Is There Sufficient Evidence for a Causal Association between Antiretroviral Therapy and Diabetes in HIV-infected Patients? A Meta-analysis

Running title: ART, diabetes and metabolic syndrome

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ABSTRACT

Background: The associations of antiretroviral therapy (ART) with diabetes and metabolic syndrome are inconsistent and vary widely across primary epidemiological studies. A comprehensive and more precise estimate of these associations is fundamental to establishing plausible causal links between ART and these cardio-metabolic disorders.

Methods: We identified epidemiological studies that compared mean fasting plasma glucose (FPG) concentrations and proportions of diabetes and metabolic syndrome between HIV-infected patients naïve and exposed to ART. Mean difference (MD) in FPG concentrations and odds ratios (OR) of diabetes and metabolic syndrome were pooled using random-effects meta-analyses.

Results: Data on 20,178 participants from 41 observational (30 cross-sectional, 1 case control and 10 cohort) studies were included in the meta-analyses. Mean FPG concentrations (Pooled MD: 4.66 mg/dl, 95% confidence interval [CI] 2.52 to 6.80, 24 studies) and the odds of diabetes (Pooled OR: 3.85, 95% CI 2.93 to 5.07, 10 studies) and metabolic syndrome (Pooled OR: 1.45, 95% CI 1.03 to 2.03, 18 studies) were significantly higher among ART-exposed patients, compared to their naïve counterparts. ART was also associated with significant increases in FPG levels in studies with mean ART duration ≥ 18 months (Pooled MD: 4.97 mg/dl, 95% CI 3.10 to 6.84, 14 studies), but not in studies with mean ART duration < 18 months (Pooled MD: 4.40 mg/dl, 95% CI –0.59 to 9.38, 7 studies).

Conclusion: ART may potentially be the single most consistent determinant of diabetes in people living with HIV worldwide. However, given the dominance of cross-sectional studies in the meta-analysis, the association between ART and diabetes may not be interpreted as cause and effect.

INTRODUCTION

In contrast to the declining trends in AIDS-specific deaths, the era of highly active antiretroviral therapy has been marked by an increase in non-AIDS-defining illnesses, notably cardio-metabolic events, among people living with HIV [1]. Antiretroviral therapy (ART) potentially underlies the pathogeneses of cardio-metabolic disorders, such as diabetes mellitus and metabolic syndrome, in most people living with HIV [2,3]. While blood glucose levels tend to be slightly elevated in antiretroviral-naïve HIV-infected persons through mechanisms that remain unclear, evidence suggests that ART may exacerbate this effect by increasing insulin resistance and altering lipid metabolism [2,4]. Expectedly, these mechanisms may potentially explain a link between ART and the metabolic syndrome, given that the latter is a constellation of cardio-metabolic abnormalities that may involve elevated fasting plasma glucose concentrations [3]. In addition, metabolic syndrome — widely acknowledged as a risk factor for type II diabetes in the general population — has also been compared to the pre-diabetic state, the only distinction being the differences in diagnostic markers [5,6]. Diabetes and metabolic syndrome are among the chief drivers of the global epidemic of cardiovascular disease [7–10]. With approximately 36 million people currently living with HIV worldwide [11], and a projected 18 million incident cases by 2030 [12], ART-associated diabetes and metabolic syndrome may portend substantial public health burden, potentially worsening the already-existing global burden of cardiovascular disease. However, the associations of ART exposure with diabetes mellitus and metabolic syndrome have not been consistent and vary widely in magnitude across primary epidemiological studies, with certain studies reporting significant direct associations [13–16], and other studies reporting no significant effects [17–20]. Therefore, we aimed to obtain comprehensive and more precise estimates of the magnitudes of these associations. We also

sought to investigate study-level factors that may influence the associations of ART with diabetes and metabolic syndrome in people living with HIV worldwide. Assessing these associations may provide a comprehensive evidence-base for investigation plausible causal links between ART and these cardio-metabolic disorders.

MATERIALS AND METHODS

The study background, rationale and methods were specified in advance and documented in a study protocol registered in the PROSPERO database (CRD42014008855).

Study selection

CUN, AMS and OAU independently screened potentially eligible studies by their titles, abstracts and full texts, and any disparities were resolved following discussions with the other investigators. We selected studies that compared mean fasting plasma glucose concentrations and prevalence estimates of diabetes and metabolic syndrome between ART-exposed and ART-naïve HIV-infected adults. Other criteria for study selection are summarised in Table 1.

Search strategy

We searched PubMed, EMBASE and the World Health Organisation (WHO) International Clinical Trials Registry Platform for all relevant articles published to date. The search was conducted using medical subject heading (MeSH) terms and keywords: blood glucose*/, diabetes mellitus*/, metabolic syndrome X*/; highly active antiretroviral therapy*/, antiretroviral therapy*/, antiretroviral-naïve.mp/, HAART-naïve.mp/, HIV */. The electronic search was limited subsequently to studies of humans (see Appendices 1 and 2). We also scanned the bibliographies of relevant articles identified by the search.

