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Endothelial dysfunction and cardiovascular diseases in people living with HIV on specific highly active antiretroviral therapy regimen: A systematic review of clinical studies

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ABSTRACT

Despite the improved efficacy of highly active antiretroviral therapy (HAART) in viral suppression, emerging evidence indicates an increased burden of noncommunicable diseases in people living with HIV (PLWH). Immune activation and persistently elevated levels of inflammation have been associated with endothelial dysfunction in PLWH, likely contributing to the development of cardiovascular diseases (CVDs). Here, electronic search databases including PubMed, Google Scholar, Cochrane Library, and Science Direct were used to retrieve scientific evidence reporting on any association between markers of endothelial function and CVD-related outcomes in PLWH on HAART. Extracted data was subjected to quality assessment using the Downs and Black checklist. Most (60 %) of the results indicated the presence of endothelial dysfunction in PLWH on HAART, and this was mainly through reduced flow mediated dilation and elevated serum makers of adhesion molecules like ICAM-1, VCAM-1, and P-selectin. The summarized evidence indicates an association between persistently elevated markers of endothelial dysfunction and a pro-inflammatory state in PLWH on HAART. Only a few studies reported on improved endothelial function markers in PLWH on HAART, while limited evidence is available to prove that endothelial dysfunction is associated with CVD-risk, which could be attributed to therapeutic effects of HAART. Limited studies with relatively high quality of evidence were included in this systematic review. In conclusion, results from this review lay an important foundation for future research, even a meta-analysis, that will improve the understanding of the contributing factors to the burden of CVDs in PLWH on HAART.

1. Introduction

It has been more than four decades since the human immunodeficiency virus (HIV) was first discovered [1]. However, this condition continues to be one of the leading causes of death in low- and middle-income countries, especially those in the sub-Saharan Africa [2]. With the World Health Organization (WHO) documenting about 38.4 million active cases of HIV globally at the end of 2021 [3]. The Joint United Nations Programme on HIV/Acquired Immune Deficiency Syndrome (UNAIDS) indicates approximately 7.5 million active cases in South Africa alone [2]. HIV describes a compromised immune response that hinders the body's ability to fight-off or recover from infection. However, the discovery of nucleoside reverse transcriptase inhibitors (NRTIs) proved important for the early treatment of HIV [4,5]. The early availability of this class of drugs was fundamental for advancements in new generations of antiretroviral drugs, especially the discovery of

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highly active antiretroviral therapy (HAART) [5]. The latter describes a combination of drugs from at least two different classes, including protease inhibitors (PIs) and currently remains the leading regimen for the management of HIV [6].

The benefits of HAART in prolonging the lives of people living with HIV (PLWH) are well-known [7,8], however emerging evidence indicates that continued use of this combination therapy may render the endothelium susceptible to damage that may lead to endothelial dysfunction [9–11]. This consequence describes diminished vasodilation and vasoconstriction that is likely to be accompanied by coagulation and a prothrombotic state [12,13]. Available evidence already indicates the importance of flow mediated dilation (FMD) as a non-invasive measure of endothelial dysfunction to predict cardiovascular disease (CVD)-risk in PLWH on HAART [14]. People living with HIV (PLWH) present with an increased CVD risk when compared to individuals without the virus, especially in the presence of other comorbidities such as obesity, diabetes, hypertension, and kidney diseases [15–17]. Plasma levels of oxidative products and pro-inflammatory markers, including high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-6, as well as reduced nitric oxide (NO) bioavailability are all considered viable predictors of endothelial dysfunction [18–20]. Cellular adhesion molecules (CAMs), including E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) can also serve as biomarkers to predict endothelial dysfunction [21,22]. Due to ongoing research indicating a rising toll of cardiovascular-related complications in PLWH [23,24], it has become essential to determine whether prominent biomarkers of endothelial dysfunction can be used to predict CVD-risk in PLWH, especially those on HAART.

This systematic review contributes to already available evidence that is meant to underscore the importance of factors that lead to increased risk of CVD in PLWH on HAART [25,26]. It systematically evaluates literature of scientific studies reporting on any association between markers of endothelial function and CVD-risk in PLWH on HAART. Specific emphases are placed on understanding the potential correlation between endothelial dysfunction and CVD-risk in PLWH on HAART.

2. Methodology

This systematic review was compiled following the Cochrane Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (Supplementary file 1). The updated Cochrane Handbook for Systematic Reviews of Interventions guidelines were followed [27]. The systematic review was not registered with the International Prospective Register for Systematic Reviews (PROSPERO), but this database and other online registries were searched to make sure this review is not replicated.

