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Antiretroviral therapy and cardiovascular risk in low- and middle-income countries (LMICs): A systematic review and meta-analysis

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Abstract

Background: Effective use of antiretroviral treatment (ART) is known to reduce HIV/AIDS-related morbidity and mortality significantly. However, as life expectancy increases, the risk factors for cardiovascular disease become more prevalent. Data on the risk of cardiovascular diseases in relation to antiretroviral therapy in low- and middle-income countries (LMIC) remain limited.

Objective: In this review, we examined the association between antiretroviral therapy and cardiovascular disease (CVD) risk factors (hypertension, diabetes, dyslipidaemia) among people living with HIV (PLHIV) in LMIC.

Methods: We conducted a systematic review and meta-analysis of studies on LMIC published between 2007 and 2018. Studies published in English and indexed in PubMed, Scopus, Cochrane, and Google Scholar were critically reviewed, and the effect of estimates were pooled for hypertension, diabetes, and high lipid profiles using a random-effects meta-analysis. In all, twenty-one studies were included involving 12,229 participants after screening.

Results: There was no link found between ART use and diabetes (RR = 0.88, 95% CI: 0.58 - 1.33). ART use was, however, associated with hypertension (RR = 1.74, 95% CI: 1.21 - 2.50), increased total cholesterol (RR = 2.72, 95% CI: 1.75 - 4.23), high triglycerides concentration (RR = 1.64, 95% CI: 1.50 - 1.80), elevated LDL-cholesterol (RR = 2.72, 95% CI: 1.75 - 4.23)., and decreased HDL-cholesterol (RR=0.65, 95% CI: 0.58 - 0.77).

Conclusion: There is an association between antiretroviral therapy and raised LDL, triglycerides, total cholesterol, and hypertension in LMIC, hence the need to provide tailored education on CVD risk factors among PLHIV. Moreover, there is a need to formulate policies and programmes aimed at addressing CVDs among PLHIV in LMIC.

Keywords: HIV, antiretroviral therapy, cardiovascular disease, risk factors, LMIC

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INTRODUCTION

In recent years, studies have shown that access to antiretroviral therapy (ART) has significantly increased the life expectancy of persons living with human immunodeficiency virus (PLHIV) [1-3]. The increase in life expectancy among people living with HIV (PLHIV) leads to a higher likelihood of experiencing the long-term effects of HIV and its treatment [3,4]. This phenomenon coincides with a documented global trend of rapidly increasing uptake of antiretroviral therapy (ART). The extended lifespan allows for the potential chronic impacts of both the virus and its treatment to become more evident over time [5]. Globally, in the span of 7 years, ART treatment coverage more than doubled, increasing from 7.5 million people (23%) in 2010 to 19.5 million people (53.3%) in 2017 [6]. As of June 2020, globally, 26 million people living with

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HIV (PLHIV) had access to antiretroviral therapy (ART), marking a 2.4% improvement from the 25.4 million who had access at the end of 2019 [6]. Incidentally, HIV infection and antiretroviral therapy (ART) are independently associated with an increased risk of developing CVDs. Various factors, such as chronic inflammation, immune activation due to HIV, and potential side effects of ART, contribute to this elevated risk [5,4], such as atherosclerosis, hypertension and diabetes mellitus (DM) [4,5,7].