Data extraction

CUN, AMS and OAU independently extracted data from each study using a piloted form and any discrepancies were also resolved by consensus with the other investigators. Data on the

following study-level characteristics were extracted: article citation, country of origin, country income group, geographical region, study design, sample size, mean age, proportion of females, proportion of current smokers and drinkers, number of ART-exposed and ART-naïve patients, mean CD4 count, mean duration of ART, proportion of patients on protease inhibitors, mean concentrations of fasting plasma glucose in ART-exposed and ART-naïve patients, and the proportions of diabetes and metabolic syndrome in ART-exposed and ART-naïve patients. Country income groups were defined according to World Bank development indicators [21]. Diabetes mellitus was defined as a fasting plasma glucose concentration ≥ 126 mg/dl (7 mmol/l) or a two-hour post-prandial blood glucose level ≥ 200mg/dl (11.1 mmol/l) [22]. Metabolic syndrome was defined as the presence of central obesity (waist circumference ≥ 94 cm for men and ≥ 80 cm for women) with any two of the following four criteria: serum triglyceride levels ≥ 150 mg/dl (or lipid lowering treatment); serum high density lipoprotein levels < 40 mg/dl in males and < 50 mg/dl in females (or specific treatment for this condition); blood pressure ≥ 130/85 mmHg (or antihypertensive treatment); fasting plasma glucose levels ≥ 100 mg/dl (or previously diagnosed type II diabetes mellitus) [23].

Risk of bias assessment

The methodological quality of each study was assessed using a domain-based checklist adapted from the Cochrane risk of bias tool for non-randomised studies [24] (Table 2). We investigated five potential sources of bias, including: the selection of participants (selection bias), assessment of the exposure (information bias), assessment of the outcomes (information bias), adjustment for potential confounders, and loss to follow-up of patients (attrition bias). Statistical analysis We pooled the weighted mean differences (MD) in fasting plasma glucose concentrations and the odds ratios (OR) of diabetes and metabolic syndrome in each study using the Dersimonian-Laird random-effects model, which is appropriate to

account for heterogeneity across the included studies [25]. The odds ratios of diabetes and metabolic syndrome were computed from their proportions in ART-exposed and ART-naïve patients. Heterogeneity across the included studies was measured using the I-squared statistic (I^2) for which a value between 75% and 100% indicated considerable heterogeneity [26]. Chi-square tests for heterogeneity were also performed to determine the statistical significance of heterogeneity at 5% level. We investigated publication bias in each meta-analysis using funnel plots and performed leave-one-study-out sensitivity analyses to ascertain the stability of the pooled effect estimates, which entailed omitting one study at a time while computing the meta-analyses. Random-effects subgroup and meta-regression analyses were performed on all study-level baseline characteristics to identify factors that may potentially modify the pooled associations, as well as possible sources of any observed heterogeneity across studies included in the meta-analyses [27]. The subgroups were categorized according to well-established predictors of cardio-metabolic disorders in people living with HIV (such as age ≥ 40 years, male sex, current smoking status) [28], and the potential for statistical interactions between obvious categories (such as study designs, country income groups, geographical regions and risk of bias categories) [27,29]. The effect estimates were reported with 95% confidence intervals (CI). Stata version 14 for Windows (Stata Corp, College Station, Texas) and Cochrane Review Manager (RevMan) software were used for all analyses and generation of figures.

RESULTS

Study selection and characteristics

The study selection process is shown in Figure 1. From 602 records identified through electronic database searching, 19 records from cross-references, and 28,417 records from the WHO International Clinical Trials Registry Platform, we excluded 560 abstracts and 11 duplicate records. Of 50 remaining full texts assessed for eligibility, nine articles were

withdrawn, leaving 41 studies that were deemed eligible for inclusion in the meta-analyses [13–20,30–62]. In total, there were 20,178 participants, with approximately twice as many ART-exposed as there were ART-naïve patients. The average age of the total study population was 42 years and women accounted for 40%. Most studies were conducted in low- and middle-income countries, including Brazil [19,40,41,59], Cameroon [39,42,51,57], Ethiopia [20,30,54], Ghana [56], India [33,49,52.53.60], Nigeria [32,38,55], South Africa [17,31], Sri Lanka [61], Thailand [14] and Zambia [46]. However, the studies conducted in high-income countries were generally larger in size, comprising more than half of the total study population. Table 3 summarizes other characteristics of the included studies.

Risk of bias within included studies

Selection bias was low in only ten studies (24%); information bias with respect to assessment of the exposure was low in all 41 studies, but unclear or high with respect to outcomes assessment in seven studies (83%); 34 studies (83%) adjusted for at least one important confounder; and loss to follow-up was less than 20% in eight out of 10 included cohort studies (Figure 2).