2.1. Search strategy

Electronic databases including PubMed, Google Scholar, Cochrane Library, and Science Direct were searched to retrieve relevant literature. This included scientific studies, from 1996 until June 2023, reporting on any association between markers of endothelial function and CVD-related outcomes in PLWH on HAART. The primary search was conducted through PubMed, using advanced search and clinical queries adjusting for keywords and clinical subject headings (Supplementary file 2). Keywords and subject headings (including relevant synonyms) used during the search included ‘endothelial function’, ‘human immune deficiency virus’, ‘inflammation’, and ‘highly active antiretroviral therapy’.

2.2. Eligibility criteria

The review included primary publications reporting on endothelial function among PLWH on HAART. We specifically included clinical studies, randomized controlled trials, cross-sectional, cohort, retrospective, case-control, and longitudinal studies on PLWH on HAART (≥18 years old). Studies reporting on PLWH who were HAART-naïve as their main study population with HIV-negative individuals as their control group were excluded from our pool of interest. Moreover, studies reporting on PLWH on HAART with cancer, neuropathies, and those with existing CVD-risk including hypertension, diabetes mellitus, coagulopathies, and lipodystrophy with its associated symptoms were also excluded. We further excluded PLWH on HAART who were pregnant, lactating, those making use of children, and those reporting on individuals taking other drugs such as statins and aspirins to recover endothelial function. The focus of the current review was on clinical applications; hence animal and in-vitro studies were excluded. Publications not in the English language were excluded, provided they could not be translated. Studies were deemed relevant if they reported on indicators or measurements of endothelial function, including FMD, as well as biomarkers like E/P-selectin, ICAM-1, and VCAM-1. Since both oxidative stress and inflammation are major pathological features of endothelial dysfunction [28,29], levels of malondialdehyde (MDA), hs-CRP, TNF-α, IL-6, as well as NO bioavailability were also assessed as potential contributors to endothelial dysfunction and CVD-risk. The current study was conducted to address the following: Patient/-population, Exposure, Comparison, and Outcomes (PECO).

2.2.1. Population

Study population included PLWH (≥18 years of age).

2.2.2. Exposure

PLWH on any type of HAART regimen, including drug combinations of atazanavir (ATV), ritonavir (RTV), lopinavir (LPV), efavirenz (EFV), tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC).

2.2.3. Comparison

Studies reporting on PLWH on HAART and HAART-naïve or HIV-negative individuals.

2.2.4. Outcome/s

Primary outcomes were indicators and markers of endothelial function. Secondary outcome was CVD-related outcomes, including markers of oxidative stress and inflammation.

2.3. Data extraction and quality assessment

The main extracted data items from eligible studies included the type of HAART regimen used and exposure period, as well as study outcomes/key findings on the status of endothelial function in PLWH on HAART. Other extracted items were sample size, country, as well as CD4 count and viral load of study participants (Supplementary file 3). Importantly, data on risk factors of endothelial dysfunction and CVD-risk including the age, sex, and ethnicity of participants were extracted from all the eligible studies.

2.4. Quality assessment

The quality of evidence for all the included studies was independently assessed using the Downs and Black Checklist (Supplementary file 4) [30]. The adopted checklist consisted of twenty-seven (27) domains, which are efficient at informing on the quality of evidence. For all the included studies, quality assessment was based only on the data available in the published full-text article. Two authors independently assessed the quality of evidence of each article, while disagreements were addressed by consulting a third author. Rater agreement expressed as a Cohen’s Kappa (K) value was determined using IBM Statistical Package for the Social Sciences (SPSS) version 29.0, to verify the validity and reliability of the rater outcomes.

3. Results

3.1. Characteristic features of included studies

The search strategy and selection process for eligible studies is demonstrated in Fig. 1. The search strategy of online databases initially identified 393 related records. However, after removing nonqualifying studies, only ten clinical studies were deemed suitable and included in this systematic review. All included studies reported on endothelial function and relevant CVD-related parameters in PLWH on HAART. In terms of regional distribution, most studies were from the United States (n = 4) and Switzerland (n = 2), while other countries presented with one study, including South Africa (n = 1), Denmark (n = 1), France (n = 1), and Botswana (n = 1). In terms of sex and age, 70 % of the participants were male, with an average age of 40 years (Table 1). With included evidence further showing that NRTI base regimen was the most prescribed HAART (n = 7 studies), which was followed by PI-base regimen (n = 6 studies) (see Fig. 2).

