

The Pathological Link Between Elevated Markers of Inflammation, Endothelial Activation, and Cardiovascular Diseases in People Living with HIV on Combination Antiretroviral Therapy: A Systematic Review

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Introduction: Despite administering combination antiretroviral therapy (cART), people living with the human immunodeficiency virus (PLWH) have been identified to be at an elevated risk of cardiovascular diseases (CVDs). Notably, inflammation and endothelial activation are likely factors associated with increased CVD risk in PLWH. Thus, the present study reviews evidence reporting on the potential link between increased markers of inflammatory, endothelial activation, and CVD risk in PLWH on cART.

Methodology: Web databases incorporating Cochrane libraries, PubMed, Web of Science, Google Scholar, and ScienceDirect were searched to identify suitable clinical research reports. The validity and reliability of the quality of the included evidence were appraised utilising the Downs and Black checklist.

Results: Fifteen clinical research reports were incorporated within the present study, involving PLWH on cART (n=7117). We classified these research reports based on short-term (≤ 12 months) and prolonged exposure (> 12 months) to cART of PLWH. Overwhelming results showed that short- and long-term exposure to cART are closely associated with elevated markers of inflammation that were consistent with the existence of endothelial activation in PLWH on cART. Prominent inflammatory markers, which were elevated included interleukin-6 (IL-6), high sensitivity C-reactive protein (hsCRP) and tumor necrosis factor alpha (TNF- α). While those indicating endothelial activation included soluble intercellular and vascular adhesion molecule-1 (sICAM-1 and sVCAM-1). The quality of included research reports was relatively high, while there was very limited information on the effect of the specific type of cART.

Conclusion: The current study supports the hypothesis indicating a close association between elevated inflammatory markers and endothelial activation potentially contributing to CVDs in PLWH on cART. However, these effects may be associated with prolonged exposure to cART in conjunction to specific cART-drug regimen combinations. Nonetheless, the available evidence is still very limited, and more research is needed to confirm these findings.

Keywords: inflammation, endothelial activation, combination antiretroviral therapy, human immunodeficiency virus

Introduction

The spread of the human immunodeficiency virus (HIV) continues to increase globally, with 39 million recorded cases to date. Consequently, only 29.8 million of people living with HIV (PLWH) globally are undergoing combination antiretroviral therapy (cART) which prolongs their lifespan.^{1,2} The increase in lifespan among PLWH is accompanied by the manifestation of cardiovascular diseases (CVDs), one of the major factors contributing to increased cases of mortality in PLWH.^{3,4} Emerging evidence indicates that the continued use of cART may be implicated in the manifestation of endothelial activation in PLWH.^{5,6} Endothelial activation is considered as one of the major predictors of CVDs and is characterized by sustained blood vessel constriction, which can subsequently lead to heart failure.^{7,8} Inflammation is the necessary process within the body to respond to an undesired stimulus, however exacerbation of this process may cause undesirable outcomes linked with endothelial dysregulation.⁹ Evidently, there is a close association between elevated inflammatory markers and increased risk of CVDs among PLWH,¹⁰ even independent of cART.^{11,12} However, such evidence remains to be fully understood, especially with the continued or effective use of cART among PLWH.

Several inflammatory markers including interleukin-6 (IL-6), cluster differentiation-14 (CD14), and high sensitivity C-reactive protein (hsCRP) are continuously deliberated on for their potential implication during the development of CVDs in PLWH.^{13,14} In fact, our recent review indicates that elevated circulating levels of hsCRP, together with abnormal lipid profiles, may potentially signal increased CVDs in PLWH on cART, in particular those within the African continent.¹⁵ However, there is still lack of literature reviewing the pathological involvement of a broad spectrum of inflammatory molecules incorporating tumor necrosis factor alpha (TNF- α) in conjunction to its receptors and monocyte chemoattractant protein-1 (MCP-1) during the development of cardiovascular complications in PLWH. This is essential since it has already been established that persistent levels of inflammation are implicated in the development of many diseases,^{16,17} beyond their role during the manifestation of endothelial activation in PLWH.^{18,19}