ART use is known to contribute to enhanced inflammatory processes coupled with host immune responses, which, together with other contributing factors, promote the development of atherosclerosis in individuals with HIV [8-11]. Some studies have shown that HIV-infected macrophages and latent viral reservoirs can adversely affect vascular and myocardial function by releasing inflammatory cytokines that regulate the immune response, including tumour necrosis factors, interleukins (such as IL-6 and IL-1β), and interferon-gamma (IFN-γ) [12]. Multiple observational studies have reported an association between antiretroviral therapy (ART) and an increased risk of cardiovascular disease (CVD). However, definitive evidence of a direct causal relationship remains limited, largely due to confounding factors and the inherent difficulty in isolating the specific effects of ART from those of HIV infection and other comorbid conditions. [13,14]. In sub-Saharan Africa (SSA), the association between antiretroviral therapy (ART) and cardiovascular diseases (CVDs) is unclear. This is due to a nutrition transition characterised by an increased prevalence of CVDs and other non-communicable diseases, which are influenced by changing dietary habits and lifestyles [5]. While previous reviews have explored these associations, there remains a lack of LMIC-specific pooled estimates, which are vital for informing regional guidelines given potential variations in cardiovascular metabolic risk across ethnic populations. In this review, we argue that understanding the overall impact of ART on CVD risk is critical. This knowledge will aid in developing care strategies to scale up ART, ultimately enhancing life expectancy among people living with HIV (PLHIV) [5,15]. Some evidence suggests that there may be variations in cardio-metabolic risk levels among people of African origin compared with Europeans [9,16]. This present systematic review and meta-analysis therefore assessed the associations between ART and CVD risk factors among adult PLHIV in low- and middle-income countries (LMIC).

MATERIALS AND METHODS

Design and settings

In this study, we adopted a quantitative approach to review existing evidence on the association between ART and cardiovascular risk factors in LMIC (according to World Bank Economic Classification), using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach of reporting The study aimed to determine whether or not PLHIV who receive ART medication for at least three months have an increased risk of cardiovascular diseases (hypertension, diabetes, and dyslipidemia) compared with PLHIV who are not on ART medication.

Protocol registration and search strategy

The protocol for the review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42018084661). The inclusion criteria followed the Population, Intervention, Comparator, and Outcome (PICO) format. A comprehensive search of peer-reviewed literature was conducted across the following electronic databases: Google Scholar, PubMed, Scopus, and Cochrane Central, using a set of identified search terms and keywords (Table 1). These databases were selected based on their broad indexing of high-quality, peer-reviewed literature, their extensive coverage of studies related to HIV and cardiovascular diseases, and their frequent use in systematic reviews on similar topics.

Selection of papers

Papers published between 2007 and 2018 were screened for relevance in a three-stage process, and a full-text review by two independent reviewers, as follows:

1. Study titles were first screened for relevance by one of the reviewers. A different reviewer cross-checked the screening to ensure that only papers with titles that qualified were included in the next stage.

2. In stage two, the abstracts of all papers selected were screened by two independent reviewers, paying attention to the review question, inclusion criteria, and the outcome of interest.

3. Full texts of potentially relevant papers were then printed out and read by the same independent reviewers to ascertain their relevance and usefulness to the review. A spreadsheet was used to enter the relevant information for each paper during the screening process.

To minimise interobserver variability in the screening and coding process, several measures, including discussions to clarify points of dissent in the selection of the papers, were put in place.

The 2007 – 2018 timeframe was specifically chosen as it reflects the period of widespread implementation and scale-up of standardised first-line ART regimens across many LMICs following updated global health guidelines, making the evidence more relevant to current practice. Quality assessment was performed using the Downs and Black 12-point scoring system [17].

This validated checklist assesses the quality of both randomised and non-randomised studies using criteria for reporting clarity, external validity, internal validity (bias and confounding), and statistical power. The assessment of study quality focused on data analysis, variables related to study objectives, description of inclusion and exclusion criteria, characteristics of the study participants, data

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collection methods, and whether the findings were discussed in an appropriate way and limitations the study objectives, the description of inclusion and exclusion criteria, the characteristics of the study participants, the data collection methods, and whether the findings were discussed appropriately and limitations were indicated.

Data extraction and management

We designed a data extraction tool and piloted the extraction tool among the participating authors to ensure comparability of results. The tool was used by two independent reviewers to extract relevant data from the included studies. The information collected on the extraction form included author, year of publication, study title, design, type, geographic area and setting, patient sampling & locations, age, sex, sample size, ART use, hypertension, diabetes, and dyslipidemia. Duplicate records were identified using EndNote X9 reference manager. In instances where multiple articles reported the same study, data were extracted from the most recent publication.

