	VS (ART)	2752	31	8.5	1.6	1.57	1.00, 2.46
Triant et al, 2007 [27]	Cohort	1996–2004	38	MI	USA	3851	4.4	HIV	3851	189	11.1	Non-HIV	1044589	26142	7	1.6	1.75	1.51, 2.02
Vaughn and Detels 2007 [28]	Cohort	1990–2000	37	CVD	USA	5667	2.7	PI	–	–	–	–	–	–	–	–	6.22	3.13, 12.39
								Non-PI				–					3.18	1.99, 5.09
Worm et al, 2010 [29]	Cohort	1993–2003	49	MI	Europe, USA, Australia	33308	5.4	Abacavir/year	–	–	–	–	–	–	–	–	1.07	1.00, 1.14
								Indinavir/year				–					1.12	1.07, 1.18
								Lopinavir+ritonavir/year				–					1.13	1.05, 1.21
								Abacavir				ART-naïve					1.7	1.17, 2.47
								Didanosine				ART-naïve					1.41	1.09, 1.82

ART, antiretroviral therapy; CHD, coronary heart disease; CVD, cardiovascular disease; DC, drug conservation arm; IHD, ischaemic heart disease; MI, myocardial infarction; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RCT,randomized controlled trial; VS, viral suppression arm.

with ART with HIV-uninfected people. Five studies compared PLHIV treated with ART with PLHIV without any treatment. Each of the identified studies was internally age-matched; the median age of the study populations was 40 (range 34–46) years. Table 1 gives the study characteristics in detail.

RR of CVD for PLHIV not on treatment vs. HIV-uninfected people

Three identified studies reported the risk of CVD for PLHIV [19,24,27]. Lang *et al.* [19] compared 74958 PLHIV in France based on the France Hospital Database on HIV (FHDH) with uninfected people aged from 35 to 64 years. The estimated age- and sex-standardized RR of MI was 1.50 (95% CI 1.3, 1.7). Obel *et al.* [24] reported the RR of IHD for 3953 PLHIV compared with 373 856 control subjects to be 1.39 (95% CI 0.82, 2.36) and 2.12 (95% CI 1.62, 2.76) for the pre-highly active antiretroviral therapy (HAART) and HAART eras, respectively. This study was based in Denmark and the study population consisted of adults older than 16 years of age; both HIV-infected subjects and control subjects were well matched in terms of distributions of age, sex, emigration, loss to follow-up and comorbidities. Another study, conducted in the USA by Triant *et al.* [27], compared 3851 PLHIV and 1 044 589 HIV-uninfected people and estimated the RR of acute MI to be 1.75 (95% CI 1.51, 2.02). This study compared PLHIV with the control group where the study populations were aged 18 years or older. The RR was adjusted for age, gender, race, hypertension, diabetes and dyslipidaemia.

The pooled RR of CVD among PLHIV without treatment was 1.61 (95% CI 1.43 to 1.81; $P < 0.001$) compared with HIV-uninfected people (Fig. 2a). There was no statistically significant evidence of heterogeneity ($I^2 = 18.4\%$; $P = 0.29$).

RR of CVD for PLHIV with treatment vs. HIV-uninfected people

We investigated the effect of ART on the risk of CVD. We identified three relevant studies estimating the RR for ART compared with HIV-uninfected people [11,17,24]. Benito

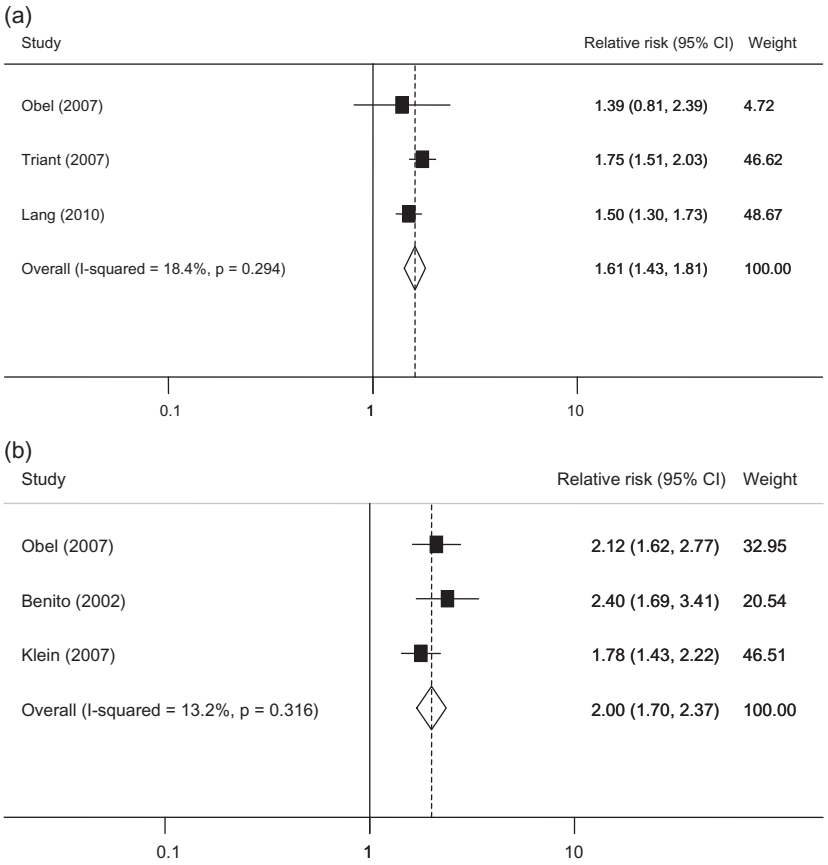


Fig. 2 Forest plots of studies and pooled estimate of relative risk of cardiovascular disease (a) in people living with HIV (PLHIV) versus HIV-uninfected people and (b) in PLHIV exposed to antiretroviral treatment versus HIV-uninfected people. CI, confidence interval.