Pooled association of ART with blood glucose concentration

Figure 3 displays the meta-analysis of the association between ART and fasting plasma glucose concentrations. Mean fasting plasma glucose levels were compared between ART-exposed and ART-naïve patients in 24 studies, 12 of which reported significantly higher mean concentrations in ART-exposed patients [14,19,30,38,41,46,49,56,58–61]. Overall, mean fasting plasma glucose levels remained significantly higher in ART-exposed patients, compared to their naïve counterparts (Pooled MD: 4.66 mg/dL; 95% CI 2.52 to 6.80; $P < 0.001$; 5,069 participants). Heterogeneity across the included studies was considerable ($I^2 = 81.2$ %) and statistically significant ($P < 0.001$). Analysis of publication bias revealed a

symmetrical funnel plot (Supplementary Figure 1), and the pooled estimate did not change as to alter the interpretation of the association following serial exclusion of the included studies (Table 4).

Table 5 presents the results of subgroup and meta-regression analyses. With the exception of sample size differences between studies, meta-regression analyses revealed no statistically significant differences between study-level subgroup estimates of the pooled association of ART with increased fasting plasma glucose concentration. The strength of the pooled association was significantly greater among studies with more than 200 participants (Pooled MD: 6.54 mg/dl; 95% CI 5.04 to 8.04; 12 studies), compared to studies with 200 participants or less (Pooled MD: 2.93 mg/dl; 95% CI 0.12 to 5.74; 12 studies) (P = 0.020 for interaction). Nonetheless, the qualitative interactions of the subgroup and meta-regression were also noteworthy. For instance, even though the difference between estimates of the pooled association were not statistically significant across the other study-level subgroups, it was observed that ART was significantly associated with increased blood glucose levels in studies where the mean duration of ART was at least 18 months (Pooled MD: 4.97 mg/dl; 95% CI 3.10 to 6.84; 14 studies), whereas no significant association was observed in studies with mean ART duration of less than 18 months (Pooled MD: 4.40 mg/dl; 95% CI -0.59 to 9.38; 7 studies). Unexpectedly, we found no significant associations between ART exposure and increased blood glucose levels in studies where the mean BMI was at least 25 kg/m 2 (Pooled MD: 1.87 mg/dl; 95% CI -5.75 to 9.49; 3 studies) and studies with more smokers than nonsmokers (Pooled MD: 4.13 mg/dl; 95% CI -0.04 to 8.29; 3 studies), whereas studies with mean BMI < 25 kg/m 2 (Pooled MD: 4.70 mg/dl; 95% CI 2.95 to 6.44; 16 studies) and fewer smokers than non-smokers (Pooled MD: 5.17 mg/dl; 95% CI 3.43 to 6.91; 11 studies) reported significant associations between ART exposure and increased blood glucose concentrations. However, in comparison to the numbers of participants in studies with mean

BMI < 25 kg/m 2 (n = 3,446) and studies with fewer smokers than non-smokers (n = 2,843), the numbers of participants in studies with mean BMI ≥ 25 kg/m 2 (n = 625) and studies with more smokers than non-smokers (n = 413) may have been too small to detect a statistically significant association between ART and blood glucose levels.

Pooled association of ART with diabetes mellitus

As shown in Figure 4, prevalence estimates of diabetes were compared between ART-exposed and ART-naïve patients in ten studies, five of which revealed significantly higher odds of having diabetes in the ART-exposed group [13,14,47,54,56]. Among 7,946 participants with reported diabetes status in the ART-exposed groups, 519 (6.5%) had diabetes, as opposed to 63 of 3,379 (1.9%) in the ART-naïve groups. Overall, the odds of having diabetes mellitus were approximately four times higher in ART-exposed patients, compared to their naïve counterparts (Pooled OR: 3.85; 95% CI 2.93 to 5.07; P < 0.001; 11,328 participants). Studies included in the meta-analysis were not heterogeneous (I^2 = 0%). Analysis of publication bias revealed the absence of small-study effects as indicated by the absence of funnel plot asymmetry (see Supplementary Figure 2), and sensitivity analysis showed no change in the pooled estimate that would alter the interpretation of the overall association of ART with increased odds of diabetes. (Table 4).

There were no significant differences between subgroup estimates of the pooled association between ART exposure and diabetes. Nonetheless, in contrast to studies with less than 200 participants (Pooled OR: 1.79; 95% CI 0.49 to 6.57; 3 studies), studies with more than 200 participants were likely to report a significant association (Pooled OR: 4.06; 95% CI 3.06 to 5.38; 7 studies) (Table 5).