Measurement of effect

Outcomes were reported as risk factors and summarised as proportions with a 95% confidence interval. The prevalence of cardiovascular disease (CVD) risk factors, including dyslipidaemia, hypertension, and diabetes, was also determined to estimate the prevalence ratios or relative risks of developing these comorbidities among individuals on antiretroviral therapy (ART+) compared with those not on antiretroviral therapy (ART-).

Data synthesis

Data were statistically analysed using Review Manager (RevMan) software, version 5.3 (The Cochrane Collaboration, London, England, UK). A random-effects meta-analysis model was used owing to the likelihood of heterogeneity across studies. Risk Ratios comparing the ART-positive and ART-negative groups were calculated and summarised. The exposure variable was the use of ART, and the outcome variables were cardiovascular risk factors: diabetes, hypertension, and dyslipidaemia. These outcome variables were defined according to the standard international criteria: World Health Organisation [1] and National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] [2].

Sensitivity analysis

Sensitivity analyses were carried out to investigate the effect of non-eligible studies on the effect size. This was done by doing the meta-analysis of the data twice. The first analysis included all studies, and the second included only those known to be eligible. We also applied the leave-one-out method to determine the effect of any one of the included studies on the effect size. The exercise did not have any significant change on the effect size.

RESULTS

Figure 1 depicts the stages involved in identifying relevant studies for review. Out of 3,898 references pooled from the various databases used, after removing duplicates and excluding studies based on title and abstract screenings, 45 were subjected to full-text analysis. Of the 45 studies, 21 were finally included based on the overall requirement for selection in the systematic review. The 24 studies that were eliminated at this stage were mostly because they either reported only means or general prevalence of CVD risk factors without comparing ART and treatment-naïve PLHIV.

Table 1 lists the features of the studies that were published between 2007 and 2018. Participants (n = 12,229) were people living with HIV on antiretroviral therapy (ART) and people living with HIV who were not on ART, males and females aged 18 to 75 years. All investigations were carried out in eight (8) LMICs. Sixteen (16) studies involved a cross-sectional study design, three (3) used a cohort study design, and one (1) case-control study design, in which the intervention was the use of ART. Based on the quality assessment, seven studies were rated as high quality and fourteen as medium quality. The prevalence (percentage) of all CVD risk factors was higher among individuals

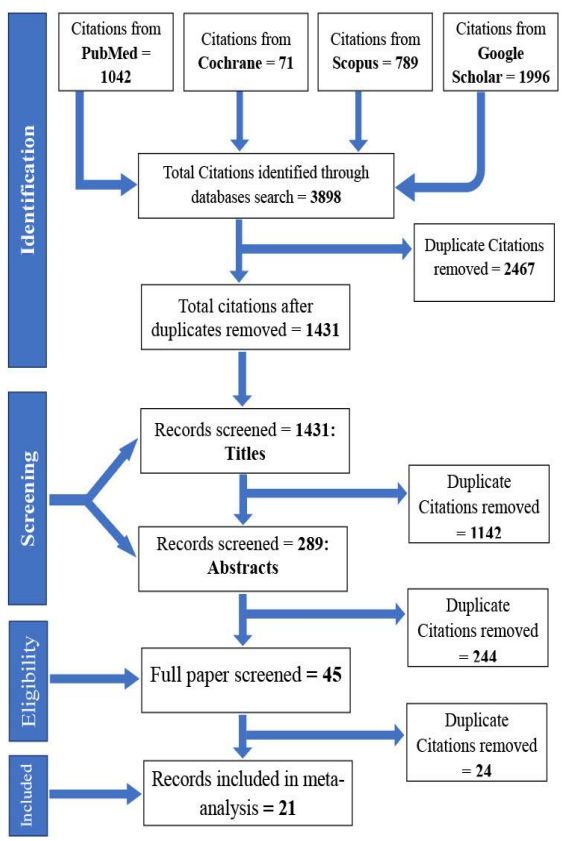

Figure 1. Flow diagram showing the selection process for inclusion of publications in the review