et al. [11] compared 80 HIV-infected people who were exposed to PI-based regimens with 256 uninfected people aged 19 to 49 years. The estimated RR of CVD was 2.40 (95% CI 1.69, 3.46) after adjusting for age, sex, blood pressure, diabetes, smoking, cholesterol and left ventricular hypertrophy. The study reported by Klein *et al.* [17] compared 6702 HIV-infected people who were exposed to PI and other ART regimens with uninfected people and estimated the RR of MI to be 1.78 (95% CI 1.43, 2.22). We conducted a meta-analysis on estimates from these three studies (note that we included the RR for the HAART period from the Obel *et al.* study).

The pooled RR of CVD among PLHIV with treatment was 2.00 (95% CI 1.70 to 2.37; $P < 0.001$) compared with HIV-uninfected people (Fig. 2b). There was no statistically significant evidence of heterogeneity ($I^2 = 13.2\%$; $P = 0.32$). In summary, the risk of CVD is two times higher among ART-treated PLHIV than HIV-uninfected people.

RR of CVD among those on treatment vs. treatment-naïve PLHIV

ART and the risk of CVD

We also investigated the effect of ART on the risk of CVD among HIV-infected people with and without ART. We identified eight relevant studies estimating the RR for various ART regimens compared with treatment-naïve PLHIV [7,8,12,14,20,22,23,29]. Currier *et al.* reported that the hazard ratio of CHD associated with exposure to ART was 2.06 (95% CI 1.42, 2.99), which was adjusted for diabetes, hyperlipidaemia, renal failure and hypertension [7]. Aboud *et al.* estimated the OR of CVD and CHD to be 1.13 (95% CI 0.72, 1.80) and 1.02 (95% CI 0.57, 1.85), respectively, for people exposed to ART when adjusted for age and gender [8]. Bozzette *et al.* calculated an adjusted HR of serious cardiovascular events to be 1.22 (95% CI 0.77, 1.92) and 1.28 (95% CI 0.71, 2.30) among PLHIV who were exposed to NNRTI- and PI-based ART, respectively [12]. Durand *et al.* estimated the OR of MI to be 1.74 (95% CI 1.18, 2.56), 1.60 (95% CI 1.06, 2.43) and 1.50 (95% CI 1.07, 2.12) among PLHIV who were exposed to abacavir, didanosine and stavudine, respectively, after adjusting for age and sex [14]. Lang *et al.* calculated an adjusted OR of MI to be 2.01 (95% CI 1.11, 3.64) among PLHIV who were exposed to abacavir-based ART [20]. Mary-Krause *et al.* estimated the adjusted relative hazard of MI to be 0.93 (95% CI 0.19, 4.65), 1.38 (95% CI 0.67, 2.83) and 2.56 (95% CI 1.03, 6.34) among PLHIV who were exposed to NRTI-, NNRTI- and PI-based ART, respectively [22]. Obel *et al.* calculated an adjusted RR of MI to be 2.00 (95% CI 1.10, 3.64) among PLHIV who were exposed to abacavir-based ART [23]. Worm *et al.* reported an adjusted RR of MI in the data collection on adverse events of anti-HIV drugs (D:A:D) study to be 1.70 (95% CI 1.17, 2.47) and 1.41 (95% CI 1.09, 1.82) in PLHIV who were exposed to abacavir and didanosine, respectively [29].

We estimated the pooled RR to be 1.52 (95% CI 1.35, 1.70; $P = 0.001$) for CVD among PLHIV who were treated with ART compared with treatment-naïve PLHIV (Fig. 3a). There was no statistically significant evidence of heterogeneity between the studies ($I^2 = 0.0\%$; $P = 0.597$). In summary, PLHIV who are on ART have a 52% higher risk of CVD compared with PLHIV unexposed to any ART.

PIs and the risk of CVD

We investigated the effect of specific antiretroviral classes on the risk of CVD among PLHIV using PIs compared with PLHIV not receiving any antiretrovirals. We identified two relevant studies estimating the RR for PI-based ART compared with treatment-naïve PLHIV [12,22]. We estimated the pooled RR to be 1.65 (95% CI 0.86, 3.19; $P = 0.133$) for CVD among PLHIV who were treated with a PI-based regimen compared with treatment-naïve PLHIV (Fig. 3b). There was no statistically significant evidence of heterogeneity between the studies ($I^2 = 36.3\%$; $P = 0.210$).

