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# The effect of HIV infection, antiretroviral therapy on carotid intima-media thickness: A systematic review and meta-analysis

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## Abstract

**Aims—**We performed a systematic review and meta-analysis on the effect of HIV infection and antiretroviral therapy (ART) on carotid intima-media thickness (cIMT) to elucidate the role of HIV infection and ART. Also, an analysis on the role of ethnicity and gender on cIMT in HIV-infected populations was performed.

**Main methods—**We searched the PubMed, Web of Science, the WHO websites and International AIDS Society for published observational studies were conducted by two independent reviewers for studies comparing HIV-infected antiretroviral-experienced patients and/or inexperienced with healthy controls on cIMT. The primary outcome was the standardized mean difference (SMD) of cIMT.

**Findings—**Twenty studies (five cohort, 15 cross-sectional, and two both cohort and cross-sectional studies) were identified comprising 7,948 subjects (4,656 HIV-infected; 3,292 controls). In cohort studies, the standardized mean 1-year change in cIMT between HIV-infected patients and uninfected controls was not significantly different (0.16 mm/yr; 95% CI, −0.16, 0.49; p=0.326). In 17 cross-sectional studies, the SMD in cIMT was significantly higher in HIV-infected than uninfected persons (0.27 mm; 95% CI, 0.04, 0.49; p=0.027). HIV-infected patients on ART exhibited significantly higher SMD in cIMT compared to those not on ART (0.75 mm; 95% CI, 0.30, 1.19; p=0.001). No confounding effect of gender and ethnicity could be established using meta-regression p> 0.05.

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**Significance—**HIV infection itself and ART appear to influence the progression of cIMT and hence may be risk factors for cardiovascular events. No firm conclusions could be drawn on the effect of ethnic/race and gender differences on cIMT in HIV-infected populations.

### Keywords

human-immunodeficiency virus (HIV); antiretroviral therapy (ART); carotid intima-media thickness (cIMT); ethnicity; gender

## Introduction

As the HIV-infected population continues to age, cardiovascular disease is becoming an increasingly important problem. This is particularly true as emerging data indicate that even after controlling for traditional cardiovascular risk factors, HIV-infected patients have increased rates of atherosclerosis-related disease [1–2]. There are concerns that the long-term use of antiretroviral drugs may promote atherogenesis, as these drugs can adversely affect cardiovascular risk factors [3–4]. Advances in antiretroviral therapy have greatly improved the survival of patients infected with the human immunodeficiency virus. However, in recent years, the incidence of premature myocardial infarction and cerebrovascular disease in HIV-infected patients receiving antiretroviral therapy has increased [5–7]. It is conceivable that this increase may be, at least in part, a consequence of the metabolic syndrome that clusters with antiretroviral therapy. On the other hand, HIV infection may set in motion atherogenic mechanisms, irrespective of antiretroviral therapy and the associated metabolic sequelae [8–10]. Other studies, however, have associated both HIV and antiretroviral therapy (ART) with the increased cardiovascular disease (CVD) risk [11].

Contradictory findings have been reported on the difference in carotid intima-media thickness (cIMT) between individuals of African ethnicity/race in contrast with non-African HIV-uninfected populations. For example, some studies have reported higher cIMT in individuals of African origin than in non-African counterparts [12–17] while one study did not find significant differences [18]. Also, studies have demonstrated that persons of male gender have higher cIMT than female in non-HIV-infected populations [16, 19–22]. It is unclear whether such ethnicity/race or gender differences on cIMT also exist in HIV-infected persons.

cIMT is a valid measure of subclinical atherosclerosis, which has consistently been related to future cardiovascular events in population studies [23–24], and also correlated with the extent of coronary atherosclerosis [23, 25–28]. The use of cIMT as a surrogate marker of CVD risk among HIV-infected patients has been widely investigated [1, 29, 30] and accepted for assessing large numbers of HIV-infected individual for CVD risk, especially young populations, due to its non-invasive nature [31]. It has been alluded that, because HIV and atherosclerosis are both inflammatory in nature, arterial wall markers of inflammation (cIMT) are increased in HIV-infected patients. Moreover, studies have shown that the magnitude of association between HIV infection with cIMT is similar to that of traditional risk factors (e.g. smoking and diabetes) [29] and larger observational studies have attested

that the association of increased cIMT to CVD risks are similar disregarding the site of measurement [31, 32] though at different rates [30]. In this review we have collected papers written in English language that have studied cIMT in HIV. We have attempted to interpret the different results in published studies to dissect out the precise role of this surrogate marker in different populations. Here, we systematically reviewed and carried out meta-analysis on the effects of HIV infection and ART on cIMT to provide additional information on the role of HIV infection *per se*, and the effect of antiretroviral therapy. We also analyzed the role of ethnicity/race and gender on cIMT in HIV-infected populations.

## Methods

### Publication Search

We searched PubMed, Web of Science and relevant websites such as those of the WHO and International AIDS Society during the year 2014. Additionally, we conducted a manual search by screening the references of pertinent articles and identifying any additional relevant publications that were not previously included.

We included observational studies; both prospective cohort and cross-sectional studies. Details of the search strategy are shown in Table 1.

### Inclusion criteria

The selected studies met the following criteria:

1. Observational study, that is, cross-sectional/case control or prospective cohort
2. Evaluation of effect of HIV and /or combination anti retroviral therapy (cART) on cIMT
3. Outcome variable is cIMT presented as mean ± standard deviation or median ± interquartile range
4. Article published in English
5. Publication quality score according to Newcastle-Ottawa scale of at least five stars [33]
6. Publications published between year 2000 and 2014
7. Follow-up period of at least one year for cohort studies

### Exclusion criteria

1. Duplicate publications or multiple articles reporting identical outcomes measured over the same time period on the same population.
2. Articles including patient age of under 17 or above 65 years because cIMT analyses have shown that cIMT is age-related and more so from age 65 and above in men and women [34]. Also, studies have alluded that carotid arterial wall is not affected by either age or gender up to the age of about 18 years [35–36].

## Data extraction

Two authors independently conducted the literature search and extraction of relevant articles. Articles were independently judged for quality by the two authors using the Newcastle-Ottawa scale. This instrument is recommended for use by the Cochrane Collaboration Review Group on HIV infection and AIDS [37]. Articles extracted had to meet the following criteria: 1. Description of patient selection (four criteria); 2. Study-control group comparability (one criterion); and 3. Outcome assessment (three criteria). Assigning a star for each qualifying item scored each item in the three groups of criteria. A Quality Assessment tool for Diagnostic Accuracy Studies 2 (QUADAS 2) was used to evaluate the risk of bias and applicability of primary diagnostic accuracy studies [33]. Any arising differences between the two independent authors on article selection were resolved by consensus.

From the articles identified, we registered study design, sample size, technique of measuring cIMT, use or non-use of cART, matched variables, mean age, site measured, and follow-up period for cohort studies.

Studies with no follow-up but that compared HIV-infected patients on cART or not with HIV-uninfected controls were classified as cross-sectional. Also, in this category were studies comparing HIV-infected patients on cART with HIV-infected cART-naïve patients. Studies with follow-up comparing HIV-infected patients and HIV-uninfected controls were categorized as cohort.