Within a pathological state, endothelial activation may typically be marked by abnormally increased levels of soluble intercellular adhesion molecule-1 (sICAM-1), vascular adhesion molecule-1 (sVCAM-1), endothelial selectin (sE-selectin), and leukocyte selectin (sL-selectin) in PLWH.^{20,21} Interestingly, this state may persist despite viral suppression in PLWH.²² Thus, it remains essential to review this evidence to understand the potential physiopathology of increased inflammatory and endothelial activation markers in PLWH on cART. Evidence emitting from this systematic review remains essential to inform on relevant markers that could be essential for effective management of PLWH, especially reducing the risk of CVDs that may be linked with sustained exposure to cART-treatment.

Methodology

The present study was assembled following the Cochrane Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), ([Supplementary file 1](#)). Additional guidance in assembling this systematic review was obtained from the updated Cochrane Handbook for Systematic Reviews of Interventions guidelines.²³ It is worth noting that the protocol for the present study was not registered with the International Prospective Register for Systematic Reviews (PROSPERO). However, duplication of existing protocols was avoided by screening online registries including PROSPERO, Cochrane Collaboration, and Cochrane libraries for any similar work.

Search Strategy

To identify clinical research reports in line with achieving the aims and objectives of the present systematic review, a web database search on Cochrane libraries, PubMed, Web of Science, ScienceDirect, and Google Scholar was conducted, until the end of January 2024. The literature search was done by two independent authors, while consulting a librarian when formulating the search strategy ([Supplementary file 2](#)). Medical Subject Headings and key terms used on the web databases incorporated, “inflammation and endothelial activation in HIV”, and “respective inflammatory and endothelial activation markers in HIV”. We imposed restrictions on the year of publication to retrieve clinical research reports published in the last decade (from 2014 until January 2024), looking at any association between inflammation and endothelial activation, as a major predictor of CVDs, in PLWH.^{24,25}

Eligibility Criteria

The principal objective of the present study was to establish a link between levels of inflammatory markers and indicators of endothelial function in PLWH on cART. The comparators were cART-naïve PLWH or HIV-negative persons. Included research reports were of varying designs ranging from pilot, cross-sectional, randomized controlled trials, and observational studies on adults (≥ 18 -years-old) PLWH. Exclusions incorporated review articles, animal studies or literature not outlining markers of inflammation or endothelial function in PLWH on cART, or those reporting on participants with co-infections such as hepatitis virus, tuberculosis, AIDs, and the corona virus, or those with pre-existing CVD-risks such as hypertension, obesity, and diabetes at participant enrolment. The present systematic review was assembled to evaluate the following: Population, Exposure, Comparison, and Outcomes (PECO).

Population

Study population incorporates adult (≥ 18 -years-old) PLWH on cART.

Exposure

Combination antiretroviral therapy (cART) exposed PLWH, with no restrictions on the type of cART regimen. Briefly, these incorporated (but not limited to) drug combinations of efavirenz (EFV), maraviroc (MVC), raltegravir tenofovir disoproxil fumarate (TDF), (RAL), rilpivirine (RPV), or emtricitabine (FTC).

Comparison

Research reports on cART-naïve PLWH or HIV-negative individuals.

Outcome/s

Makers/indicators of inflammation and endothelial function.

Data Extraction

Data extracted from research reports deemed eligible for inclusion was performed by two independent reviewers. This incorporated the authors' name and publication year, region in which the study was conducted, study design, sample size of PLWH on cART, intervention (type of cART regimen), and the study's key observations in line with our study objectives.