NRTIs and the risk of CVD

We investigated the effect of using NRTIs on the risk of CVD among PLHIV. We identified five relevant studies estimating the RR for NRTI-based ART compared with treatment-naïve PLHIV [14,20,22,23,29]. We estimated the pooled RR to be 1.59 (95% CI 1.38, 1.83; $P = 0.133$) for CVD among PLHIV who were treated with an NRTI-based regimen compared with treatment-naïve PLHIV (Fig. 3c). There was no statistically significant evidence of heterogeneity between the studies ($I^2 = 0.0\%$; $P = 0.896$). We also investigated the impact of individual NRTI drugs, where possible. We estimated the pooled RR of CVD among PLHIV to be 1.80 (95% CI 1.43, 2.26; $P < 0.001$), 1.47 (95% CI 1.23, 1.77; $P < 0.001$) and 1.46 (95% CI 1.17, 1.82; $P < 0.001$) for people treated with abacavir, non-abacavir and didanosine, respectively, each with no statistically significant evidence of heterogeneity [Fig. 3c(ii–iv)].

NNRTIs and the risk of CVD

We also investigated the effect of NNRTIs on the risk of CVD among PLHIV. We identified two relevant studies estimating the RR of CVD for people on NNRTI-based ART compared with treatment-naïve PLHIV [12,22]. We estimated the pooled RR to be 1.18 (95% CI 0.71, 1.94; $P = 0.519$) for CVD among PLHIV who were treated with a NNRTI-based regimen compared with treatment-naïve PLHIV. There was no statistically significant evidence of heterogeneity between the studies ($I^2 = 0.0\%$; $P = 0.554$) (Fig. 3d).

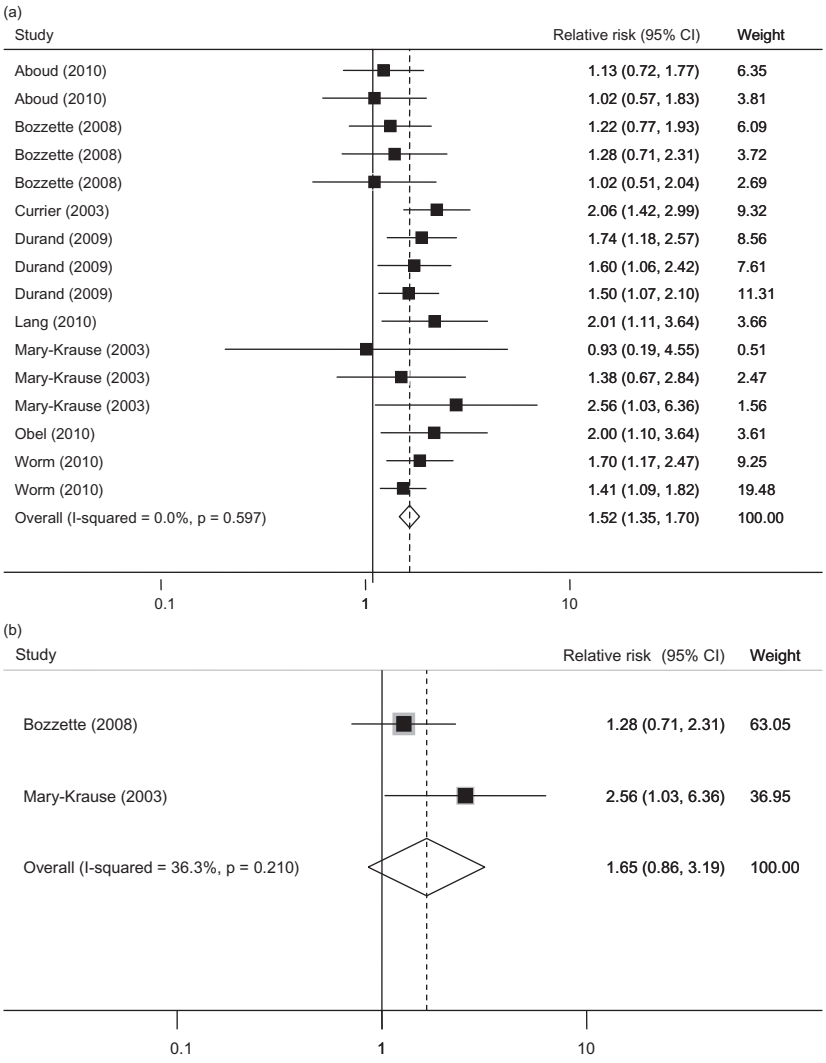


Fig. 3 Forest plots of studies and pooled estimate of relative risk of cardiovascular disease in people living with HIV (PLHIV) exposed to (a) antiretroviral treatment versus no treatment; (b) protease inhibitor (PI)-based antiretroviral treatment versus no treatment; (c) (i) nucleoside reverse transcriptase inhibitor (NRTI)-based antiretroviral treatment versus no treatment; (ii) abacavir-based antiretroviral treatment versus no treatment; (iii) non-abacavir-based antiretroviral treatment versus no treatment; (iv) didanosine-based antiretroviral treatment versus no treatment; (d) nonnucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral treatment versus no treatment. CI, confidence interval.