## Statistical analysis

After extracting the individual study results, pooling was performed by weighting/standardizing the mean of cIMT by the study size. The sum of the products of mean of cIMT and sample size for all studies was determined which was then divided by the sum of the sample sizes of all studies involved to obtain the weighted/standardized mean cIMT. Standardized mean differences (SMD) together with corresponding 95% confidence intervals (CI) comparing HIV-infected and uninfected patients, and cART use and non-use were computed and used to construct forest plots. The presence or absence of publication bias was determined using a funnel plot (graphical representation of a measure of study size as a function of effect size). To test the publication bias, the Egger's regression test was performed to determine I-square (index for heterogeneity). MedCalc Statistical Software version 16.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016) was used to complete the meta-analysis. Subgroup and meta-regression analysis was conducted on cross-sectional studies using R software version 3.3.3 to investigate the sources of heterogeneity. We conducted subgroup analyses for duration of cART use, age, duration of HIV, current CD4 count, nadir CD4 count, viral load, and smoking predominance as these have been identified as effect modifiers for cIMT [11, 19, 34]. Furthermore, subgroup analysis was conducted on gender and ethnicity/race predominance since these have been reported to have cIMT differences in healthy populations [12–21]. Sensitivity analysis by omitting one study at a time and meta-regression were also conducted on cross-sectional studies to determine sources of heterogeneity. All significance tests were done at 95% confidence interval and 5% level of significance.

# Results

## Study characteristics and quality

Table 2 shows the study characteristics. The systematic literature search identified 56 articles. At first selection 29 articles were excluded because they were duplicate publications reporting identical outcomes measured over the same time period on the same population, had no control group or study population involved elderly older than 65 years; thus, 27 articles remained. An additional 9 articles were identified through searches of references. Thirty-six articles met the general study criteria, but only 22 met the minimum of 5-star quality criteria. Two studies were excluded because they were systematic reviews, thus remaining with 20 studies in this review (Figure 1). Fifteen studies were cross-sectional and five cohort. Two studies were cross-sectional derived from cohort studies and therefore included in both cohort and cross-sectional studies. Studies used different anatomic sites to measure cIMT; seven studies measured cIMT at one site of the unilateral carotid artery, three studies at multiple sites of the bilateral common carotid artery, three studies used mean of 12 sites of the bilateral carotid artery, six studies measured cIMT at 2 sites of the bilateral carotid artery, and one study did not specify the site of measurement (Table 2). Most patients on cART used a combination of two nucleoside reverse transcriptase inhibitors (NRTI's) plus a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI).

## Cohort studies

Within the 5 cohort studies there were 862 patients (630 HIV-infected and 232 HIV-uninfected). Mean age was 42.5 and 40.7 years for HIV-infected and uninfected patients, respectively. All cohort studies except one [39] were matched by gender, age and body mass index (BMI). In two studies [39, 40], there were more African Americans in the HIV-infected group. In three studies the HIV-infected patients were on cART [1, 38–39] with mean duration of 3 years while the remaining two studies compared ART-naïve HIV-infected with HIV-uninfected control [40, 41]. The sites of measurement of carotid artery are indicated in Table 2. One study [1] used a mean of 12 measurements at the common carotid artery; another [38] measured only at the right common carotid artery while three studies [39, 40, 41] measured at the common carotid artery and the bulb and/or internal carotid artery. Mean duration of HIV infection was 7.2 years. Mean duration of follow-up was 44.5 months ranging from 12 to 144 months.

Assessment of publication bias was not performed in cohort studies as there was an inadequate number of studies (only 5) to properly assess a funnel plot or use more advanced regression-based methods.

## Cross-sectional studies

**HIV-infected vs. HIV-uninfected—**Within the 17 cross-sectional studies there were 7,086 patients (4,026 HIV-infected and 3,060 HIV-negative). The mean age was 41.6 and 41.4 years for HIV-infected and non-infected, respectively. The BMI was 24.7 $kg/m^2$ and 25.7 $kg/m^2$ for HIV-infected and non-infected, respectively. Eight studies indicated the mean duration of HIV since diagnosis was 7.5 (range, 1.5–13) years. Three studies [42–44] investigated only male groups while two [45–46] included only female. Thirteen studies

[1, 39, 42, 44, 46–54] reported smokers in both groups but with a significantly higher proportion of HIV-infected smokers in seven studies [1, 39, 42, 44, 47–49]. Nine studies indicated ethnicity/race [11, 39, 42–46, 48, 53].

Eleven studies [1, 3, 38, 40–41, 48–53] were matched for age and gender. Some studies were also matched for BMI [3, 11, 40–41, 52], race [38, 48, 52] and smoking habits [3, 38, 50, 52]. One study was matched for age, smoking habits and HIV infection risk factors [54]. One study investigated only HIV-infected ART-naïve vs. HIV-uninfected controls [48] while one study [11] included adolescents (17–23 years) only. Three studies [1, 38, 53] involved HIV-infected exclusively on cART vs. HIV-uninfected controls.

Review of the funnel plot demonstrated asymmetry with 9 studies to the right of the combined effect size and 8 studies to the left (Figure 2). Quantitatively, Egger's regression indicated the presence of publication bias (intercept=5.28467, 95% CI: 1.97 to 8.59, t=3.39, P=0.00198).

**HIV-infected on cART vs. HIV-infected cART-naïve—**Four studies compared cART-experienced and naïve HIV-infected patients [42–43, 48, 54]. In two studies [42, 43], three cART regimens - namely, NNRTI, NRTI and PI were used while in one study [54] only PI was used and the other study [47] did not specify the type of regimen used. For all studies, patients had used cART for at least one year, and the mean duration of cART was 3.7 years. One study [43] involved only men. Two studies [42, 47] were not matched while one study [54] was matched for age, risk factors for HIV infection, cigarette use and $CD4^+$ cell count and another [43] matched for age and non-smoking groups.

## Data synthesis

**Cohort studies—**All five studies compared HIV-infected and uninfected groups on the 1-year progression of cIMT. Three studies compared HIV-infected on cART [1, 38, 39] while two studies compared HIV-infected cART-naïve [40, 41] with healthy controls. Overall, SMD of 1-year cIMT progression between HIV-infected patients and uninfected controls was not significant (SMD, 0.16mm; 95% CI, −0.16, 0.49; p=0.326). Heterogeneity between the studies was moderate ($I^2$, 72.3%; p=0.006). Of the three studies, which compared HIV-infected on cART with healthy controls, two studies [1, 39] had higher 1-year cIMT progression than controls. On the contrary, the two studies [40, 41], which compared HIV-infected ART-naïve with HIV-uninfected controls, exhibited higher 1-year cIMT progression for controls than HIV-infected ART-naïve patients (Figure 3).