Pooled association of ART with metabolic syndrome

Prevalence estimates of metabolic syndrome were compared between ART-exposed and ART-naïve patients in 18 studies [14,16,18–20,31,33,34,36,37,39,41,43–45,50,51,55]. Among 5,548 ART-exposed patients with reported metabolic syndrome status, 1048 (18.9%) were diagnosed with metabolic syndrome, compared to 214 (14.2%) of 1,506 patients in the ART-naïve group. In addition, the odds of being diagnosed with metabolic syndrome were significantly higher among ART-exposed patients, compared to ART-naïve patients (Pooled OR: 1.45; 95% CI 1.03 to 2.03; P = 0.037; 7,052 participants) (Figure 5). Heterogeneity across the included studies was substantial (I^2 = 69.4%) and statistically significant (P < 0.001). Funnel plot was symmetrical (Supplementary Figure 3) and sensitivity analysis revealed no significant change in the pooled effect estimate following the sequential exclusion of studies from the meta-analysis (Table 4). Subgroup and meta-regression analyses also revealed no significant differences between subgroup estimates of the pooled association between ART exposure and metabolic syndrome. Nonetheless, the analyses revealed qualitative differences in the pooled association between studies of patients who were at least 40 years of age (Pooled OR 2.34; 95% CI 1.22 to 4.49; 7 studies) and those who were younger (Pooled OR: 1.14; 95% CI 0.67 to 1.95; 8 studies); studies with more women than men (Pooled OR: 1.66; 95% CI 1.28 to 2.14; 6 studies) and fewer women than men (Pooled OR: 1.49; 95% CI 0.81 to 2.72; 7 studies); and studies of patients from low/middle-income countries (Pooled OR 1.61; 95% CI 1.26 to 2.04; 10 studies) and those from high-income settings (Pooled OR: 1.27; 95% CI 0.63 to 2.53; 8 studies) (Table 5).

DISCUSSION

We present the first pooled analyses estimating the associations of ART with diabetes mellitus and the metabolic syndrome in people living with HIV worldwide. Overall, our findings revealed significant associations of ART with increased risks of diabetes and metabolic syndrome. HIV-infected patients on ART had approximately four and 1.5 greater

odds of developing diabetes mellitus and metabolic syndrome respectively, compared to patients naïve to ART. Importantly, there were no statistically significant variations in these pooled estimates across different socio-demographic and clinical characteristics, which suggests that ART may potentially be the single most consistent determinant of diabetes and metabolic syndrome in people living with HIV.

Meta-regression analyses provided limited explanation for the observed heterogeneity across the included studies, but identified potential modifiers of the pooled associations. Schoenbach [63] and Kamangar [64] described two types of effect modification: quantitative modification occurs when the strength of the association between two variables differ significantly across subgroups of the modifier but the direction of the association remains the same, whereas qualitative modification is present when there is an association between two variables in one subgroup and not the other (or when the association in both subgroups occur in opposite directions). While our analyses revealed no quantitative modifiers, we found ART duration, age and sex to be qualitative moderators of the associations of ART with increased odds of blood glucose concentration and metabolic syndrome.

Regarding ART duration, the observed association of ART exposure with increasing blood glucose levels in HIV-infected patients on ART for longer than 18 months but not in patients with shorter ART durations may suggest a plausible dose-response relationship between ART exposure and blood glucose levels. While our interpretation of this interaction somewhat contradicts previous studies reporting a lack of association between ART duration and fasting blood glucose concentrations [30,42], we cannot rule out the possibility that these two rather small-sized studies may not have been adequately powered to detect a significant association.

The observed associations of ART with increased odds of metabolic syndrome in HIV-infected patients above 40 years of age and in studies with more women than men, but not in younger patients or studies with fewer women than men, are broadly consistent with older

age and female sex as risk factors for cardio-metabolic disorders in HIV-infected persons exposed to ART [4,65]. In addition, the moderating influences of sex on the association between ART and metabolic syndrome is broadly consistent with higher rates of central obesity among women [66], especially given that central obesity remains a constant in the (IDF) definition of metabolic syndrome [23].

Our findings may have important clinical and public health implications, especially for people living with HIV in low- and middle-income countries where care and treatment guidelines for HIV-infected patients do not entail baseline and routine blood glucose monitoring and other cardio-metabolic screening [67]. While our findings also suggest that downstream measures for preventing diabetes mellitus and other cardio-metabolic disorders in HIV-infected individuals may be more effectively targeted at patients considered to be high-risk, such as those aged over 40 years and those on antiretroviral therapy for more than 18 months, future studies should also investigate the phenotypes on the HIV clinical spectrum that are most susceptible to the effects of ART on diabetes mellitus and metabolic syndrome, as well as the efficacies of targeted interventions in the defined phenotypes.