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receiving ART compared to those who were ART-naïve; diabetes (6.7% vs. 6.5%), hypertension (36.6% vs. 26.6%), Total Cholesterol (41.1% vs. 16.3%), Triglycerides (53.5% vs. 32.5%), and LDL-Cholesterol (62.3% vs. 34%), respectively (Table 2). Figure 2 shows the prevalence of CVD risk factors among ART-positive and ART-naïve patients.

Fifteen studies assessed the impact of ART on diabetes [18-31]. There was no significant association between persons on ART and risk of developing diabetes (RR = 0.88, 95% CI: 0.58 - 1.33; Z = 0.61, p = 0.54, I2 = 72%) (figure 3a). Ten studies assessed the impact of ART on Hypertension [18,21,24,25,28,31-33]. ART was found to increase the risk of hypertension significantly (RR = 1.74, 95% CI: 1.21 -

Table 1. Study characteristics

Author	Year	Age Range (years)	Male	Female	Country	Location	Study Design	Sample Size
Fred Stephen Sarfo *et al.*	2018	30 - 75	132	569	Ghana	Facility	Cross Sectional	701
IndumatI V *et al.*	2013	≥20	127	73	India	Facility	Case-Control	200
Nirdesh Jain *et al.*	2013	>18	66	19	India	Facility	Cross Sectional	80
Carey RAB *et al.*	2013	≥20	100	96	India	Facility	Cross Sectional	196
Gibson B. Kagaruki *et al.*	2011	>18	317	354	Tanzania	Facility	Cross Sectional	671
Annie Phoebe Kalyanasundaram *et al.*	2007	>18	167	195	India	Facility	Cross Sectional	363
Jureeporn Jantarapakde *et al.*	2014	>18	268	312	Thailand	Community	Cross Sectional	580
E. M Manuthu *et al.*	2006	≥20	124	171	Kenya	Facility	Cross Sectional	295
Abdurehman Eshete Mohammed *et al.*	2014	21 -75	133	270	Ethiopia	Facility	Cross Sectional	403
Joel A. Dave *et al.*	2012	20 - 50	196	653	South Africa	Facility	Cross Sectional	849
Piconi, Stefania *et al.*	2012	n.s	n.s	n.s	Uganda	Facility	Cross Sectional	79
Solomon Mekonnen Abebe *et al.*	2013	<20	147	320	Ethiopia	Facility	Cross Sectional	467
Emmanuel Maganga *et al.*	2013	>18	156	298	Tanzania	Facility	Cohort	454
Jennifer Manne-Goehler *et al*	2014	>40 years	n.s	n.s	South Africa	Community	Cohort	4547
Robert N Peck	2012	>18	156	298	Tanzania	Facility	Cross Sectional	454
Naomi S Levitt *et al.*	2013	>18	331	549	South Africa	Community	Cross Sectional	880
Alfred Osoti *et al.*	2014	>18	108	192	Kenya	Facility	Cross Sectional	300
Justin R Kingery *et al.*	2012	>18	156	298	Tanzania	Facility	Cross Sectional	454
Eduardo Rodriguez-Arboli *et al.*	2013	>18	34	46	Tanzania	Community	Cohort	80
Piconi, Stefania *et al.*	2012	n.s	n.s	n.s	Uganda	Facility	Cross Sectional	79
JoelA.Dave *et al.*	2015	>18	97	0	South Africa	Facility	Cross Sectional	97