3.2. Quality of included studies

The quality of included studies (n = 10) was assessed using the modified Downs and the Black checklist. Majority of the studies had good quality of evidence, with one study [31] classified as having excellent quality after rating 25 out of 27 possible scores. Two studies had the lowest rating (17 and 18 scores out of 27 possible scores) but were classified as having fair quality of evidence. Based on the 5 evaluated domains, all studies had excellent reporting bias, with a median of 10 (9–11) out of 10 possible scores and a good rater agreement (Cohen's kappa) value of (K = 0.58) between two independent reviewers, and external validity with a median of 2 (0–2) out of the three possible scores and a slight rater agreement value (K = 0.14). The included studies had good internal validity, demonstrated by a median score of 5 (4–6) out of 7 possible scores (K = 0.41) and a median of 4 (2–6) out of the 6 possible scores (K = 0.25). All studies had great power of ≥90 % indicating that these studies had no errors of omissions (type 2 error) to their findings, as supported by a median score range of 1 (0–1) and a (K = 1.0) (Supplementary file 5).

3.3. Conflicting evidence on the status of endothelial dysfunction in PLWH on HAART

There is a considerable interest in understanding the status of CVD risk in PLWH, especially the role of endothelial function as a major predictor of cardiac abnormality [26,41,42]. A PubMed search shows a rapid growth in studies that have been published reporting on markers of endothelial function in PLWH on HAART [42–44]. With summarized evidence showing a potential role of endothelial dysfunction in PLWH