This meta-analysis was limited by a number of factors. First, the observational nature of the included studies potentially precludes any causal inferences. Arguably, the ethical dilemma associated with the random allocation of HIV-infected patients to a placebo group diminishes the feasibility of a randomised controlled trial, emphasizing the need for observational data in estimating causality [68]. However, no temporal information is available for most of the studies included in the meta-analyses, given that the majority of these studies are cross-sectional. It may very well be that HIV-infected patients with greater body mass indices are healthier than HIV-infected patients with lower body mass indices, and that this healthier state is associated with better compliance to ART or better access to antiretroviral drugs, so that there may be reverse causation, where diabetes and metabolic syndrome (untoward

effects of increased body mass index) lead to a greater exposure to ART. Indeed, the results of the subgroup and meta-regression analyses, which provide weighted estimates for the associations according to study design, show no significant association of ART with blood glucose or metabolic syndrome in the cohort studies and an extremely high association of ART with metabolic syndrome with a wide confidence interval in the single case control study. Although the cross-sectional studies show consistently positive associations of ART with blood glucose, diabetes and metabolic syndrome, but these associations may not be interpreted as cause and effect.

Secondly, our findings are not generalizable to HIV-infected populations in the Eastern Mediterranean region, especially considering the high rates of diabetes in this region [7]. Given that geographical region may be used as proxy for genetic trait [69], the dearth of data from this region potentially limits any comprehensive assessment regarding what genetic traits may be most susceptible to the effects of ART on diabetes and metabolic syndrome. The inclusion of a larger proportion of HIV-infected patients from high-income countries, compared to low- and middle-income countries, also compromises generalization, given that the global prevalence of HIV and its untoward effects are driven by rates in low- and middle-income countries [11].

Thirdly, we acknowledge that the lack of data on glycated haemoglobin (HbA1c) levels is an important limitation of our study, especially with HbA1c now considered to be a better predictor of long-term diabetes risk than fasting plasma glucose concentrations in the general population [70].

Furthermore, most of the included studies were assessed to have a high risk of selection bias. However, subgroup and meta-regression analyses revealed no significant differences in the pooled estimates between studies with high/unclear and low risks of selection bias (see Table 5). In other words, the pooled estimates were not affected by selection bias.

Some of the unexplained heterogeneity across the included studies may have been driven by individual-level differences, such as differences in blood glucose concentrations prior to commencing antiretroviral therapy, varying histories of antidiabetic treatment, potential variations in the pharmacodynamic interactions between antiretroviral drugs and oral hypoglycaemic agents [71], and individual differences in lifestyle behaviours, such as alcohol abuse. However, individual-level differences were not examined in the meta-analyses.

We could not examine the impact of certain lifestyle factors (such as smoking and alcohol use) and HIV-related characteristics (such as ART regimen, CD4 count, and HIV infection duration) on the associations of ART with diabetes mellitus and metabolic syndrome, given the insufficient number of studies required to perform these analyses [26].

We did not examine the impact of antiretroviral therapy on gestational diabetes mellitus (GDM), given the dearth of evidence on this subject. Available data suggest that GDM prevalence estimates are statistically comparable between HIV-infected and HIV-non-infected pregnant mothers [72]. Similarly, the American Diabetes Association 2016 guidelines have not recommended different GDM screening protocols for HIV-infected and non-infected pregnant mothers [73].

Lastly, with only two cohort studies in which the association between ART and diabetes mellitus were examined [17,47], it was impossible to distinguish ART-associated diabetes from diabetes developed prior to the commencement of ART [4].

In spite of the above limitations, the timeliness of our study in filling an important gap by providing the most comprehensive and precise estimates quantifying the associations of ART with diabetes and metabolic syndrome in people living with HIV is noteworthy. Other important strengths of our study include: novel findings of moderators of the associations of ART on diabetes and metabolic syndrome; rigorous search strategies and methodological

assessments which were conducted by independent investigators; absence of small-study effects; and stability of the pooled estimates as confirmed by sensitivity analyses.

In conclusion, the findings may preclude a cause and effect interpretation of the associations of ART with diabetes and metabolic syndrome, they (findings) add to a growing body of evidence, suggesting that the odds of developing diabetes or metabolic syndrome are high, above and beyond the role of traditional risk factors, among people living with HIV on antiretroviral treatment. These associations may also be modified by age, sex, and the duration of antiretroviral exposure, suggesting that this meta-analysis of over 20,000 HIV-infected patients potentially supports the need for regular blood glucose monitoring and other cardio-metabolic screening in people living with HIV on ART. Future studies should investigate the phenotypes on the HIV clinical spectrum that are most susceptible to the effects of ART on cardio-metabolic disorders, as well as the efficacies of targeted treatments for the identified phenotypes.

ACKNOWLEDGEMENT

CUN acknowledges support from the University of Warwick Chancellor's Scholarship (ID 1160088). OAU acknowledges support from the Marie Curie International Postdoc Fellowship Grant (2012-0064).

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOURSHIP

Study concept and design: CUN, SS, OAU. Data extraction: CUN, AMS, OAU. Data analysis and interpretation: All. Drafting the manuscript: CUN. Revision and approval of submission: All.