RR of CVD between PI-based and non-PI-based ART

To identify whether the risk of CVD depends on the class of ART, we collated data from available studies. We calculated the RR of CVD for PLHIV treated with PI-based ART compared with PLHIV receiving ART not containing a PI. One randomized controlled trial (RCT) and four observational studies were relevant for inclusion in this analysis. Coplan *et al.* reported that the RR of MI for people on PI-based ART was 1.18 (95% CI 0.32, 4.41) compared with those on NRTI-only-based ART [13]. Holmberg *et al.* reported that the RR for people on PI-based ART was 4.92 (95% CI 1.28, 32.3) compared with those on non-PI-based ART [15]. Iloeje *et al.* reported that the RR for people on PI-based ART was 1.71 (95% CI 1.08, 2.74) compared with people on non-PI-based ART [16]. The cohort study conducted by Kwong *et al.* found that the RR of MI for people receiving PI-based ART was 1.37 (95% CI 1.15, 1.62) compared with people receiving NRTI-only ART [18]. Another cross-sectional study [25] found an increased RR of CVD in those on PI-based ART compared with those on non-PI-based ART.

Pooling the four estimates, we calculated that the RR of CVD was 1.41 (95% CI 1.2, 1.65; $P < 0.001$) for people on

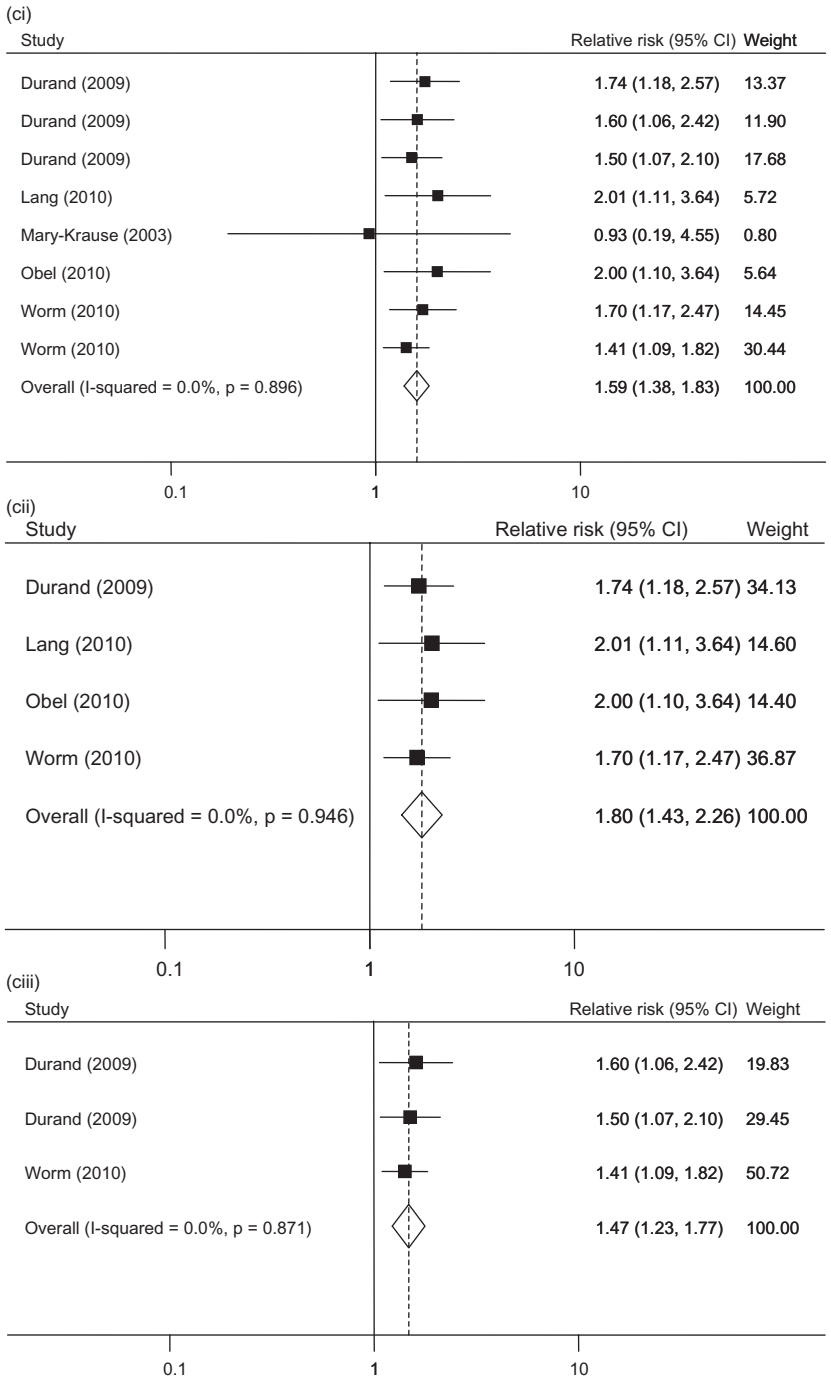
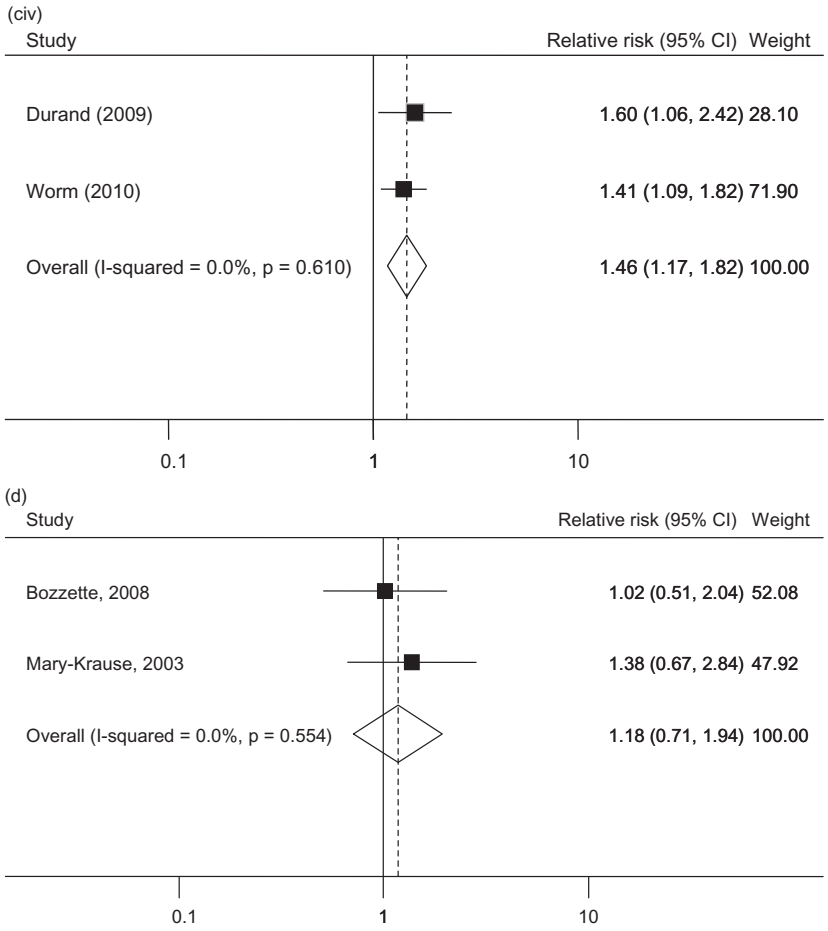