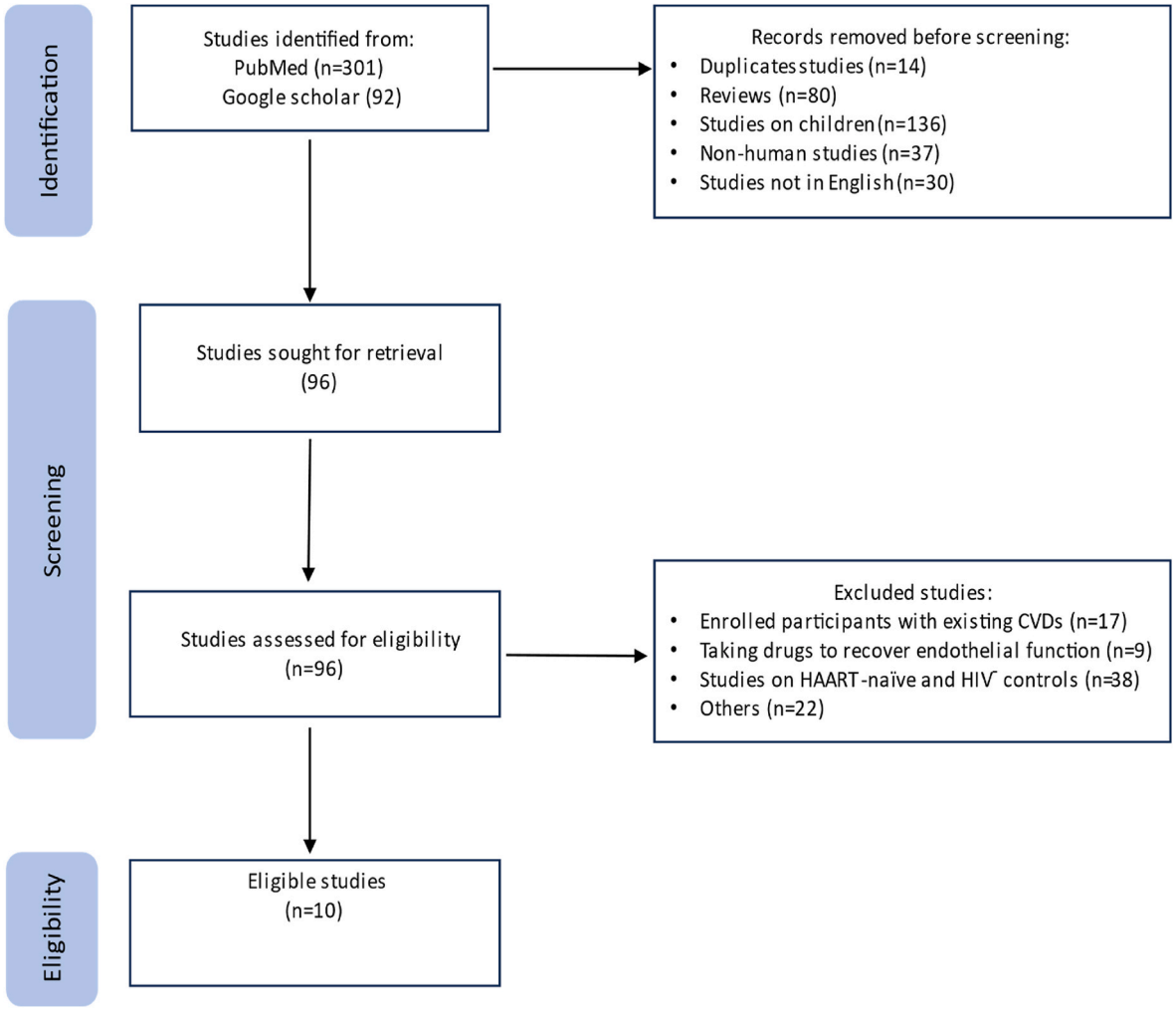

Fig. 1. Flow diagram depicting study selection and inclusion process. Briefly, the search strategy of online databases initially identified 393 related records on PubMed, Google Scholar, Cochrane Library, and Science Direct. However, after removing duplicates and irrelevant studies, only ten clinical studies were deemed suitable and included in this systematic review. All incorporated studies reported on the modulation of endothelial function and relevant cardiovascular disease-related parameters in PLWH on HAART.

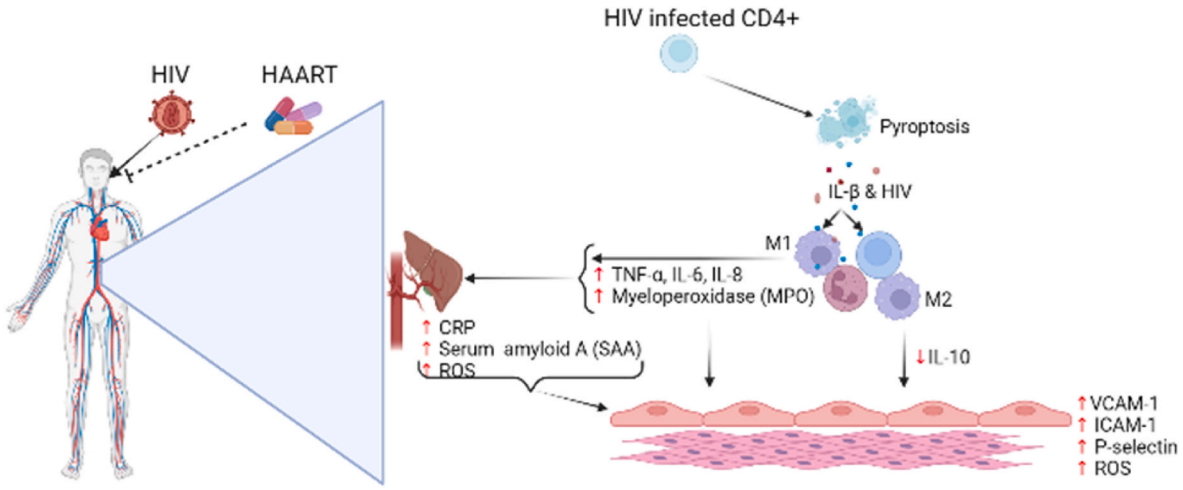

Fig. 2. Upon infection with HIV, the virus infiltrates cluster differentiation positive ($CD4^+$) T-lymphocytes and induce pro-inflammatory intracellular micro-environment marked by increased IL-β. The $CD4^+$ T-lymphocytes undergo pyroptosis showering adjacent uninfected immune cell (including $CD4^+$ T-lymphocytes) with IL-1β and new viral cells. Interleukin-1β activates M1 macrophages to secrete pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) and neutrophils to release myeloperoxidase (MPO). The increased release of pro-inflammatory cytokines stimulates hepatocytes to release the acute phase response proteins serum amyloid A and C-reactive proteins, while elevated levels of MPO promotes the formation of reactive oxygen species (ROS). pro-inflammatory cytokines (IL-6, IL-8, and TNF-α), MPO, and the cute phase response proteins induces endothelial activation marked by elevated serum levels of VCAM-1, ICAM-1, P-selectin, and endothelial ROS. Sustained secretion of pro-inflammatory cytokines (IL-6, IL-8, and TNF-α), MPO, acute phase response proteins, and ROS overpowers the anti-inflammatory response pathway by M2 macrophages preceding chronic inflammation and endothelial dysfunction (Created with BioRender.com).