**Cross-sectional studies—**Using the 17 cross-sectional studies comparing SMD in cIMT for HIV-infected and uninfected, the pooled SMD of cIMT is shown in Figure 4. Significant increase in standardized mean of cIMT was observed in HIV-infected compared to HIV-uninfected patients (0.27 mm; 95% CI, 0.04, 0.49; p=0.027). Of 17 studies, eight [1, 11, 39, 42, 47, 51, 52, 54] demonstrated greater elevation in cIMT in HIV-infected than uninfected. Five of these studies [11, 42, 47, 52, 54] had small numbers of HIV-infected cases (<80 patients), which were characterized by wide 95% CI (standard error (SE) ranging from ±0.72 to ±1.30 mm). Of the remaining nine studies, seven studies [24, 43, 45, 46, 48, 50, 53] were close to or at the line of no difference (SMD ≈ 0.0); most of which were relatively

large (>200 study cases). Of these, two studies [43, 53] had relatively small sample sizes (≤150 cases) with wide CI. (SE ±0.39mm each). Two studies [44, 49] depicted greater cIMT in HIV-uninfected than infected patients.

Heterogeneity among studies was significant ($I^2$, 94%; p<0.01) (Figure 4). Subgroup analysis for age, duration of HIV, duration of cART use, nadir CD4, current CD4 count, viral load, and smoking predominance revealed that heterogeneity for all subgroup analyses was high (Shown in supplementary figures 1–7). This implies that there are studies with variable observed effects than would be expected by chance alone. Sensitivity by omission of one study at a time and meta-regression showed that only nadir CD4 and smoking were important confounders (Shown in supplementary tables S1-S2 and figures S4 and S7). Studies reporting relatively higher SMD were likely to include cases in the smokers predominant group [1, 39, 42, 47, 51, 52] and with nadir CD4 count of 200 cells/mL or lower [1, 39, 42] (Figure 4, Figure S7, Figure S4).

Subgroup analysis by ethnicity/race showed significant difference in SMD of cIMT between subgroups (SMD=0.20mm, CI=0.01, 0.39; p<0.01). The subgroup dominated by individuals of African origin exhibited no significant difference (SMD=0.0mm; p=1.0), the subgroup dominated by Caucasians/others had significantly higher SMD of cIMT (0.27 mm; p<0.01) and the subgroup matched for race (equal proportion) also showed significantly higher SMD of cIMT (0.46mm; p<0.01) (Figure 5). Overall, heterogeneity in this subgroup analysis was high ($I^2$, 84%; p<0.01). Meta-regression analysis could not establish the confounding effect of race (Table S2). However, a smaller number of studies and cases contributed data to the African origin predominant subgroup (680 cases, 2 studies) and equal proportion subgroup (142 cases, 2 studies) compared to the Caucasian/other race predominant subgroup (1800 cases, 5 studies), implying that the analysis is unlikely to produce conclusive results on the effect of ethnicity/race on cIMT.

Subgroup analysis by gender (Figure 6) demonstrated statistically significantly subgroup effect (p<0.01) entailing that gender influences cIMT. A sufficient number of studies (4–7) and cases (>1800) in each subgroup, hence covariate distribution is of little concern. However, there was moderate to substantial unexplained heterogeneity between studies in each subgroup (equal gender proportion group: $I^2$ = 58%; male dominated subgroup: $I^2$ = 92% and female dominated subgroup: $I^2$ = 97%), meaning that validity of the effect estimate in each subgroup is uncertain. The subgroup “Equal proportion” had moderate heterogeneity, but by omitting Vigano et al. [11] the heterogeneity would drop to 0%. The estimate would also change from 0.18 to 0.11 and would be more consistent (lower p-value). This study included only adolescents (age 17–23 years) and had few study cases (42 cases).

Figure 7 shows four studies comparing HIV-infected on cART and cART-naïve patients. The results show significantly increased standardized mean difference of cIMT in the group of HIV-infected on cART compared to the cART-naïve group (SMD, 0.75mm; 95% CI, 0.30, 1.19; p=0.001). Heterogeneity for these studies was substantial with $I^2$ of 75.2% (p=0.007). However, most of these studies (three out of four) were mostly small; with HIV-infected cases less or equal to 150.

## Discussion

This review summarizes 20 studies examining cIMT, an early marker for atherosclerosis in HIV-infected patients. We tried to find evidence for the influence of HIV infection (causing a chronic inflammatory state) and cART on this marker. Furthermore, subgroup analyses were conducted to find out existence of cIMT differences according to ethnicity/race and gender in HIV-infected populations.

The findings in this review show that HIV-infected patients have significantly higher values of SMD of cIMT than HIV-uninfected for cross-sectional studies but not significant in cohort studies. Also, HIV-infected patients on cART exhibited markedly higher values than cART-naïve. Furthermore, ethnicity/race subgroup analysis had few studies in the African origin dominated and equal proportion subgroups leading to inconclusive findings on the effect of ethnicity/race on cIMT. Likewise, though the difference was significant between gender subgroups, due to considerable unexplained heterogeneity within subgroups, the effect of gender on cIMT is uncertain.

Controversial results on effect of HIV *per se* and HIV-associated factors such as cART on cIMT have been reported. Several studies have shown association between HIV-infection and modest increase in cIMT in both observational [55–57] and longitudinal studies [1]. Most meta-analysis studies also have reported increased cIMT in HIV-infected individuals compared to healthy controls [58, 59]. However, some studies have reported no association of HIV infection with cIMT in both observational [60, 61] and prospective studies [62].

The explanation given for higher cIMT in the HIV-infected group compared to uninfected is that any immunosuppressive condition, including HIV infection, may have an impact on both systemic inflammation and other human environmental factors, such as co-infections that may influence atherogenesis [63]. Arterial stiffness is increased in chronic inflammatory disorders and is related to disease duration, cholesterol, and the inflammatory mediator C-reactive protein (CRP) and the cytokine that stimulates production of IL-6 [64]. These findings suggest that HIV infection itself may increase the risk for cardiovascular disease [59] although mechanisms have not been fully explained by differences in cIMT.

The results show increased cIMT in HIV-infected on cART than in cART-naïve patients. It is argued that thicker cIMT could be associated with HIV-related risk factors, such as HIV viremia, immune activation and cART, and classical cardiovascular risk factors such as smoking, hypertension and dyslipidemia [65–67]. Some cART regimens have been reported to be independently associated with CVD [68]. HIV infection *per se* may change the lipid metabolism by decreasing high-density lipoprotein (HDL) cholesterol, and at the same time, by increasing low density lipoprotein (LDL) cholesterol and total cholesterol which are known to be CVD risk factors [63]. It remains to be determined whether these modifications are due to direct effect of cART or caused indirectly, by their metabolic side-effects [69]. It is also controversial whether specific cART regimens have greater influence on cIMT than others. Thus, while two studies Seminari et al. [54] and Sun et al. [58] demonstrated association with PI use, other studies have found no association between PI-regimen use and cIMT [1,64].