n.s: not specified

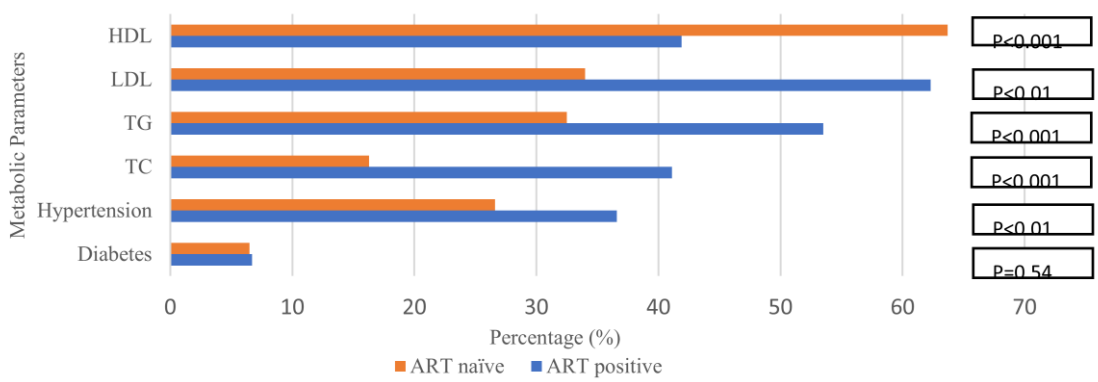
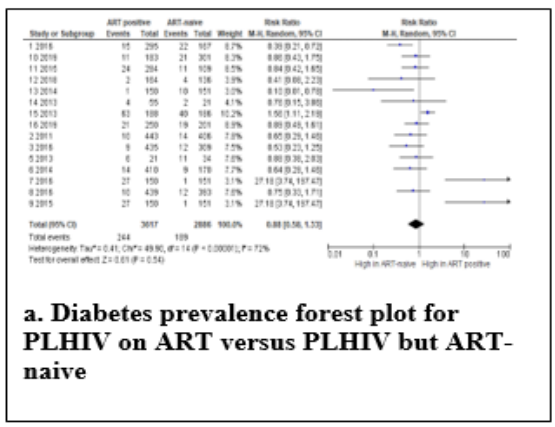


Figure 2. Pooled prevalence of metabolic risk factors among ART naïve and ART patients

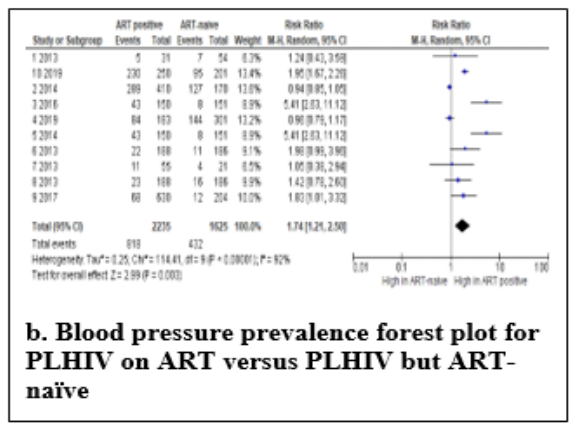
2.50; Z = 2.99, p < 0.01, I2 = 92%) (Figure 3b). Eight studies assessed the impact of ART on triglyceride [18,21,30,31,33-36]. Intake of ART was found to significantly increase the risk of high triglycerides (RR = 1.64, 95% CI: 1.50 - 1.80, Z = 10.4, p < 0.01, I2 = 77%) (Figure 3c). Eight studies assessed the impact of ART on total cholesterol [18,21,30,31,33-36]. Intake of ART was found to significantly increase the risk of high cholesterol (RR = 2.72, 95% CI: 1.75 - 4.23, Z = 4.46, p < 0.01, I2 = 85%) (Figure 3d).

Eight studies assessed the impact of ART on LDL cholesterol [18,30,31,33-37]. Intake of ART was found to significantly increase the risk of high LDL cholesterol (RR = 2.72, 95% CI: 1.75 - 4.23; Z = 4.46, p < 0.01, I2 = 85%) (figure 3e). Eight studies assessed the impact of ART on LDL cholesterol [18,30,31,33-37]. Intake of ART was found to significantly increase the risk of low HDL cholesterol (RR = 0.65, 95% CI: 0.58 - 0.77; Z = 5.48, p < 0.01, I2 = 71%) (Figure 3f).