ETHICS

Ethical approval was not required of this meta-analysis of published data.

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Table 1: Inclusion and exclusion criteria

	Inclusion	**Exclusion**
Participants	HIV-infected	HIV-negative
	18 years of age and above	Under 18 years of age
Exposure	HAART	HIV monotherapy
Comparator	HAART-naïveté	No HAART-naïve group
Outcomes	Fasting plasma glucose	Other cardio-metabolic parameters/disorders
	Diabetes mellitus	Coronary heart diseases
	Metabolic syndrome	
Study type	Cross-sectional studies	Expert reviews
	Case-control studies	Conference proceedings
	Cohort studies	
	Randomised controlled trials	
	Abstracts	

HAART, highly active antiretroviral therapy

Table 2: Risk of bias assessment criteria for appraising the included studies

Domain	Assessment criteria
Sampling of participants (Selection bias)	*Low risk:* • Participants are sampled randomly • Similar recruitment strategies for ART-exposed and naïve participants • Sample size was justified *High risk:* • Participants are not selected randomly • ART-exposed and naïve participants recruited differently • Sample size was not justified *Unclear risk*: • Sampling strategy was not described • Sample size was not calculated
Assessment of exposure (Information bias)	*Low risk*: • Well-defined exposure criterion *High risk*: • Exposure criterion not well defined e.g. studies may define ART exposure based on treatment duration of at least one month, which misclassifies certain ART-

	exposed patients as ART-naïve *Unclear risk*: • Exposure criterion not stated
Assessment of outcomes (Information bias)	*Low risk*: • Blood glucose levels and diabetes risk are assessed similarly between ART-exposed and ART-naïve participants • Blood glucose levels and diabetes risk are assessed using validated methods *High risk*: • Blood glucose levels and diabetes risk are assessed differently between ART-exposed and ART-naïve participants • Blood glucose levels and diabetes risk are not measured using validated methods *Unclear risk*: • Methods for assessing blood glucose levels and diabetes risk are not clearly described
Adjustment for confounding	*Low risk*: • At least one major confounder is controlled *High risk*: • No attempt at adjusting for confounders
Follow-up of participants – for cohort studies (Attrition bias)	*Low risk:* • Loss to follow-up is less than 20% *High risk*: • Loss to follow-up is 20% or more

Adapted after the Cochrane risk of bias tool for non-randomised studies

Table 3: Characteristics of the included studies

First author	Year	Study design	Country	Income group	Region	N	F (%)	Age (years)	BMI (kg/m^2)	CD4 (cells/µL)	Smokers (%)	ART duration (months)	PI (%)
Abebe [30]	2014	Cross-sectional	Ethiopia	Low/Middle	Africa	252	72.2	35.3±10.2	–	364±199	–	–	0
Abrahams [17]	2015	Cohort	South Africa	Low/Middle	Africa	103	100	33.5±2.5	27.9±3.5	372±53	–	–	0
Awotedu [31]	2010	Cross-sectional	South Africa	Low/middle	SSA	196	81	36.9±10.4	–	–	–	–	–
Ayodele [32]	2013	Cross-sectional	Nigeria	Low/Middle	Africa	265	67.5	38.7±8.7	23.2±4.5	313±230	1.9	17.3±11.0	0
Bajaj [33]	2013	Cross-sectional	India	Low/middle	S/E Asia	70	28.6	–	–	–	–	49.5±27.0	–
Bergersen [34]	2003	Cross-sectional	Norway	High	Europe	283	20.0	43.1±10.2	23.0±3.3	384±206	54.5	33.0±2.0	–
Bergersen [15]	2006	Cross-sectional	Norway	High	Europe	263	19.4	43.1±20.1	–	313±230	1.9	–	–
Blumer [35]	2008	Cohort	Netherlands	High	Europe	39	–	42.3±7.0	–	260±148	–	3.0	100
Bonfati [18]	2007	Cross-sectional	Italy	High	Europe	1243	28.2	43.2	23.6±3.3	–	60.2	–	–
Bonfati [36]	2012	Cohort	Italy	High	Europe	188	24.5	39.5±11.1	–	–	–	18.5±8.8	46.5
Calza [37]	2011	Cross-sectional	Italy	High	Europe	755	–	37	–	–	–	–	–
Denue [38]	2013	Cohort	Nigeria	Low/Middle	Africa	229	51.1	43.5±9.3	24.4±4.1	246±166	5.7	24.0	0
Dimodi [39]	2014	Cross-sectional	Cameroon	Low/middle	SSA	463	74.7	–	–	–	5.1	–	3.2
Domingos [40]	2009	Cross-sectional	Brazil	Low/Middle	America	292	40.0	41.0±13.0	–	–	15.4	40.4	60.2
Eira [41]	2012	Cross-sectional	Brazil	Low/Middle	America	56	–	42.8±7.1	26.0±9.5	328±183	57.1	92.4±40.8	–
Ekali [42]	2013	Cross-sectional	Cameroon	Low/Middle	Africa	143	72.0	39.5±9.8	24.5±3.4	253±167	–	43.5±21.3	0
Fontas [13]	2004	Cohort	Multi-centre	High	Europe	7483	24.0	39±7.4	–	488±265	44.5	23.6±12.5	78.0
Hansen [43]	2009	Cross-sectional	Denmark	High	Europe	466	18.6	45.5±10.2	25.1±8.6	519±233	–	60.0±51.5	73.0
Howard [44]	2014	Cross-sectional	UK	High	Europe	100	–	–	–	–	–	–	40.7
Jantarapakde [14]	2014	Cross-sectional	Thailand	Low/Middle	Western Pacific	580	53.8	37.0±8.2	22.4±3.5	406±208	16.3	37.8±30.2	14.9
Jerico [45]	2005	Cross-sectional	Spain	High	Europe	710	28	42±9.2	23.4±4.0	489±284	69.5	70.5±45.9	74.7
Kiage [46]	2013	Cohort	Zambia	Low/Middle	Africa	118	55.9	35.0±7.9	20.5±2.8	136±50	4.4	3.0	0
Lin [47]	2011	Cohort	Taiwan	High	Western Pacific	1344	–	–	–	–	–	49.5±27.0	–
Magenta [48]	2011	Cohort	Switzerland	High	Europe	74	12.0	40.0±10.0	24.9±4.8	258±112	65.0	20.4±8.3	100
Malapati [49]	2014	Cohort	India	Low/Middle	South-East Asia	229	–	46.3±9.3	24.4±4.1	246±167	–	12.0	0
Maloberti [50]	2013	Cross-sectional	Italy	High	Europe	108	–	43.6±7.7	–	–	–	–	–
Mbunkah [51]	2014	Cross-sectional	Cameroon	Low/Middle	Africa	173	71.1	38.7±11.4	23.7±3.8	332±168	2.9	–	28.9