Quality Assessment

The Downs and Black Checklist consisting of twenty-seven (27) questions under five domains, namely reporting bias, internal validity, external validity, selection bias, and power was employed to judge the quality of evidence and risk of bias reported by each of the included research reports²⁶ ([Supplementary file 3](#)). The quality of evidence and risk of bias for all the included research reports were evaluated using their full-text articles by two independent authors. Discords were resolved by discussions and taking counsel from an additional independent author. Upon reaching a consensus, rater agreement was determined using the Cohen's Kappa (K)-value to confirm the validity and reliability of the rating. The K-value was calculated using the IBM Statistical Package for the Social Sciences (SPSS) version 29.0. Cohen's Kappa rater agreements were classified in accordance with McHugh et al, (2012).²⁷

Results

Characteristic Features of the Included Research Reports

Our web search strategy identified 911 research reports outlining the link between inflammation and endothelial activation in PLWH ([Figure 1](#)). After excluding research reports not meeting our eligibility criteria, only Fifteen (15) research reports remained to be included in the present study, making up a total of 7117 included participants ([Figure 1](#)). Majority of the incorporated research reports were conducted in the United States ($n=7$), followed by Italy ($n=3$). With Spain, the Netherlands, Ireland, Slovenia, and Uganda contributing one ($n=1$) study each. Briefly, participants had an average age of 48.79 years, predominantly male ($n=73\%$) and of Caucasian ethnicity (64%). However, from the fifteen included research reports four failed to report on the ethnicity of their participants.