on HAART (Table 1). However, the presented evidence indicated some conflicting results, with many factors potentially contributing to this outcome. For example, earlier evidence by Stein et al. [32] indicated that PLWH present with endothelial dysfunction, marked by reduced FMD after taking HIV PIs or NRTIs for a period of ≥6 months. Flammer et al. [31] also did not show any improvement in endothelial function as measured using FMD after taking zidovudine for up to 6 months. Murphy et al. [36] did not see any effect on endothelial function in PLWH measured by FMD after switching from RTV to ATV for 6 months. Kristoffersen et al. [35] affirmed these results, showing that PLWH present with endothelial dysfunction as seen with reduced FMD after taking a combination therapy of TDF/FTC/EFV, 3TC/ZDV/EFV, 3TC/ABC/EFV or TDF/FTC/RAL, in which the study participants were monitored for 24–67 days. Mosepele et al. [39] also showed that PLWH presented with endothelial dysfunction, marked by elevated ICAM-1 and VCAM-1 after taking NNRTIs or a combination of TDF/3 TC, ZDV/3 TC, or ABC/3 TC for 14 months. Although these findings suggest the presence of endothelial dysfunction in PLWH on HAART, there were fewer participants (12–145) enrolled in these studies.

Other included studies within the current review do support improved outcomes in markers of endothelial function in PLWH on HAART (Table 1). For example, Torriani et al. [33] showed that PLWH on HAART presented with improved endothelial function demonstrated by increased FMD after taking NRTIs plus EFV or LPV/r for up to 6 months. A follow up study by Calmy et al. [34] showed that PLWH presented with a marked decrease in markers of endothelial dysfunction, including VCAM-1, P-selectin, leptin, and D-dimer after taking RTV boosted SQV/d4T, TDF/3 TC, and TDF/FTC for up to 3 months. Kumar et al. [37] also showed a favourable decline in thrombotic activity (marked by D-dimer) and endothelial activation (marked by VCAM-1) in PLWH after taking FPV/RTV or EFV/ABC/3 TC for up to 24 months. Such positive effects are also confirmed in PLWH by Porith et al. [38], after taking ZDV/RTV plus a fixed combination of either ABC/3 TC or FTC/TDF for 24 months. Interestingly, recent studies by different groups [39,40] indicate that NNRTI or PIs can improve endothelial function by reducing markers such as FMD, ICAM-1 and VCAM-1, when used for a period of 14–18 months. Notably, the duration of these studies spanned from as short as 24 days, up to 24 months, however with most studies reporting a duration of 6 months. And study duration was evenly distributed between those indicating the negative or positive effects of HAART on endothelial function in PLWH.

3.4. *HAART may potentially lower CVD-risk in PLWH on HAART*

Since endothelial dysfunction may potentially serve as a predictor of cardiovascular abnormality (Hadi et al., 2005), it was important to determine whether elevated markers of endothelial dysfunction were linked to CVD-related outcomes in PLWH on HAART. Noteworthy, fewer of the included studies (n = 4) support the notion that endothelial dysfunction is not linked with CVD-risk in PLWH on HAART [31,35–37]. The introduction of HAART for viral suppression, contributed to enhanced endothelial health, blocking the development of atherosclerosis. Atherogenic factors as well as diminished maximal myocardial perfusion were predominant markers to indicate CVD-risk in PLWH on HAART (Table 1). Whereas the predominantly used HAART regimen consisted of a varied combination of ATV-free PIs, TDF/FTC or (3 TC)/EFV, 3TC/ZDV/ABC, TDF/FTC/RAL, and ATV, which was for a period of 6–24 months [31,35–37]. Notably, a study by Stein et al. [32] provided the only evidence indicating that increased CVD-risk was consistent with endothelial dysfunction in PLWH on HAART, as shown by increased levels of total cholesterol, triglyceride, and very low-density lipoprotein (vLDL). Here, the type of HAART regimen (because this evidence is about two decades ago), or even the study design being a non-randomized control trial, could be a contributing factor in such negative results. Nonetheless, well-designed additional studies are required to verify these findings.

3.5. *Implications of oxidative stress and inflammation during endothelial dysfunction in PLWH on HAART*

Oxidative stress and inflammation are the leading pathological complications that are increasingly linked with the development of endothelial dysfunction [45,46], well beyond its role in causing other CVD-related complications [46]. Thus, it remained essential to establish whether there is a link between elevated markers of oxidative stress and inflammation with endothelial dysfunction in PLWH on HAART. Notably, only one study reported on oxidative stress, through oxidised LDL, which was in PLWH on HAART [31]. Oxidised LDL characterizes a

Table 1
A synopsis of studies reporting on endothelial dysfunction and cardiovascular disease (CVD)-risk in people living with human immunodeficiency virus (HIV) on highly active antiretroviral therapy (HAART).