Fig. 3 (Contd.)

PI-based ART compared with those on non-PI-based ART (Fig. 4). There was no statistically significant evidence of heterogeneity for this outcome ($I^2 = 0.0\%$; $P = 0.488$). This indicated that PI-based ART is associated with a greater risk of CVD than non-PI-based therapy.

RR of CVD with duration of treatment

To identify the RR of CVD associated with the duration of ART, we combined the estimates of five studies. The pooled annual RR of CVD among HIV-infected people with



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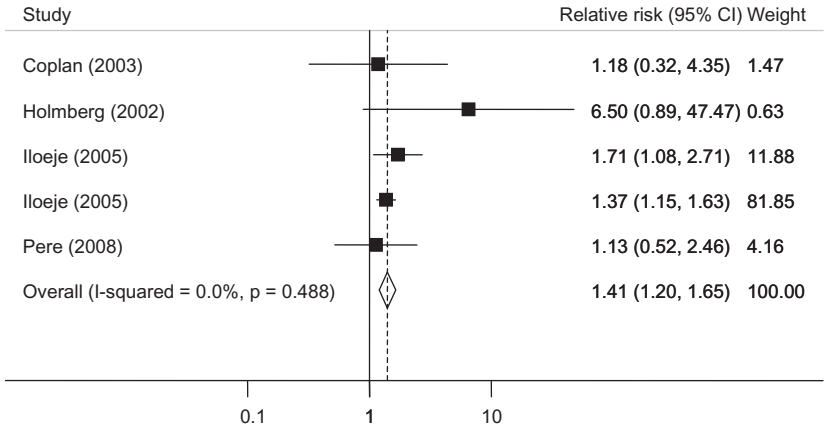

Fig. 4 Forest plot of studies and pooled estimate of relative risk of cardiovascular disease in people living with HIV (PLHIV) exposed to protease inhibitor (PI)-based antiretroviral therapy (ART) compared with PLHIV exposed to non-PI-based ART.

exposure to ART was 1.07 (95% CI 1.04, 1.10) (Fig. 5a). However, there were some differences between classes of ART, and specific drugs, in the calculated RRs of CVD for each year of exposure. To identify the RR of CVD associated with each major class of drugs, we pooled the estimates of available studies. We calculated a pooled annual RR estimate of 1.11 (95% CI 1.05, 1.17) (Fig. 5b) for PI-based ART; 1.05 (95% CI 1.01, 1.10) for NRTI-based ART (Fig. 5c); and 1.04 (95% CI 0.99, 1.09) for NNRTI-based ART (Fig. 5d). Within the NRTI class of antiretrovirals, abacavir is believed to specifically be associated with increased risk of CVD. From available studies, we calculated a pooled annual RR of CVD associated with abacavir use of 1.09 (95% CI 1.02, 1.16) (Fig. 5e). We also found a statistically significant association between the annual RR of CVD and lopinavir/ritonavir (within the PI class) of 1.19 (95% CI 1.03, 1.39) (Fig. 5b). One study [20] also reported a greater annual risk of CVD for use of amprenavir/fosamprenavir ± ritonavir, with a RR of 1.53 (95% CI 1.21, 1.93). Moderate levels of heterogeneity were observed between studies in most pooled analyses (Fig. 5a–c).