On the contrary, various studies have demonstrated that traditional cardiovascular risk factors, rather than HIV *per se* and HIV-related factors, independently predict increase in cIMT among HIV-infected individuals [60–62, 70–71]. One recent study in Uganda reported no association between high sensitivity C-reactive protein (hsCRP) and cIMT at common carotid artery (CCA) segment but cIMT was correlated with traditional CVD risk factors such as waist circumference, triglycerides and total cholesterol [68]. If this is true, then the inflammatory effect of HIV on cIMT could be obscured by effect of traditional risk factors such as age for predicting cIMT. On the other hand, Grunfeld et al. [30], Pacheco et al. [60] and Hanna et al. [62] argue that carotid artery segment measurements can be affected differently in HIV-infected patients and since cIMT is not uniformly measured as per consensus in cIMT measurements in the studies [72], conflicting results are imminent. Moreover, cIMT measured at common carotid artery is regarded a weak predictor of atherosclerosis when plaque measurement is missing [73]. Furthermore, though most meta-analyses based on observational studies report an association between HIV and HIV-related factors and cIMT [58, 59], it is argued that small studies tend to report positive results while larger studies cluster around the line of no difference [60].

It is worthy to note that; while cross-sectional studies showed significantly elevated cIMT in HIV-infected than uninfected individuals, such significance was non-existent in cohort studies. Several possible explanations for this discrepancy are possible. One possible explanation could be that cross-sectional studies are characterized by confounding effects compared to cohort studies, which could lead to the divergence in the results [74]. Also, due to the fact that the effects of HIV and cART on cIMT [68, 73] are dynamic and cumulative, such discrepancies in results may be expected [30]. Moreover, since three out of the five cohort studies [38, 40–41] were small while the other two studies [1, 39] had a small number of controls (HIV-uninfected individuals), the divergence in results between cross-sectional and cohort studies may arise.

In our study, subgroup analysis was inconclusive on the effect of gender on cIMT, and this is inconsistent with findings in other studies [29, 72–73], which demonstrated significantly higher cIMT in HIV-infected male compared to their female counterparts. However, upon multivariate analysis in the Albuquerque study [72], after accounting for traditional cardiovascular risk factors, male gender was an independent predictor of elevated cIMT only in the age below 40 years. Jarauta et al. [19] and Sinning et al. [75], studying atherosclerosis in healthy HIV-uninfected persons with no cardiovascular risk factors, found that cIMT in males was higher than in females up to the age less than 55 years. A recent study comparing cIMT between predominantly male HIV-infected patients with mean age of 49.4±10.5 years and reference values of age- and gender-matched uninfected persons reported greater cIMT compared to controls [76]. Another more recent study conducted in Thailand comparing cIMT between virologically suppressed HIV-infected patients and uninfected individuals, upon multivariate analysis in the HIV-infected group, found that cIMT greater than or equal to 0.9mm was predicted by male gender [77]. Several studies have attributed this gender difference in cIMT to gender hormones, specifically the protective effect of estrogen on coronary atherosclerosis [78–80].

Furthermore, the subgroup analysis by ethnicity/race could not substantiate drawing conclusions on the effect of ethnicity/race on cIMT because of fewer studies in two out of three subgroups. On the contrary, the study by Albuquerque [73] reported increased cIMT among nonwhite HIV-infected adults but significantly higher in the age group under 40 years. Other studies have also demonstrated higher cIMT in non-HIV-infected blacks compared to whites in young adulthood [14]. The study by Rosero et al. [18] found significantly higher mean arterial wall thickness in black women compared to Hispanic and white women, though an insignificant difference was observed in men. The reasons for the race/ethnicity differences in cIMT are not clear. Hao et al. [14] and Bennet et al. [13] failed to explain the race/ethnicity difference in cIMT by differences in cardiovascular risk factors.

It is important to note that the results of this review should be interpreted with caution. Firstly, biases inherent to the study design of the original cross-sectional and cohort studies must still be regarded as significant in the final analysis. Secondly, the meta-analysis was characterized by high heterogeneity between studies, sources of which could not be identified even after subgroup and sensitivity analyses. The high between-study heterogeneity was also reported in the study by Sun et al. [57]. However, Alba et al. [81] attest that meta-analyses evaluating continuous outcomes are inherent of substantially higher heterogeneity than those of binary outcomes. Thirdly, only articles written in English were included in the meta-analysis, which could lead to language bias (location bias) and also non-inclusion of grey literature. Fourthly, the meta-analysis included a small number of studies with high variability of sample sizes among studies. Fifthly, the gender and ethnicity/race differences on cIMT was based on subgroup analyses using predominance of these factors between HIV-infected and HIV-uninfected groups in varying proportions rather than on studies among these specific groups (that is, exclusively male vs. exclusively female and exclusively Caucasian vs. exclusively African) and hence the results from the subgroup analyses may not reflect the true differences between these groups. Lastly, most subgroup analyses that were conducted had uneven distribution/inadequate number of studies between subgroups (ethnicity/race, smoking, viral load, ART duration, current CD4 count) jeopardizing drawing valid conclusions on their confounding effect on cIMT.

In a global perspective, the small negative impact of cART on premature atherosclerosis and increased cardiovascular risk is of a different scale compared to the improved outcomes with the effective treatment of HIV and many patients are living healthy lives for decades after diagnosis. Data from randomized controlled trials of cART drugs may further clarify cardiovascular adverse effects but are difficult to assess because the HIV trials may not be powered to assess cardiovascular outcomes.

## Conclusion

This review shows evidence for enhanced premature atherosclerosis caused by chronic HIV infection and cART use, measured by cIMT. Whether the negative effect of chronic HIV infection on cIMT is reversed with longstanding effective treatment is likely, further studies in chronically suppressed patients are needed. Ethnic/race and gender differences could not be established in this meta-analysis, probably due to limitations mentioned above.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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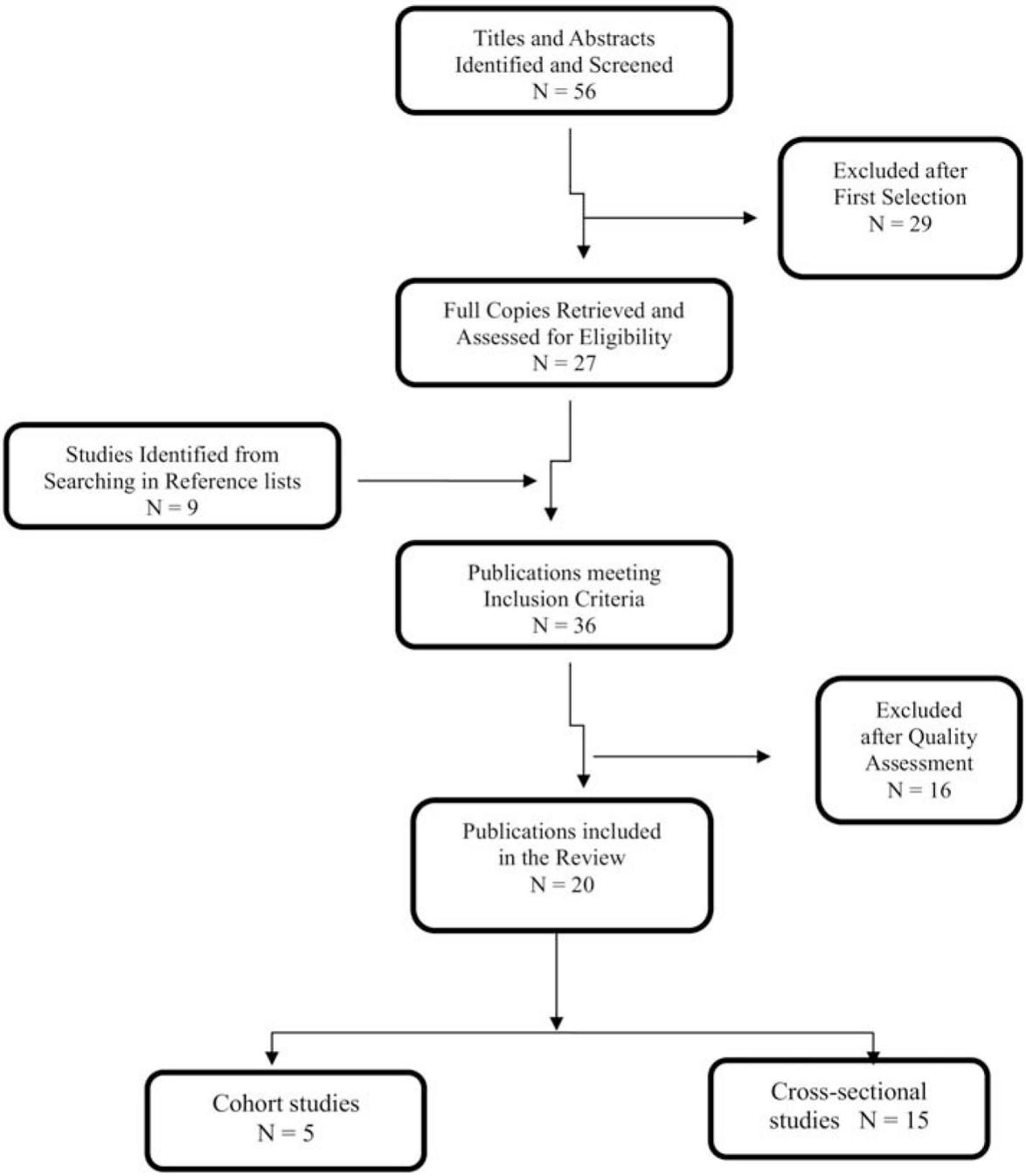