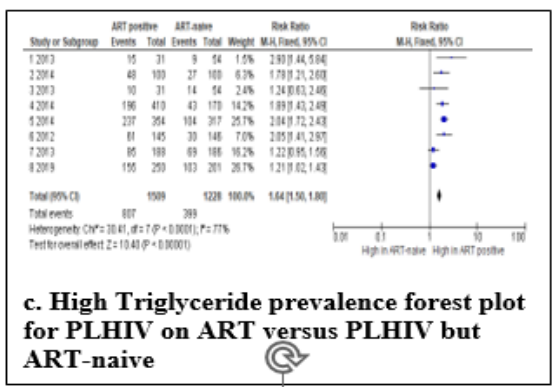
In our sensitivity analysis for comparison of the prevalence of diabetes in PLHIV on ART versus ART-naïve, we observed minimal shifts in the pooled risk ratios upon the sequential exclusion of each study. For instance, excluding Study 15 (2013) resulted in a slight increase in the pooled



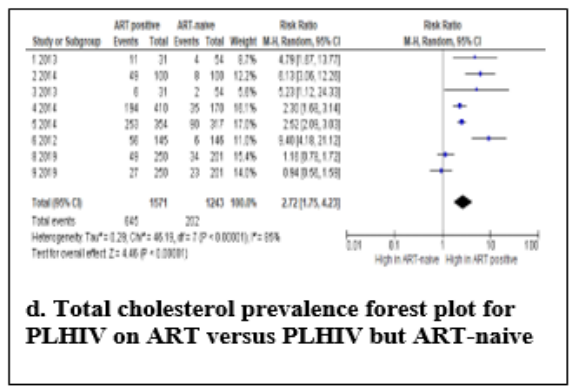
a. Diabetes prevalence forest plot for PLHIV on ART versus PLHIV but ART-naive



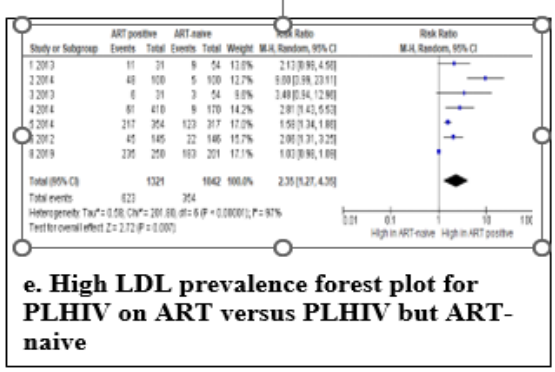
b. Blood pressure prevalence forest plot for PLHIV on ART versus PLHIV but ART-naïve



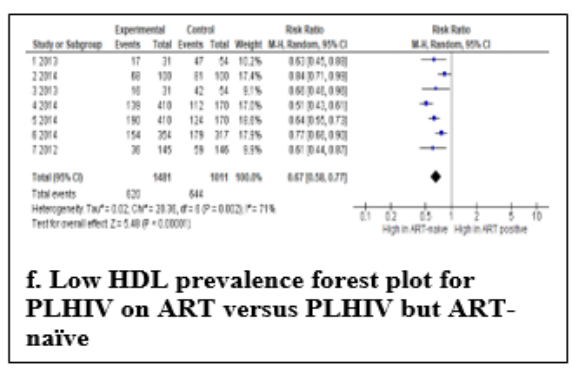
c. High Triglyceride prevalence forest plot for PLHIV on ART versus PLHIV but ART-naive



d. Total cholesterol prevalence forest plot for PLHIV on ART versus PLHIV but ART-naive



e. High LDL prevalence forest plot for PLHIV on ART versus PLHIV but ART-naive



f. Low HDL prevalence forest plot for PLHIV on ART versus PLHIV but ART-naïve

Figure 3. Forest plots on the prevalence of a. diabetes, b. hypertension, c. High triglycerides, d. High total cholesterol, e. High LDL and Low HDL for PLHIV on ART versus PLHIV but ART-naïve

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RR from 0.88 to 0.89, with the confidence intervals slightly narrowing from 0.58 - 1.33 to 0.59 - 1.22. These minor changes suggest that our findings are robust and not overly dependent on any single study.