Author, year	Country	Study design	Study population	Type of HAART regimen	Key findings
[32]	United States	Cross-sectional study	PLWH (n = 37) on HAART, with an average age of 42 years (81 % male), without chronic lifestyle diseases. No reported ethnicity	1 participant took amprenavir (APV), 11 indinavir (IDV), 6 nelfinavir (NFV), 2 RTV, 6 saquinavir (SQV), 2 abacavir (ABC), 3 didanosine (ddI), 18 lamivudine (3 TC), 8 stavudine (d4T), 6 zidovudine (ZDV), 2 delaviridine (DLV), and 3 nevirapine (NVP). Participants were monitored for ≥6 months	Participants presented with increased total cholesterol and triglyceride levels, characterized by high concentrations of very low-density lipoprotein (vLDL). This was followed by endothelial dysfunction marked by impaired flow mediated dilation (FMD)
[33]	United States	Randomized controlled trial	PLWH (n = 82) on HAART, with an average age of 35 years (91 % male). Mixed ethnic groups, White (54 %), Black/Asian (32 %), and Hispanic (15 %)	NRTIs plus EFV, NRTIs plus lopinavir/ritonavir (LPV/r), or a NRTI-sparing regimen of EFV plus LPV/r. Participants were monitored for up to 6 months	Participants presented with improved endothelial function demonstrated increased FMD
[34]	Switzerland	Randomized controlled trial	PLWH (n = 145) on HAART, with an average age of 34 years (62 % females). Thai (100 %) ethnicity	RTV boosted SQV/d4T, TDF/3 TC, TDF/FTC. Participants were monitored for up to 6 months	Participants presented with marked decrease in markers of endothelial dysfunction, soluble- vascular cell adhesion molecule 1 (VCAM-1), P-selectin, leptin, and D-dimer, whereas mediators of anti-inflammation like adiponectin and interleukin (IL)-10 were increased after initiation of HAART. However, this effect was diminished at 12 weeks after randomization, and even associated with increase in plasma HIV-RNA
[31]	Switzerland	Randomized controlled trial	PLWH (n = 39) on HAART, with an age between 18 and 65 years (77 % male). No reported ethnicity	20 participants taking ATV and 19 were on ATV-free PIs. Participants were monitored for up to 3 months	Participants on ATV presented with more pronounced effect in improved lipid profiles, including total cholesterol, high-density lipoprotein (HDL), and triglycerides. This included oxidised LDL, accompanied by endothelial dysfunction as shown by reduced FMD
[35]	Denmark	Longitudinal study	PLWH (n = 12) on HAART, with an age between 18 and 60 years (100 % male). White (100 %) ethnicity	9 participants were on TDF/FTC/EFV, 1 took 3TC/ZDV/EFV, 1 took 3TC/ABC/EFV, and 1 took TDF/FTC/raltegravir (RAL). Participants were monitored before and 5 weeks (24–67 days) after initiation of ART	Participants presented with reduced maximal myocardial perfusion and decreased myocardial perfusion reserve soon after initiating HAART. This was accompanied by endothelial dysfunction as seen with reduced FMD
[36]	United States	Randomized controlled trial	PLWH (n = 50) on HAART, with an average age of 43 years (84 % males). White (66 %) ethnicity	26 participants switched to ATV (all continued RTV); 24 remained on their PIs. Participants were monitored for up to 6 months	Participants switched to zidovudine presented with improved total cholesterol, triglycerides, and HDL levels. However, endothelial function as measure by FMD was not affected, including inflammatory and metabolic markers
[37]	United States	Randomized controlled trial	PLWH (n = 101) on HAART, with an average age of 34 years (68 % male). Mixed ethnicity, African American (60 %), Hispanic (38 %), and Asian (2 %)	51 participants took fosamprenavir (FPV)/RTV; 50 took EFV/ABC/3 TC. Participants were monitored after 24 months	Participants presented with improved cardiovascular biomarkers. This included favourable decline in thrombotic activity (marked by D-dimer) and endothelial activation (marked by VCAM-1). However, inflammation increased as reflected by high sensitivity C-reactive protein (hs-CRP)
[38]	France	Randomized controlled trial	PLWH (n = 44) on HAART, with an average age of 41 years (93 % male). No reported ethnicity	ZDV/RTV (300/100 mg), plus a fixed combination of either ABC/3 TC (600/300 mg) or FTC/TDF (200/245 mg) for 24 months	Participants presented with stable markers of inflammation (hs-CRP, IL-6) and endothelial activation (VCAM-1) during the treatment period
[39]	Botswana	Randomized controlled trial	PLWH (n = 112) on HAART, with an average age of 40 years (51 % females). Black African (100 %) ethnicity	In addition to a nonnucleoside reverse transcriptase inhibitor (NNRTIs) (73 %) or PI (26 %), the HAART regimen backbone consisted of either TDF/3 TC (49 %), ZDV/3 TC (47 %), ABC/3 TC (2 %) or 3 TC (2 %) for 14 months	Participants presented with endothelial dysfunction, marked by elevated intercellular adhesion molecule 1 (ICAM-1) and VCAM-1. Monocyte activation marker (sCD163) was also associated with increased ICAM-1. However, inflammatory marker, IL-6 was not affected
[40]	South Africa	Case-control	PLWH (n = 100) on HAART, with an average age of 43 years (75 % female). Black African (100 %) ethnicity	TDF/FTC/EFV or TDF/3TC/EFV Participants were monitored over 18 months	Participants presented with comparable markers of endothelial dysfunction and cardiometabolic profiles to HIV-free individuals. The %FMD was reduced in some participants, based on socio-economic differences