Meta-regression and subgroup outcomes

We performed univariate meta-regression to explore factors that might account for heterogeneity between study estimates of the effect of identified risk factors on CVD. We found that the type of treatment reported caused heterogeneity for estimates associated with cumulative exposure to PI-based regimens per year. Potential explanatory covariates considered were age, study design, study period, duration of follow-up, diseases, treatment groups, study location and study size. We identified that the type of treatment was significantly ($P = 0.002$) associated with heterogeneity of the risk estimates of CVD. We performed subgroup analysis using this variable and found that the revised RR of MI for lopinavir with ritonavir was 1.19 (95% CI 1.03, 1.39; $P = 0.022$) with decreased heterogeneity $I^2 = 55.9\%$ ($P = 0.132$) compared with the previous analysis ($I^2 = 67.2\%$; $P = 0.002$) for estimates associated with PI-based ART per year.

Publication bias

We found no significant evidence of publication bias in our estimates. For example, in studies comparing the RR of CVD between PLHIV without ART and HIV-uninfected people, there was no evidence of publication bias by funnel plot symmetry and Egger's method ($P = 0.796$). We found no significant evidence of publication bias in other estimates in our analysis. However, this does not preclude the possible existence of publication bias.

Discussion

In this study, we set out to collate data from available literature on the RR of CVD for PLHIV and conduct meta-analyses to calculate pooled estimates across available evidence. Our analysis suggests that PLHIV have an increased risk of CVD. Specifically, the RR of CVD for PLHIV was found to be 61% higher than that of HIV-uninfected people. The risk of CVD for PLHIV receiving ART was found to be 2.00 times greater than the risk for PLHIV who were treatment-naïve. There exists controversy regarding the class of ART in terms of the degree of risk of CVD. In an observational study of hospitalization rates in Northern California, Klein *et al.* found that PIs did not tend to increase the rates of hospitalizations for CHD among PLHIV [38]. However, other studies have reported considerably increased risk of CVD associated with PI-based ART. NRTI-based ART use is also associated with an increased risk of CVD, but not to the same extent as PI-based ART. A recently published study (published after our literature search) by Choi *et al.* [39] found that tenofovir use is associated with heart failure (HR 1.82; CI 1.02–3.24) and abacavir is associated with CVD (HR 1.48; CI 1.08–2.04). In a randomized trial, Martin *et al.* reported that abacavir was found to be a greater risk factor for CVD than tenofovir [40]. It is possible that both of these drugs contribute significantly to the risk of CVD in those who are taking ART. These estimates are not inconsistent with the pooled estimates we calculated based on other available studies. We also found that the duration of exposure to ART is an important contributor to the risk of acquiring CVD.

Most of the studies included in our analysis had CHD as the primary endpoints. CHD refers to atherosclerosis of the coronary arteries. It is important to note this distinction from other manifestations of CVD, especially as there is less evidence on the impact of ART associated with other CVD events than for CHD.

We identified in our search strategy additional literature that was relevant to our study question but did not have similar comparator groups for the meta-analysis. In a randomized trial, Phillips *et al.* explored the impact of CD4 T-cell-count guided intermittent ART, adjusting for drug concentration and viral suppression [26]. They found that continuous use of ART had a RR of CVD of 1.57 (95% CI 1.00, 2.46; $P = 0.05$) compared with intermittent ART. A cohort study reported by Lichtenstein *et al.* compared the risk of CVD for different CD4 count categories [21]. They found that the RRs of CVD for PLHIV with a CD4 count < 350 cells/μL were 1.58 (95% CI 1.09, 2.30) and 1.28 (95% CI 0.81, 2.02) compared with people with a CD4 count between 350 and 499 cells/μL and a CD4 count > 500 cells/μL, respectively. This suggests that CVD is more likely to be acquired with