**Figure 1.**

Search strategy chart. The systematic literature search identified 56 articles. After exclusion 22 studies met the minimum of 5-star quality criteria. 2 studies were cross-sectional derived from cohort studies and therefore included in both cohort and cross-sectional studies. 15 studies were cross-sectional and 5 cohort. In the final, 20 studies were included in this review

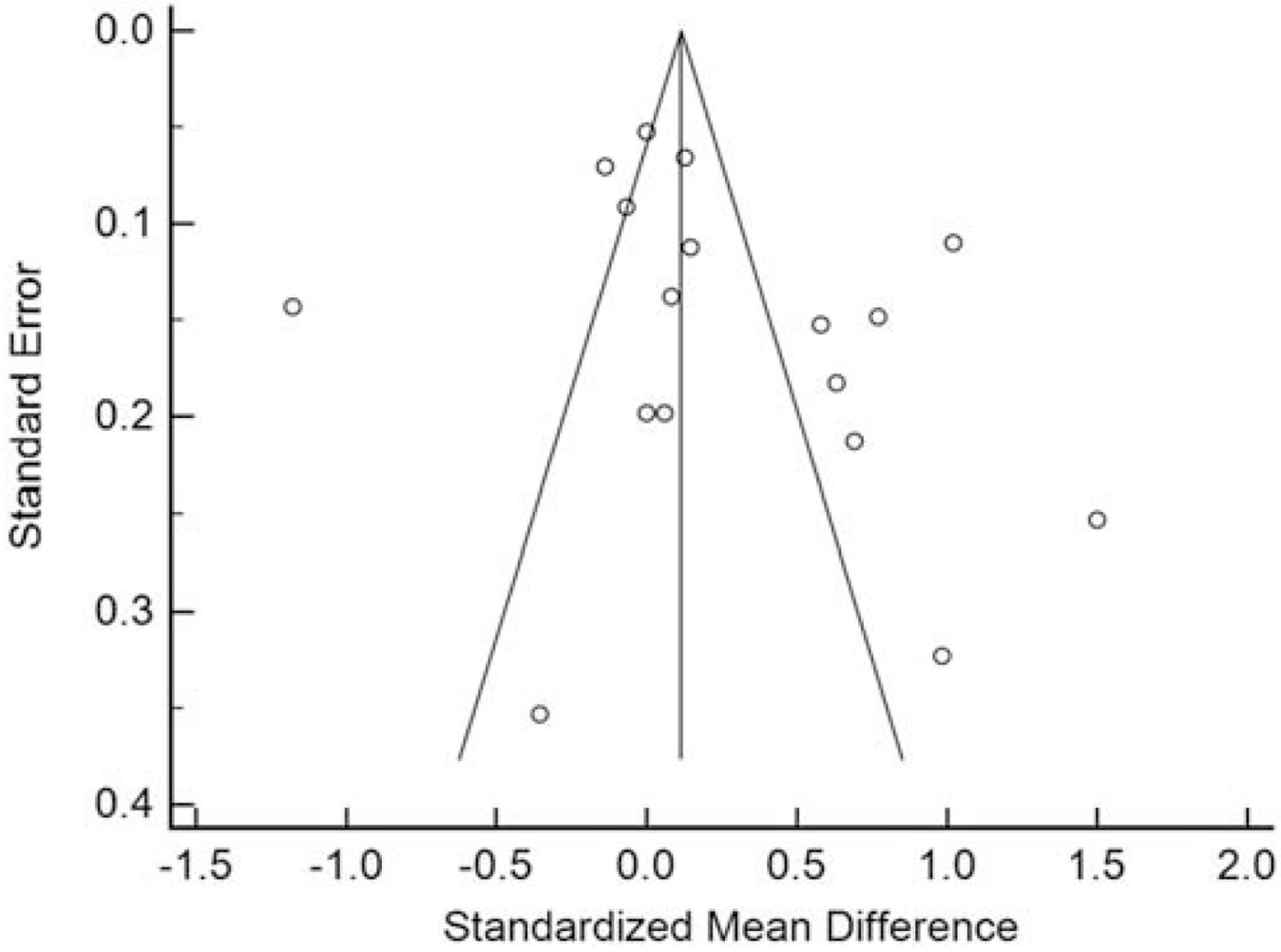


**Figure 2.**

Funnel plot for the mean differences vs. standard errors in carotid intima-media thickness (mm) in HIV-infected and uninfected groups among cross-sectional studies. Funnel plot demonstrated asymmetry with 9 studies to the right of the combined effect size and 8 studies to the left. Egger's regression indicated the presence of publication bias (intercept=5.28467, 95% CI: 1.97 to 8.59, t=3.39, P=0.00198).