variety of alterations for both lipid and apolipoprotein B components, which can promote atherosclerosis through the formation of macrophage foam cells [26,47]. Alternations in both inflammatory and immunologic mechanisms is fundamental during this process [48]. The summarized evidence showed that anti-inflammatory factors including adiponectin and IL-10 were reduced after initiation of HAART (a combination of RTV boosted SQV/d4T, TDF/3 TC, and TDF/FTC) in PLWH [34]. This is in agreement with evidence by Porith et al. [38], which showed that inflammatory (hs-CRP, IL-6) and endothelial activation (VCAM-1) markers were stable in PLWH after taking ZDV/RTV, plus a

fixed combination of either ABC/3 TC, or FTC/TDF for 24 months. These findings are however inconsistent because others have reported the opposite effects. With two studies [36,39] not showing any changes in inflammatory markers incorporating IL-6, IL-8, and TNF-α, while monocyte activation marker (sCD163) was linked with increased ICAM-1 in PLWH on HAART [39]. Further showing that different factors, especially socio-economic status in some populations, may negatively influence the effect of HAART in PLWH (Table 1). For example, Swart et al. [40] observed no significant differences in endothelial function between PLWH on HAART and HIV-free black South Africans with an average age of 43-years, while Mosepele et al. [39] observed that black Africans from Botswana with an average age of 40-years on HAART present with endothelial dysfunction. Swart et al. [40] further motivated that some of the study participants presented with endothelial dysfunction due to socio-economic differences. There is a need for additional studies to affirm the beneficial effects of HAART on reducing inflammation to further protect against endothelial dysfunction in PLWH.

4. Discussion

This review systematically discusses the close association in clinical evidence reporting on endothelial dysfunction, or its markers thereof, and CVD-risk in PLWH on HAART. Through the search of electronic databases, ten studies were identified to match the inclusion criteria, showing conflicting evidence on the modulation of markers of endothelial function in PLWH on HAART. Importantly, it was evident that most studies showed elevated makers of endothelial dysfunction in PLWH on HAART, including reduced FMD, which might be concurrent with increased serum makers incorporating ICAM-1, VCAM-1, and P-selectin (Table 1). In terms of HAART regimen, it was evident that administering treatment containing TDF, 3 TC, or EFV is associated with either lipodystrophy, inflammation, and/or endothelial dysfunction [32,34,35,39]. Recent evidence indicates persistent immune activation and inflammation in PLWH on HAART, occurring independent of viral suppression [49,50]. Despite these outcomes, it remains of interest to understand whether ethnic differences and other confounding factors hold a pivotal role in the pathogenesis of endothelial dysfunction and associated CVD-risk factors.

To date, there is still ongoing investigations to understand the link between HAART and endothelial dysfunction, both in a cellular and molecular level [15,51,52]. However, it is currently acknowledged that some HAART drug components may be beneficial on the endothelium, whilst some combinations may potentially exacerbate lipodystrophy and inflammation preceding endothelial dysfunction (Mar et al., 2013). For example, Torriani et al. [33] argued that administering HAART containing PIs, especially LPV/r increases blood vessel FMD as a measure of improved endothelial function. Contrary to these findings, Murphy et al. [36] indicated that PI-based regimen containing RTV improved lipid profile but has no apparent effect on endothelial function and inflammation as its associated risk factor. Endothelial dysfunction may be a feature in PLWH on HAART and may explain the increased prevalence of CVDs observed in this population group. However, more studies, looking at a wider pool of CVD-related outcomes are required to confirm this.