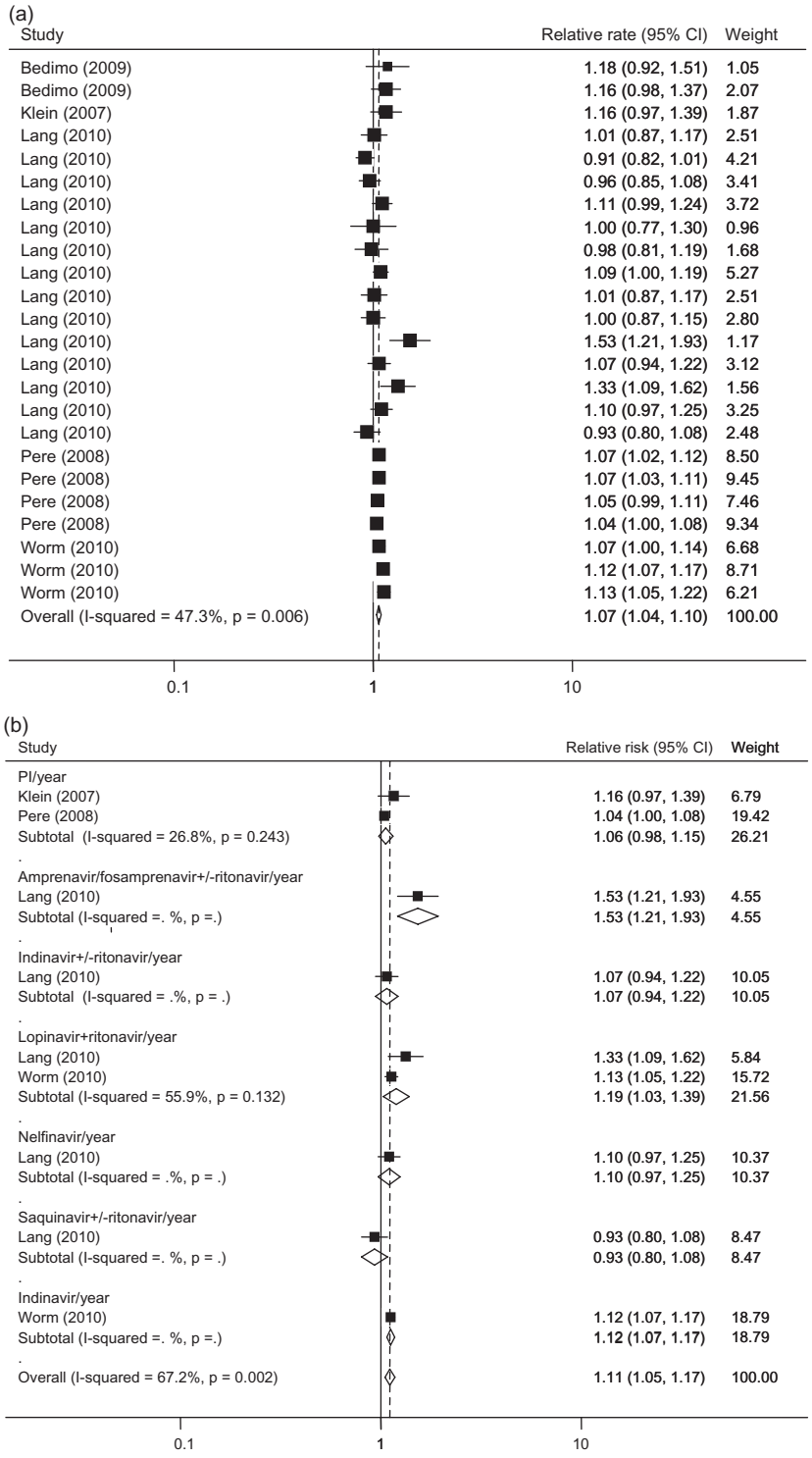

Fig. 5 Forest plots of studies and pooled estimate of annual relative rate of cardiovascular disease in (a) people living with HIV (PLHIV) exposed to antiretroviral therapy (ART); (b) PLHIV exposed to protease inhibitor (PI)-based ART; (c) PLHIV exposed to nucleoside reverse transcriptase inhibitor (NRTI)-based ART; (d) PLHIV exposed to nonnucleoside reverse transcriptase inhibitor (NNRTI)-based ART; (e) PLHIV exposed to abacavir-based NRTI. CI, confidence interval.