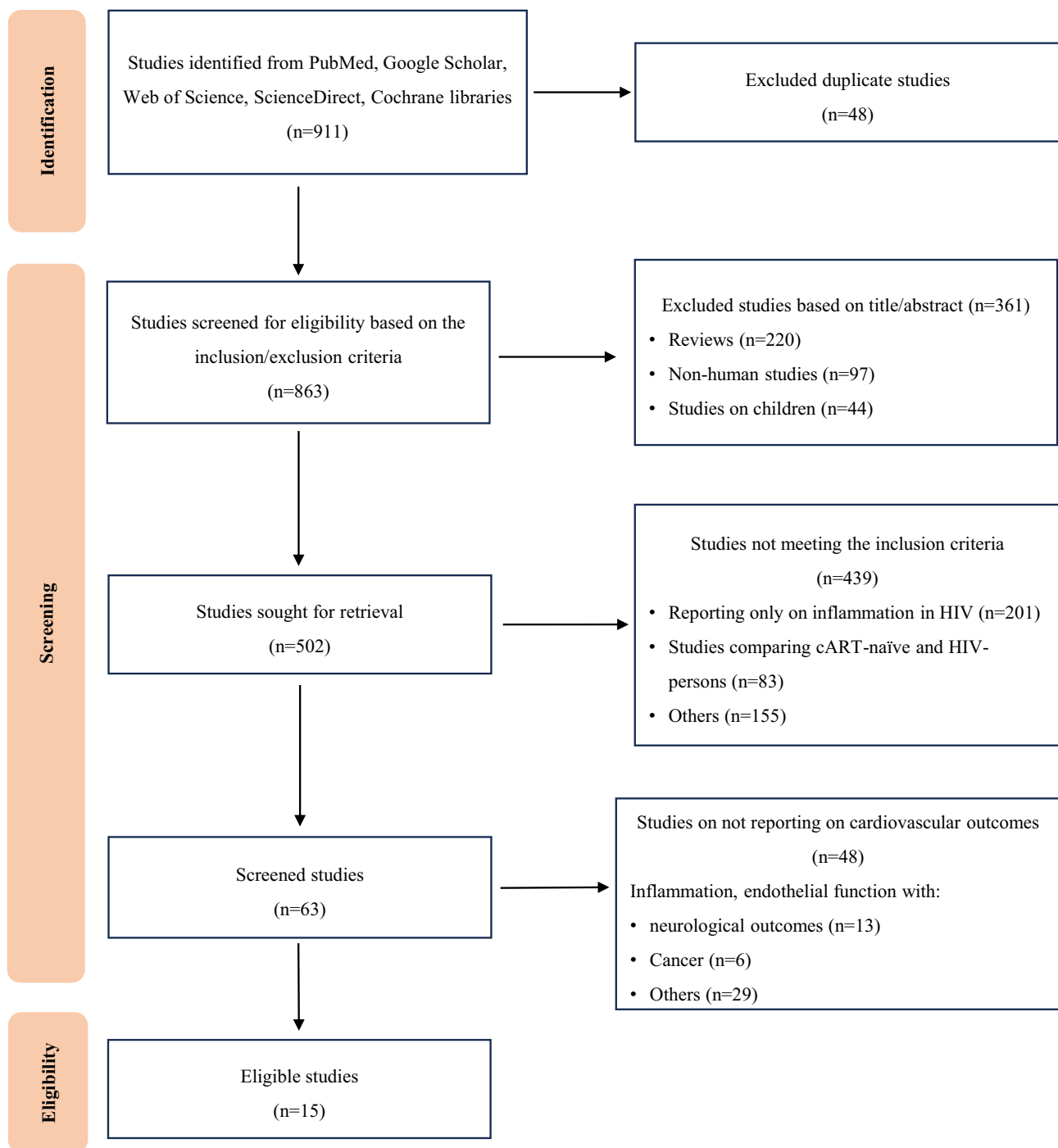


Figure 1 A PRISMA flow diagram depicting the study selection and inclusion process. Briefly, our structured search strategy identified a total of 911 research reports from PubMed, Google Scholar, Web of Science, ScienceDirect, and Cochrane libraries. After applying filters to eliminate duplicates, reviews, non-human, and child-health research reports, only 502 research reports were sought for retrieval. Out of the 502 research reports, only 15 research reports were deemed eligible for inclusion in the present systematic review, outlining the link between inflammation and endothelial activation in people living with HIV on combination antiretroviral therapy.

Descriptive Analysis of Different Types and Duration of cART Regimen within Included Research Reports

Research reports included within this study addresses different cART classes, namely “integrase strand transfer inhibitors (INSTIs), chemokine receptor 5 (CCR5) inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors. (PIs)”^{28,29} Apparently, four research reports reported on INSTIs,

Table 1 An Abstract of Research Reports Outlining the Physio-Pathological Link Connecting Inflammation and Endothelial Activation in People Living with the Human Immunodeficiency Virus (PLWH) on Combination Antiretroviral Therapy (cART) for a Period Equal or Less Than 12 months

Authors, Year	Region of Study	Study Design	Population	Intervention	Key Observations
Francisci et al, 2014 ³¹	Italy	Pilot study	PLWH on cART (n=20), having an average age of 47 years (75% male). Majority of the participants were of Caucasian (90%) ethnicity.	Received raltegravir (RAL) or maraviroc (MVC)-based regimens for a period of 12 months	Inflammatory markers like interleukin (IL-6), tumor necrosis factor alpha (TNF- α), IL-17, and monocyte chemoattractant protein-1 (MCP-1), including endothelial activation makers such as circulating vascular cell adhesion molecule-1 (sVCAM-1), and plasminogen activator inhibitor-1 (PAI-1) were elevated. But reduced by treatment.
Leng et al, 2015 ³²	United States	Observational study	PLWH on cART (n=316), having an average age of 47 years (69% male). Majority of the participants (88%) were of African American ethnicity.	The cART regimen was not disclosed; however, participants were monitored for 1 month	Inflammatory markers such as IL-6 and soluble tumor necrosis factor receptor-2 (sTNFR-2) were elevated. Moreover, IL-6 levels were linked with age, sex, HIV status, tumor necrosis factor receptor-1 (sTNFR-1), and sTNFR-2.
Calza et al, 2017 ³³	Italy	Observational study	PLWH on cART (n=62), having an average age of 47 years (77% male). Majority of the participants (94%) were of Caucasian ethnicity.	Received tenofovir disoproxil fumarate (TDF)-emtricitabine (FTC) (60%), abacavir (ABC)-lamivudine (3TC) (40%), a ritonavir-boosted protease inhibitor (PI-r) (56.5%), and efavirenz (EFV) (43.5%) and starting a rosuvastatin treatment, for 12 months	Inflammatory and endothelial activation markers such as IL-8/IL-12 and D-Dimer were decreased by treatment combination with a statin, rosuvastatin from baseline to month 12 of follow-up.
Iantorno et al, 2017 ³⁴	United states	Observational study	PLWH on cART (n=18), having an average age of 52 years (63% male). Ethnicity was not reported.	The cART regimen was not disclosed; however, participants were on treatment for at least 12 months.	Inflammatory marker IL-6 was inversely associated with endothelial activation.
DeFilippi et al, 2018 ³⁵	United States	Randomized controlled trial	PLWH on cART (n=40), having an average age of 52 years (79% male). Majority of the participants (68%) were of Caucasian ethnicity.	The cART regimen was not disclosed; however, participants were followed for 12 months	Inflammatory markers such as MCP-1 and IL-6 were positively associated with endothelial function. The inflammatory marker soluble suppression of tumorigenicity-2 (sST2) increased over time.