Mital [52]	2013	Cross-sectional	India	Low/Middle	South-East Asia	200	–	–	22.6±2.9	–	17.5	–	0
Mittal [53]	2013	Cross-sectional	India	Low/Middle	South-East Asia	40	32.5	36.1±7.2	20.3±3.8	–	–	39.6±16.5	100
Mohammed [54]	2015	Cross-sectional	Ethiopia	Low/Middle	Africa	393	66.9	–	–	–	–	–	–
Muhammad [55]	2013	Cross-sectional	Nigeria	Low/Middle	Africa	200	53.0	32.5±7.6	–	319±206	9.0	45.0±19.5	1.0
Ngala [56]	2013	Cross-sectional	Ghana	Low/Middle	Africa	305	61.0	38.5±8.7	24.0±4.7	–	–	17.0±6.3	0
Ngondi [57]	2007	Cohort	Cameroon	Low/Middle	Africa	138	58.0	36.1±7.1	23.7±4.1	–	–	12	0
Samaras [16]	2007	Case-control	Multi-centre	High/Middle	Multi-regional	788	16	43.5±9	25.0±3.5	–	–	–	50.4
Shahmanesh [58]	2004	Cross-sectional	UK	High	Europe	55	18.2	40.0±10.4	23.6±2.9	424±225	41.8	39.8±8.8	37.5
Silva [19]	2009	Cross-sectional	Brazil	Low/Middle	America	319	38.9	39.5	24.4	532±422	26.7	–	–
Silva [59]	2010	Cross-sectional	Brazil	Low/Middle	America	314	44.6	37.7±7.9	–	531±313	26.7	52.8±42.0	–
Sreekantamurthy [60]	2014	Cross-sectional	India	Low/Middle	South-East Asia	101	0	43.5±6.3	–	–	–	67.8±16.5	30.4
Tesfaye [20]	2014	Cross-sectional	Ethiopia	Low/Middle	Africa	374	68.0	32.6	–	–	–	–	–
Weerakkody [61]	2013	Cross-sectional	Sri Lanka	Low/Middle	South-East Asia	268	42.2	39.5±9.6	21.4±3.9	390±243	20.1	33.0±23.0	7.3
Wilson [62]	2009	Cross-sectional	UK	High	Europe	458	16.8	39.5±8.9	24.5±4.0	545±83	41.5	77.4±33.0	39.0

AIDS, Acquired Immune Deficiency Syndrome; ART, antiretroviral therapy; N, number of participants included in the analyses, F, females; PI, protease inhibitors; UK, United Kingdom; *Multiple, multi-centre. Values are expressed as mean ± standard deviation for age, CD4 count and duration of ART.

Table 4: Sensitivity analyses of the pooled associations of ART with blood glucose, diabetes and metabolic syndrome.