A variety of antiretroviral (ARV) drugs independently suppress HIV replication, however, their effectiveness is enhanced with adherence and improved lifestyle modifications [2]. Majority of the identified studies which reported endothelial dysfunction recruited PLWH who were exposed to at least one or more of the following HAART drugs: ATV, EFV, TDF, TFC, and RTV-boosted protease inhibitors. Highly active antiretroviral therapy containing two NRTIs (e.g., ABC/FTC/TDF) and an NNRTIs or a PI could potentially improve endothelial function [33,36,37,53]. However, contradictory findings remain regarding these drug combinations. Also noting that HAART-associated adverse health effects may be intensified by confounding risk factors including ethnicity, sex, and socio-economic status.

5. Study limitations and strengths

The major limitation of the present systematic review was extracting limited studies meeting the inclusion criteria. While another limitation was the diversity of the extracted study designs that could not support the execution of a meta-analysis. This partially implies that a mixture of study designs, including cross-sectional, case-control, and longitudinal studies limited the quality of evidence. Although the outcomes of the included studies were comparable and could be pooled purposefully, the interventions (specific HAART drugs) and comparators across the studies differed which further limited the execution of a meta-analysis. We could not fully address the differences in FMD and inflammation in our study population due to differences reporting across the included studies. Our pool of studies consisted of an uneven gender distribution with male being predominant, which could potentially influence the quality of their conclusions. An even balance gender is important for any analysis, especially to understand the effect of HAART on the vascular endothelium in PLWH. However, the reliability of evidence from the included studies assessed using the Downs and Black checklist indicated that these studies had good reporting bias and reporting power, because some were randomized controlled trials. The qualitative approach in analysing the current data brings strength by taking into consideration the many factors presented by each study before conclusions are drawn. Moreover, the included studies reported on the effects of HAART on the vascular endothelium and the potential manifestation of CVDs over deviating HIV treatment duration, which elevates the reliability of pooled data. These could also potentially explain the contrasting existing evidence on whether HAART promotes endothelial recovery, or it perpetuates endothelial dysfunction.

6. Conclusion

This systematic review acknowledges conflicting evidence informing on the status of endothelial function in PLWH on HAART. Although some evidence shows that elevated markers of inflammation, and those of endothelial dysfunction persists in PLWH, the introduction of HAART may hinder this and protect individuals against CVD-related complications. However, these findings need validation since they are based on very limited evidence, while more research is required to get a better understanding on the pathogenesis of endothelial function in PLWH on HAART at increased risk of developing CVDs.

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Author contribution

Authors, Haskly Mokoena, Sihle E. Mabhida, Joel Choshi, Phiwayinkosi V. Dludla, and Sidney Hanser conceived and contributed to drafting the original manuscript. All other authors, including, Bongani B. Nkambule, Zandile J.R. Mchiza, Duduzile E. Ndwandwe, and André P. Kengne reviewed the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

3 TC	Lamivudine
ABC	Abacavir
APV	Amprenavir
ATV	Atazanavir
CAMs	Cell Adhesion Molecules
CD4 count	Cluster Differentiation 4 Count
CVDs	Cardiovascular diseases
D4T	Stavudine
ddI	Didanosin
EFV	Efavirenz
E-selectin	Endothelial Selectin
FMD	Flow Mediated Dilation
FPV	Fosamprenavir
FTC	Emtricitabine
HAART	Highly Active Antiretroviral therapy
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
Hs-CRP	Highly sensitive C-reactive protein
ICAM-1	Intercellular adhesion molecule-1
IDV	Indinavir
IL-10	Interleukin-10
IL-6	Interleukin-6
K	Cohen's Kappa
LDL	Low-density lipoprotein
LPV/r	Lopinavir boosted ritonavir
LPV	Lopinavir
MDA	Malondialdehyde
NFV	Nelfinavir
NIH	National Institute of Health
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NO	Nitric oxide
NVP	Nevirapine
PECO	Population, Exposure, Comparison, Outcome(s)
PIs	Protease inhibitors
PLWH	People living with human immunodeficiency virus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register for Systematic Reviews
P-selectin	Platelet selectin
RAL	Raltegravir
RTV	Ritonavir
sCD163	Soluble cluster differentiation 163
SPSS	Statistical package for the social sciences
SQV	Saquinavir
TDF	Tenofovir disoproxil fumarate
TNF-α	Tumor necrosis factor-alpha
UNAIDS	United Nations on Acquired Immunodeficiency Syndrome
VCAM-1	Vascular adhesion molecule-1
vLDL	Very low-density lipoprotein
WHO	World Health Organization
DLV	Delavirdine
ZDV	Zidovudine.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.athplu.2024.01.003.

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