To assess the impact of potential biases on our findings, we conducted a Risk of Bias (RoB) assessment using the Newcastle-Ottawa Scale (NOS). Studies with a high risk of bias were further examined in a sensitivity analysis by removing them to evaluate their influence on the pooled estimates. The results remained consistent, indicating that studies with a high risk of bias did not significantly drive the observed associations. Similar patterns were observed across other outcome variables analysed, reinforcing the stability and reliability of our meta-analytic conclusions.

DISCUSSION

This review evaluated the effect of ART exposure on CVD risk factors in LMICs, where such investigations have been sparse. Except for diabetes, the review found significant associations between antiretroviral therapy (ART) and cardiovascular disease (CVD) risk factors (hypertension, diabetes, and dyslipidemia). The average risk of CVD for PLHIV receiving ART was nearly two-fold, relative to treatment-naïve PLHIV. While some systematic reviews reported that ART did not increase the risk of hypertension among PLHIV [38], other studies have shown an increased risk of CVD among PLHIV on protease inhibitor-based ART [39-41]. Indeed, a more recent study by Nartey et al. [61] estimated a 10-year moderate-to-high CVD risk using the DAD score at 52.4%, whereas the prevalence of hypertension among ART-exposed individuals was reported to be 42.4% (95% CI, 36.2 - 48.8) [62].

There was no evidence of a link between ART use and diabetes. This finding is comparable to the reports by Dimala et al. [38] and Dillon et al. [42], which found no association between ART use and blood sugar levels. In contrast, Brown and others [43], Tien et al. [44], and De Wit et al. [45] found that receiving antiretroviral therapy was associated with a higher likelihood of developing diabetes. Perhaps the inconsistency arises from differences in sample size rather than a methodological weakness. Essentially, Brown et al. [43] and Tien et al. [44] used HIV-negative clients as their control group. Thus, we could not conclusively attribute the association to antiretroviral treatment as posited by others [47,48]. Again, it should be noted that the cited studies [43-45] drew participants from different parts of the globe, North and South America, Europe, and Australia, but did not include any LMIC. Hence, variation in ethnicity and glucose metabolism appears to be a concern and presents bias, leading to doubtful internal validity. Even though the study showed no evidence of an association between antiretroviral therapy and diabetes, the meta-regression analysis did not indicate that the studies' quality was a likely explanation for the heterogeneity observed.

The present review found a significant association between antiretroviral therapy and hypertension. Patients on ART were found to have about 75% odds of having hypertension compared to their counterparts who were not on ART. This is similar to the findings of Dimala et al. [38], who reported that people living with HIV on ART showed 90% odds of having hypertension compared to people living with HIV who are not on antiretroviral therapy. In another study, Ekali et al. found that there was no association between antiretroviral therapy and hypertension, yet hypertension prevalence increased significantly as the duration of treatment increased [50]. The study, therefore, concluded that the lack of association observed between ART and hypertension could be explained by the inclusion of participants who had been on ART for a short duration. Pacacios and others cautioned that any relationship between blood pressure and antiretroviral treatment is contingent on time and treatment duration [51,52]. Nevertheless, earlier review reports also found that hypertension was significantly higher in people living with HIV on ART compared to those who are ART-naïve [53]. The effect of antiretroviral therapy on blood pressure should be recognised and addressed with other factors such as genetic, lifestyle, and environmental predispositions to hypertension.