Outcomes	Pooled estimate prior to exclusion of studies Pooled ES (95% CI)	Range of pooled estimate after sensitivity analyses	Pooled estimate after exclusion of study significantly changed interpretation of the overall association Pooled ES (95% CI)
Fasting plasma glucose	4.66 (2.52 to 6.80)	4.48 to 5.08	—
Diabetes Mellitus	3.85 (2.93 to 5.07)	3.81 to 3.85	—
Metabolic Syndrome	1.45 (1.03 to 2.03)	1.42 to 1.59	—

CI, confidence interval; ES, effect size. No study had undue influence on the pooled estimates.

Table 5: Subgroup estimates and meta-regression analyses of the pooled associations of ART with blood glucose, diabetes and metabolic syndrome.

	Blood glucose (mg/dL)			Diabetes mellitus			Metabolic syndrome		
Study-level characteristics	**N**	**Pooled MD (95% CI)**	***P*-value**	**N**	**Pooled OR (95% CI)**	***P*-value**	**N**	**Pooled OR (95% CI)**	***P*-value**
Region									
Sub-Saharan Africa	9	3.29 (-0.48 to 7.06)		4	3.35 (1.29 to 8.67)		5	1.62 (1.19 to 2.20)	
Europe	5	3.34 (1.15 to 5.53)		1	2.03 (0.43 to 9.52)		8	1.27 (0.63 to 2.53)	
South-East Asia	5	5.89 (2.67 to 9.10)		–	–		1	0.85 (0.25 to 2.91)	
The Americas	4	7.92 (5.40 to 10.44)		1	8.96 (0.53 to 152.53)		2	1.20 (0.60 to 2.40)	
Western Pacific	1	6.90 (4.89 to 8.91)	0.313	2	3.69 (2.32 to 5.88)		1	1.75 (1.10 to 2.80)	
Multi-regional	–	–		1	4.20 (2.84 to 6.23)	0.727	1	12.78 (1.75 to 93.14)	0.818
Income group									
High income	5	3.34 (1.15 to 5.53)		3	4.03 (2.82 to 5.76)		8	1.27 (0.63 to 2.53)	
Low/middle	19	5.07 (2.45 to 7.69)	0.469	7	3.62 (2.33 to 5.61)	0.434	10	1.61 (1.26 to 2.04)	0.841
Age group									
< 40 years	13	4.46 (1.43 to 7.49)		8	3.76 (2.82 to 5.02)		8	1.14 (0.67 to 1.95)	
≥ 40 years	9	5.44 (3.39 to 7.49)	0.502	2	4.89 (1.98 to 12.09)	0.643	7	2.34 (1.22 to 4.49)	0.845
Females									
≤ 50%	10	5.69 (3.86 to 7.51)					7	1.49 (0.81 to 2.72)	
> 50%	10	3.80 (0.04 to 7.56)	0.341	–	–	–	6	1.66 (1.28 to 2.14)	0.701
Body mass index									
< 25 kg/m^2	16	4.70 (2.95 to 6.44)					6	1.63 (1.09 to 2.44)	
≥ 25 kg/m^2	3	1.87 (-5.75 to 9.49)	0.146	–	–	–	4	2.34 (1.32 to 4.16)	0.795
Smokers									
≤ 50%	11	5.17 (3.43 to 6.91)							
> 50%	3	4.13 (-0.04 to 8.29)	0.692	–	–	–	–	–	–
HIV duration									
< 60 months	6	5.63 (3.10 to 8.15)							
≥ 60 months	6	4.83 (2.00 to 7.67)	0.714	–	–	–	–	–	–
PI-based ART regimen									
≤ 50%	15	4.45 (1.62 to 7.27)							
> 50%	5	3.79 (0.66 to 6.93)	0.839	–	–	–	–	–	–
ART duration									
< 18 months	7	4.40 (-0.59 to 9.38)							
≥ 18 months	14	4.97 (3.10 to 6.84)	0.615	–	–	–	–	–	–
Study design									
Case-control	–	–		–	–		1	12.78 (1.75 to 93.14)	
Cohort	7	4.11 (-0.75 to 8.96)		2	4.57 (1.83 to 11.39)		1	0.43 (0.14 to 1.08)	
Cross-sectional	17	4.93 (3.23 to 6.62)	0.479	8	3.79 (2.84 to 5.05)	0.637	16	1.45 (1.04 to 2.02)	0.610
Selection bias									
High/unclear	19	4.61 (2.08 to 7.14)		7	3.54 (2.37 to 5.29)		15	1.41 (0.97 to 2.06)	
Low	5	3.70 (1.04 to 6.36)	0.832	3	4.15 (2.85 to 6.04)	0.695	3	1.94 (0.54 to 6.97)	0.769

–, insufficient number of observations to perform analysis; ART, antiretroviral therapy; CD4, cluster of differentiation 4; MD, mean difference; MD, mean difference; N, number of studies; OR, odds ratio; PI, protease inhibitor