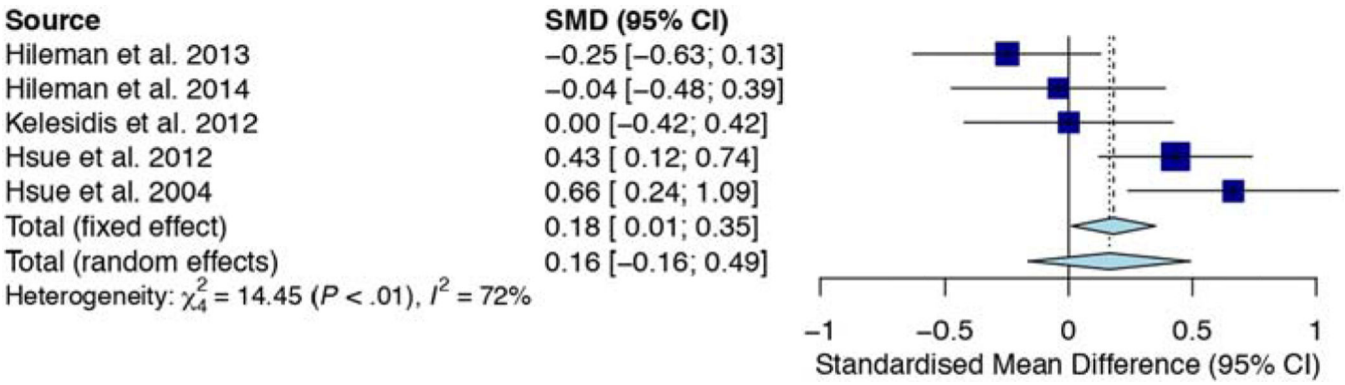


**Figure 3.**

Forest plot showing the 1-year change in carotid intima-media thickness (mm/yr.) in HIV-infected and uninfected groups among the prospective cohort studies. SMD of 1-year cIMT progression between HIV-infected patients and uninfected controls was not significant (SMD, 0.16mm; 95% CI, −0.16, 0.49; p=0.326). Heterogeneity between the studies was moderate ($I^2$, 72.3%; p=0.006).

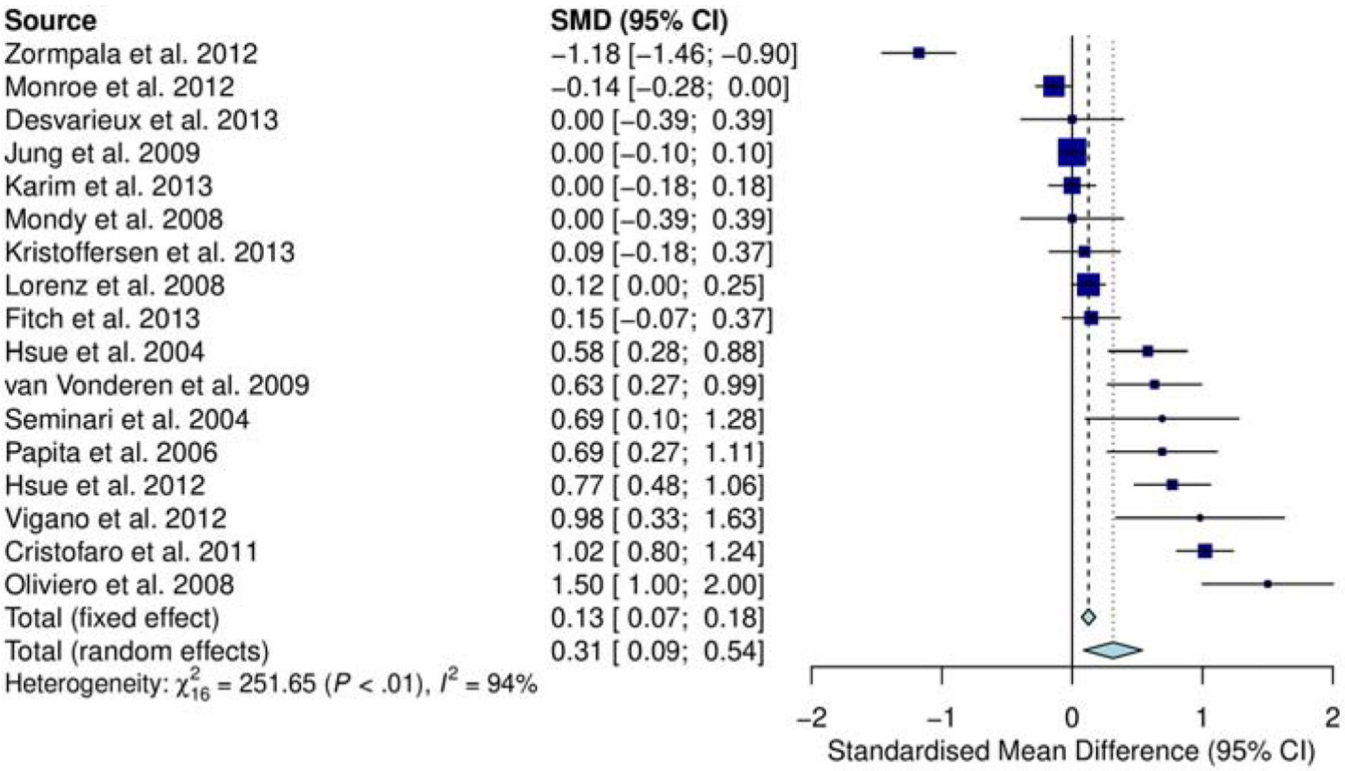


**Figure 4.**

Forest plot showing 17 cross-sectional studies comparing SMD in cIMT for HIV-infected and uninfected. Significant increase in SMD of cIMT was observed in HIV-infected compared to HIV-uninfected patients (0.27 mm; 95% CI, 0.04, 0.49; p=0.027)