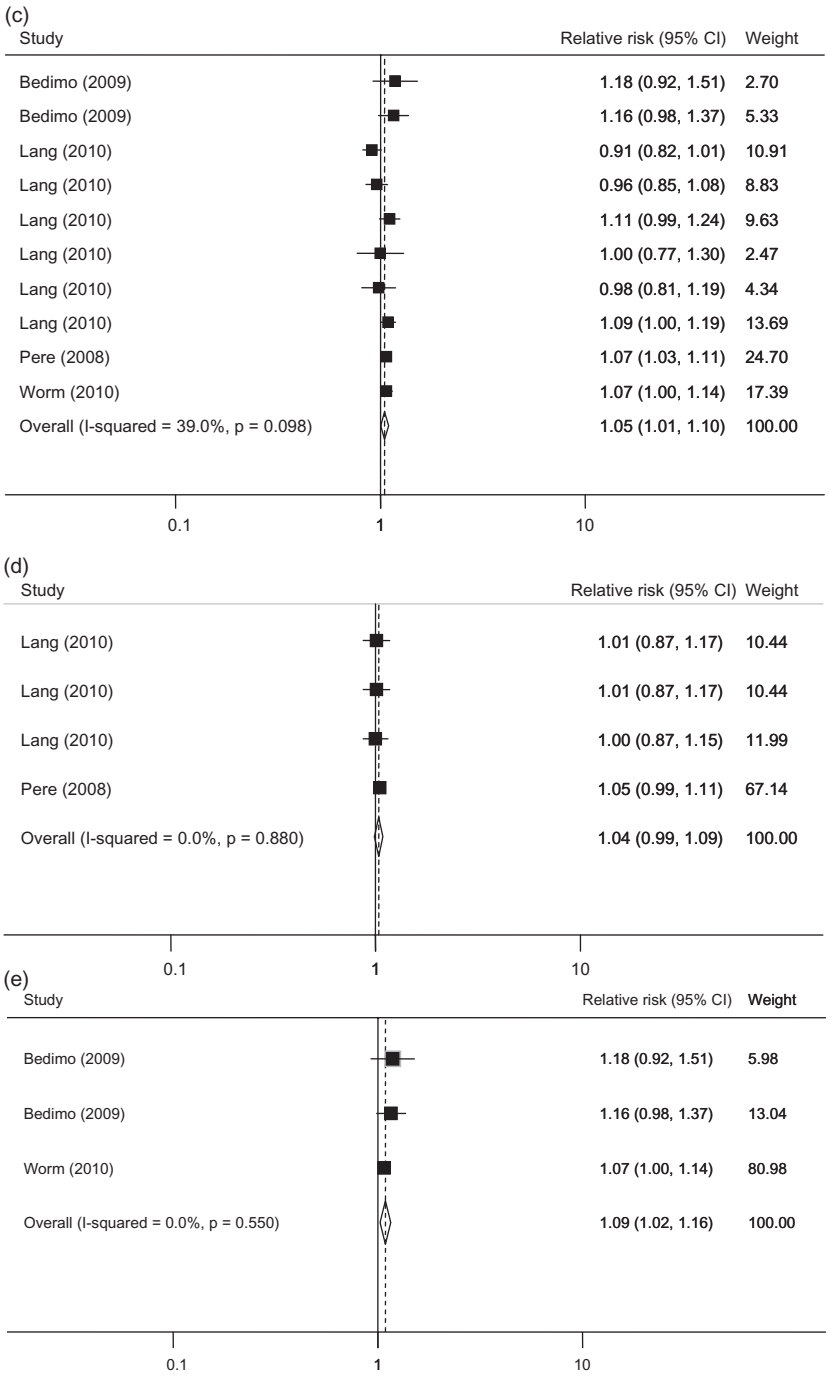

Fig. 5 (Contd.)

lower CD4 counts. Vaughn and Detels conducted a statistical analysis on clinic-based study populations and found that the use of PI- and non-PI-based ARTs was associated with CVD [6.22 (95% CI 3.13, 12.39) and 3.18 (95% CI 1.99, 5.09), respectively] [28]. We estimated the combined RR of MI for PI- *vs.* non-PI-based ART to be 1.79 (95% CI 1.05, 1.72).

Our study exclusion procedure resulted in a small number of studies for inclusion in subgroup analyses because of the limited number of studies that have measured CVD in relevant populations. However, we were able to combine estimates of all the major classes of drugs from the collated studies. Pooled estimates of RR were calculated

in subgroups in which there were at least two separate studies. In our analyses we attempted to eliminate bias and confounding wherever possible. Individual studies controlled for certain confounders between the treatment and control groups but not all studies controlled for the same variables. More specifically, age is one of the strong predictors of CVD risk in PLHIV that was well matched in each of the studies. However, some traditional risk factors, such as family history and lipoprotein levels, were missing in the majority of studies available. We were also unable to adjust for substance abuse and smoking levels, both of which may precipitate acute cardiovascular events and would probably be more common in HIV-infected people than in HIV-negative controls. As a result of differences between study categorizations, it is possible that our analysis may have some bias caused by misclassification error. This may be particularly relevant for the comparison between PLHIV receiving ART and treatment-naïve PLHIV because some of the people with unknown PI exposure could have been classified as treatment-naïve. Further, the result of greater risk of cardiovascular events seen in patients treated with PIs versus non-PIs may have been biased by the inclusion of experienced patients receiving older PIs. For individual studies in which there was some uncertainty in definitions of populations in any arm, we conducted the meta-analysis again without the questioned study, but we found our pooled estimates to be robust. Although our meta-analysis combined a relatively small number of studies, there was no strong evidence of heterogeneity among the studies; as a result, our effect measures were relatively consistent among the trials.

Our analysis shows that ART was found to be a greater risk factor among PLHIV compared with treatment-naïve patients and the increased risk was particularly found for abacavir in the NRTI group among the ART classes. In contrast, a recent meta-analysis of RCT studies (published after our literature search) found that abacavir was not associated with a greater risk of MI or major CVD events, despite the significant impact of abacavir on the risk of CVD in some cohort studies [41]. This meta-analysis included HIV clinical trial data from studies that had a follow-up period of at least 24 weeks, with the majority of included studies having approximately 1 year of average follow-up. In contrast, a 96-week RCT follow-up study found that abacavir, compared with tenofovir, was associated with a greater risk for CVD, as discussed above. Of note, it may be that short-term use of abacavir has a low risk for CVD events among PLHIV. More specifically, we found that the annual RR associated with abacavir use was very low (RR 1.09; 95% CI 1.02, 1.16), but that the risk increased with duration of ART. It is important to note that the majority of the cardiovascular events associated with the use of antiretroviral drugs were confined to patients who were already at increased absolute risk of CVD. Study type/design was not found to be a significant predictor of heterogeneity in our estimates. A longer follow-up RCT measuring the use of abacavir and other antiretrovirals associated with CVD events would assist in ascertaining the role of abacavir among all patients as they continue to use ART long-term.

We found that HIV, ART type and duration and CD4 cell count are associated with increased risk of CVD. The risk of CVD is greater in PLHIV than in people not living with HIV, and higher again for people exposed to ART, and particularly PI-based regimens, and increases with the duration of treatment. Despite being a risk factor for CVD, ART use has increased the quality and length of life of PLHIV by restoring immune function, reversing AIDS-defining events and reducing AIDS-related mortality rates. It is possible that the use of ART increases life expectancy and hence increases the average age of those taking ART in comparison to the reference group, which may lead to confounding of results.

Although the health and survival of PLHIV have improved with effective ARTs, PLHIV are at substantially greater risk of developing other comorbidities, such as CVD, compared with uninfected people. Given that CVD is responsible for a large number of deaths world-wide, this is a significant issue for the population of PLHIV, particularly as they get older and become more treatment-experienced with second-line, third-line or more complex antiretroviral regimens. Increasingly, HIV-positive populations will require long-term clinical management of numerous conditions along with their HIV infection. The reasons for the excess risk of CVD among HIV-infected people are not very well known and require considerable attention as CVD is likely to be one of the major conditions to be confronted in the future by populations of PLHIV.

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