The current review also found that there was a strong link between antiretroviral therapy use and abnormal lipid profile, indicating that patients on ART treatment are at a higher risk of developing cardiovascular disease risk factors. ART-positive patients had significantly higher concentrations of low-density lipoprotein cholesterol, total cholesterol, and triglycerides compared with ART-negative patients. These findings are very consistent with those reported in other systematic reviews associating ART with dyslipidaemia [38,54,55]. In a review of studies in Sub-Saharan Africa, Dillon et al. [4] found no significant link between ART and high TG and indicated that this was likely due to the increasing usage of non-nucleoside reverse transcriptase inhibitors (NNRTIs) based ART compared to protease inhibitors (PI) based ART, which are known to be associated with dyslipidaemia [42]. The majority of studies did not report the precise extent of patients on specific ART regimens, hence our inability to study associations between various ART agents and individual cardiovascular disease risk factors. Other studies reported the use of NNRTIs over PIs, as they constitute first-line medications in sub-Saharan Africa [38]. Associations between antiretroviral therapy and cardiovascular disease risk factors in areas with mainly PI-based ART are associated with more extreme dyslipidaemic profiles compared to NNRTIs [56-58].

Several processes have been identified as plausible ART pathways that mediate metabolic irregularities, including increased circulating inflammatory markers, chronic inflammation caused by HIV infection, and cytokines implicated in insulin and lipid control [59,60]. The relationship between ART and specific cardiovascular disease risk factors, while showing little influence on

others, suggests that the overall effect of antiretroviral therapy in PLHIV depends on the complexity and mix of factors, such as heredity and environmental predispositions [38]. The clinical implications of these findings are significant and hence suggest a paradigm shift in the management of HIV in LMICs, from a singular focus on virologic suppression to a more holistic, integrated model of chronic disease care. For healthcare providers, this necessitates the routine integration of cardiovascular risk assessment into standard HIV care. Simple, low-cost interventions such as regular blood pressure monitoring and counselling on lifestyle modifications, including diet, physical activity, and smoking cessation, should become standard practice.

Furthermore, where feasible, periodic lipid screening should be conducted, particularly for patients on long-term ART or those with other known CVD risk factors. These findings should also prompt national HIV programmes and guideline committees in LMICs to develop and disseminate clear protocols for the prevention, screening, and management of hypertension and dyslipidaemia within HIV treatment settings. This approach aligns with recent World Health Organisation (WHO) guidance on integrated NCD-HIV care, ensuring that the long-term health of PLHIV is preserved as life expectancy increases. A significant limitation of this study is the inability to perform subgroup analyses based on specific ART regimens (e.g., protease inhibitors vs. NNRTIs) or treatment duration, as this data was inconsistently reported across the included studies. These are important variables that could potentially vary CVD risk levels among PLHIV. Furthermore, this review was limited to studies published in English and indexed in specific databases, which may introduce publication and language biases.

Conclusion

There is evidence of an association between antiretroviral therapy and the development of cardiovascular disease risk factors (hypertension, dyslipidemia, triglyceride concentration, LDL, and total cholesterol) in Low and Middle-Income Countries (LMICs). Our findings can form the basis of developing structured education to prevent or minimise CVD risk factors among PLHIV, particularly in LMICs. The findings also underscore the urgent need for integrating routine cardiovascular risk screening, including blood pressure monitoring and lipid profile assessment, into standard HIV care protocols, a strategy consistent with the WHO framework for people-centred, integrated health services.

DECLARATIONS

Ethical consideration

Ethical approval was not required for this study as it was a systematic review and meta-analysis of previously published data. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with ID CRD42018084661.

Consent to publish

All authors agreed on the content of the final paper.

Funding

None

Competing Interest

The authors declare no conflict of interest

Author contribution

KA and AL conceived and designed the study. KA conducted the literature search, performed the analysis, and drafted the manuscript. FA, JA, and AL contributed to data extraction, while JA and FA contributed to the discussion. AL, KT, and AK provided critical input during manuscript revision. All authors read and approved the final version of the manuscript.

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Availability of data

Data is available upon request to the corresponding author

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