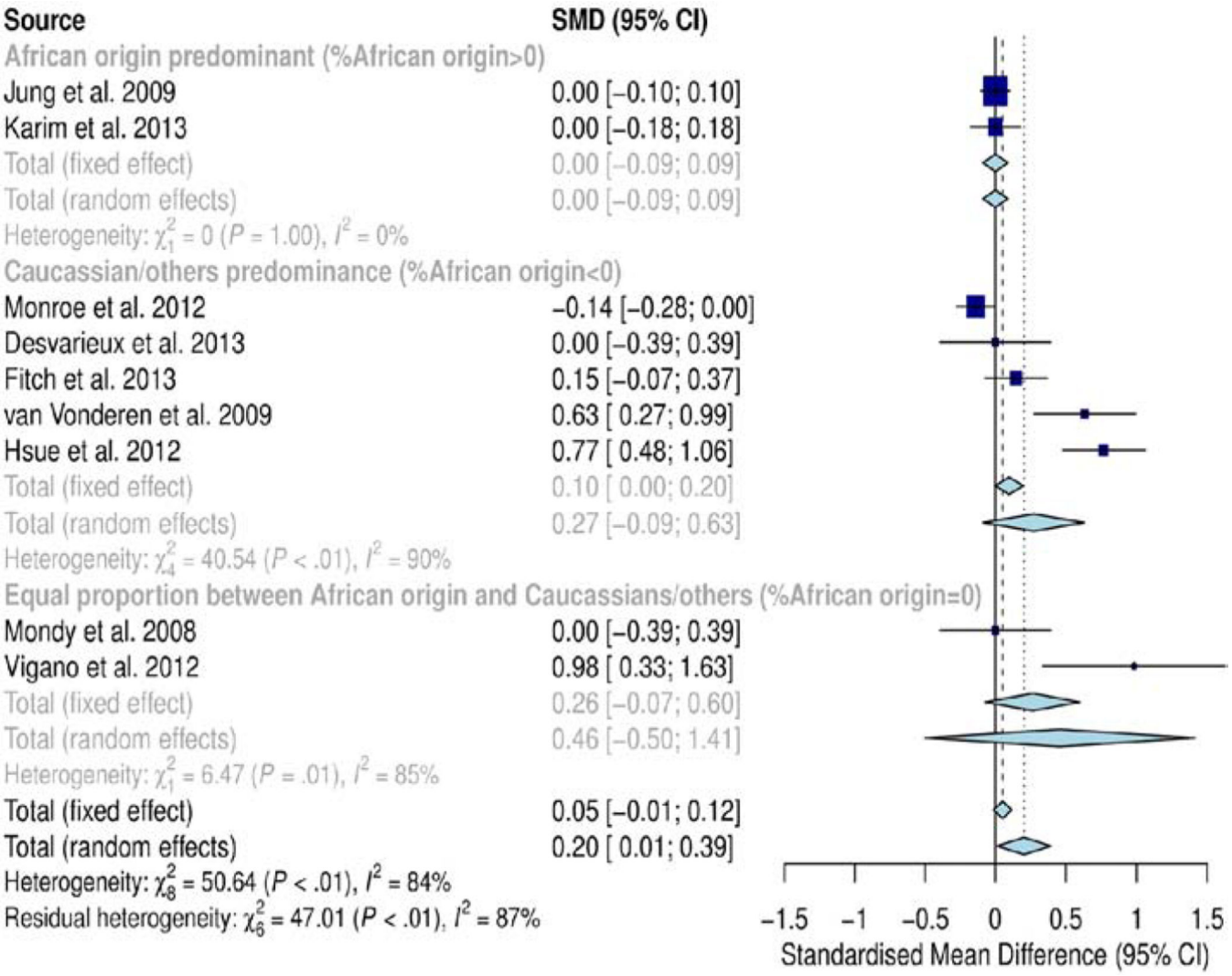


**Figure 5.**

Forest plot for race/ethnicity. Subgroup analysis by ethnicity/race showed significant difference in SMD of cIMT between subgroups (SMD=0.20mm, CI=0.01, 0.39; p<0.01). The subgroup dominated by individuals of African origin exhibited no significant difference (SMD=0.0mm; p=1.0), the subgroup dominated by Caucasians/others had significantly higher SMD of cIMT (0.27 mm; p<0.01) and the subgroup matched for race (equal proportion) also showed significantly higher SMD of cIMT (0.46mm; p<0.01). Overall, heterogeneity in this subgroup analysis was high ($I_2$, 84%; p<0.01).

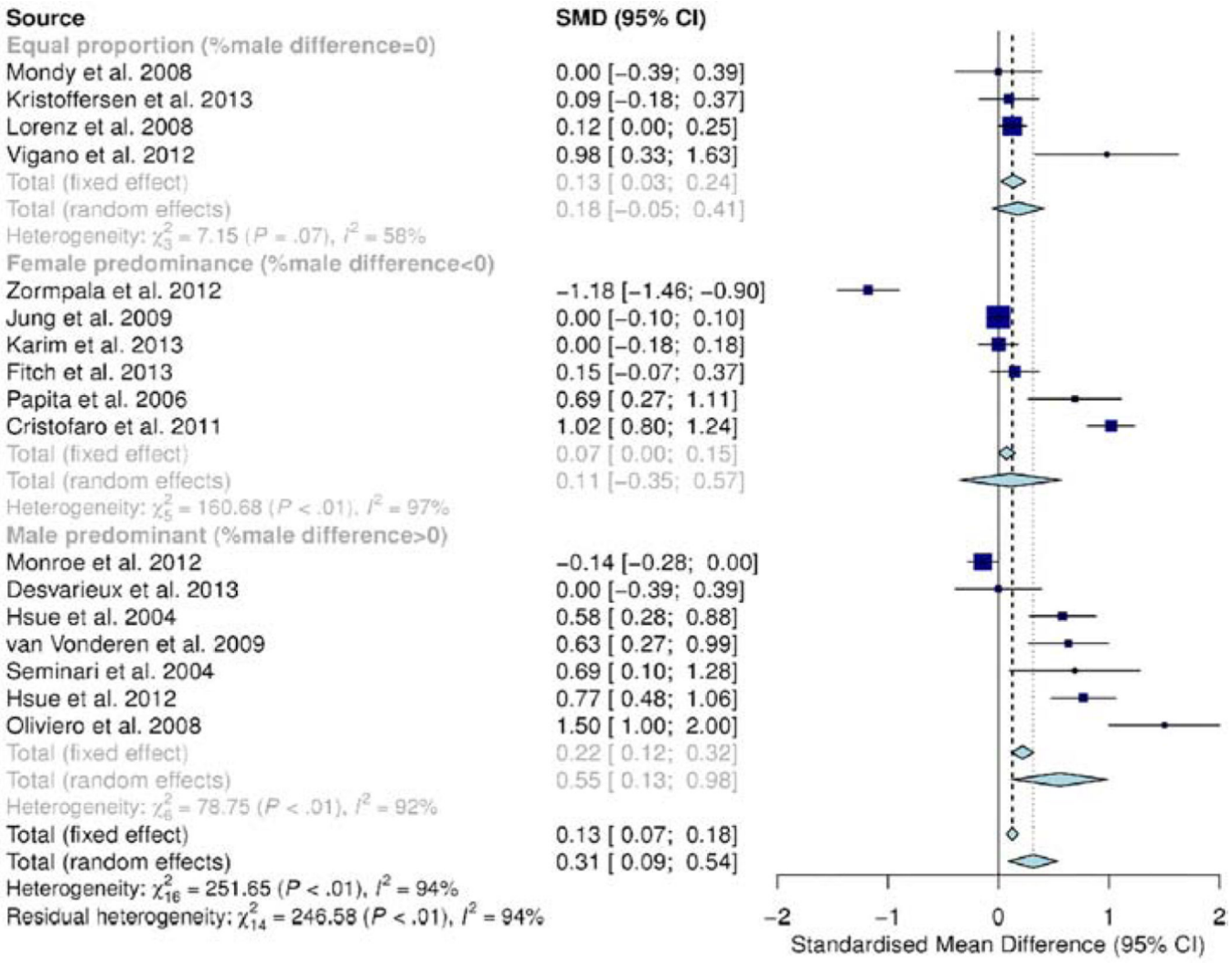


**Figure 6.**

Subgroup analysis for gender demonstrated statistically significantly subgroup effect ($p<0.01$) entailing that gender influences cIMT. There was moderate to substantial unexplained heterogeneity between studies in each subgroup (equal gender proportion group: $I^2 = 58\%$; male dominated group: $I^2 = 92\%$ and female dominated group: $I_2 = 97\%$), meaning that validity of the effect estimate in each subgroup is uncertain.

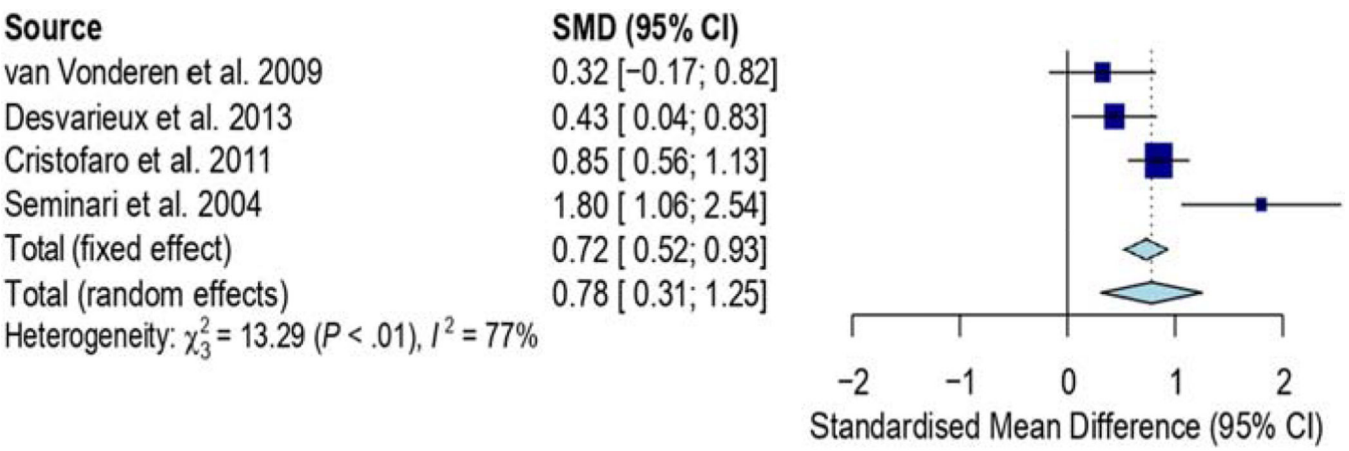


**Figure 7.**

shows four studies comparing HIV-infected on cART and cART-naïve patients. The results show significantly increased SMD of cIMT in the group of HIV-infected on cART compared to the cART-naïve group (SMD, 0.75mm; 95% CI, 0.30, 1.19; p=0.001). Heterogeneity for these studies was significant with $I^2$ of 75.2% (p=0.007).

## Table 1

Search strategy used in PubMed

| Search # | PubMed search terms |
|---|---|
| #5 | Search #3 AND #4 |
| #4 | Search #1 OR #2 |
| #3 | carotid artery stiffness [title/abstract] OR carotid stiffness [title/abstract] OR carotid intima media thickness [title/abstract] OR cIMT [title/abstract] |
| #2 | antiretroviral therapy, highly active [MesH] OR combination antiretroviral therapy [title/abstract] OR antiretroviral drug [title/abstract] |
| #1 | HIV [MesH] OR human immunodeficiency virus [title/abstract] OR HIV-infected [title/abstract] OR HIV infection title/abstract] |

Limits: Humans, English, German, Dutch, Young adults, Adults, Middle aged and Middle aged + aged.

**Table 2.**

Study characteristics

| Author | Study Design | No. | HIV+ | HIV+/ ART− | HIV+/ ART+ | HIV− | Follow-up period (months) | Site measured | Variables Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Hsue et al.2004[1] | PCO | 211 | 148 | 0 | 148 | 63 | 12 | Mean of 12 sites | Age and Sex |
| Hsue et al.2012 [39] | PCO | 347 | 300 | 300 | 0 | 47 | 28 | CCA,ICA,BCC | Demographics, Traditional risk factors, hsCRP, IMT progression |
| Kelesidis et al.2012 [38] | PCO | 91 | 55 | 26 | 29 | 36 | 144 | RCC | Age, sex, race/ethnicity, smoking, BP and menopause |
| Hileman et al.2013 [40] | PCO | 130 | 85 | 85 | 0 | 45 | 48 | CCA,BCC | CVD risk factors, Age, sex and BMI |
| Hileman et al.2014 [41] | PCO | 83 | 42 | 42 | | 41 | 96 | CCA, BCC | CVD risk factors, Age, sex and BMI |
| | | | | | | | | | |
| Papita et al.2011 [51] | CS | 99 | 63 | 7 | 56 | 36 | | RCC,CBA | Age and Sex |
| Lorenz et al.2008[3] | CS | 1460 | 292 | 0 | 292 | 1168 | | CCA/BIF | Age, sex, BMI, DM, BP, Cholesterol, use of statins and smoking |
| Seminari et al.2002 [54] | CS | 59 | 43 | 15 | 28 | 16 | | MCCA/CCCA | Age, Weight, Height, BP and HIV risk factors |
| van Vonderen et al.2006[42] | CS | 129 | 77 | 22 | 55 | 52 | | RCC/CFA/CBA | Age, BMI, Mean arterial BP, Smoking and Createnine clearance |
| Oliviero et al.2009 [52] | CS | 79 | 38 | 38 | 0 | 41 | | Mean of 12 sites | Age, sex, BMI and smoking |
| Mondy et al.2008 [53] | CS | 100 | 50 | 0 | 50 | 50 | | BCC | Age, Sex, race and BMI |
| Jung et al.2015 [45] | CS | 1792 | 1282 | 0 | 0 | 510 | | BCC | Age, race/ethnicity, Serum lipids, BP and Smoking |
| Cristofaro et al.2011 [47] | CS | 421 | 286 | 64 | 222 | 135 | | CCA | Unadjusted |
| Desvarieux et al.2013 [43] | CS | 150 | 100 | 50 | 50 | 50 | | Mean of 12 sites | Age,smoking,DM,HT |
| Fitch at el.2013 [48] | CS | 318 | 166 | 0 | 0 | 152 | | RCC& ICC | Age, race, gender, traditional CVD risks, use of statins, Ant-HT, ART use CD4 and VL |
| Karim et al.2013 [46] | CS | 584 | 170 | 0 | 0 | 414 | | RCC | Age, race, BMI, DM, Smoking, alcohol intake, IDU, non-IDU, ART, HIV and VL |
| Monroe et al.2012 [44] | CS | 856 | 534 | 0 | 0 | 322 | | RCC/ICA/CBA | Unadjusted |
| Vigano et al.2010[11] | CS | 42 | 23 | 0 | 0 | 19 | | CCA | Age, gender and BMI |
| Zormpala et al.2012 [49] | CS | 229 | 105 | 0 | 0 | 124 | | R&L CCA | Age, sex and Conversional CVD frisk factors |
| Kristoffersen et al.2013 [50] | CS | 210 | 105 | 0 | 105 | 105 | | Did not specify | Age, gender and Smoking |

*PCO – Prospective cohort study; CS- Cross-sectional; BCC – Bifurcation common carotid; CFA – Common femoral artery; CBA – Common brachial artery; LCC – Left common carotid; ICA – Internal carotid artery; RCC – Right common carotid; hsCRP-high sensitive C-reactive protein; IMT-Intima Media Thickness; BP-Blood Pressure; CVD- Cardiovascular Disease; BMI-Body Mass Index; DM-Diabetes Mellitus; HT-Hypertension; ART-Antiretroviral Therapy; IDU- Intravenous Drug Users; VL- Viral Load