(Continued)

Table 1 (Continued).

Authors, Year	Region of Study	Study Design	Population	Intervention	Key Observations
Van der Heijden et al, 2018 ³⁶	Netherlands	Randomized controlled trial	PLWH on cART (n=40), having an average age of 48 years (98% male). Participant's ethnicity was not reported.	Received RAL twice daily with a backbone of TDF-FTC or ABC-3TC, for 2.5 months	No differences in inflammatory markers like platelet reactivity measured by P-selectin, fibrinogen, platelet factor 4, betathromboglobulin, and high sensitivity C-reactive protein (hsCRP). Switching regimen did not reduce inflammation and immune activation.
O'Halloran et al, 2018 ³⁷	Ireland	Randomized controlled trial	PLWH on cART (n=310) having an average age of 36 years (83% male), with dyslipidaemia (56%). Majority of the participants (62%) were of Caucasian ethnicity.	Switched from 3TC-ABC to FTC-TDF for 12 months	Inflammation and endothelial activation markers incorporating sP-selectin, and von Willebrand factor (vWF) were not affected by switching treatment. However, switching treatment was linked with elevated soluble glycoprotein VI, indicative of altered platelet-collagen interactions.
Kumar et al, 2020 ³⁸	United States	Exploratory pilot study	PLWH on cART (n=8), having an average age of 55 years (75% male). Participant's ethnicity was not reported.	Received atazanavir (ATV) and ritonavir [®] (with a backbone of ABC-3TC or FTC-TDF) for 3 months. One participant was on ABC-dolutegravir (DTG)-3TC.	Inflammatory markers incorporating IL6, hsCRP, and TNF- α were elevated, including endothelial activation markers like sICAM-1, sVCAM-1, and sE-selectin.
González-Cordón et al, 2021 ³⁹	Spain	Randomized controlled trial	PLWH on cART (n=313), prone to manifest cardiovascular disease and having an average age of 54 years (89% male). Majority of the participants (88%) were of Caucasian ethnicity.	Switched to DTG versus remaining on a PI-r regimen for 12 months	Inflammatory markers such as hsCRP and adiponectin were diminished by switching treatment.
Cossarizza et al, 2023 ¹⁴	Italy	Randomized controlled trial	PLWH on cART (n=66), having an average age of 54 years (86% male). Majority of the participants (86%) were of Caucasian ethnicity.	Switched to Bictegravir (BIC)-FTC-tenofovir alafenamide (TAF) or DTG-FTC for 12 months	Inflammatory marker such as IL-6, including immune activation indicators such as monocytes, or CD4 ⁺ or CD8 ⁺ T cells were not affected by switching treatment.

Table 2 An Abstract of Research Reports Outlining the Physio-Pathological Link Connecting Inflammation and Endothelial Activation in People Living with the Human Immunodeficiency Virus (PLWH) on Combination Antiretroviral Therapy (cART) for a Period Longer Than 12 months

Authors, Year	Region of Study	Study Design	Population	Intervention	Key Observations
Pirš et al, 2014 ³⁹	Slovenia	Observational study	PLWH on cART (n=82), with an average age of 39 years (100% male). No reported ethnicity.	Received protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) based regime, with a majority being on cART for 56 months	Inflammatory markers such as high sensitivity C reactive protein (hsCRP) were elevated and consistent with increased concentrations of endothelial activation markers such as soluble vascular cell adhesion molecule 1 (sVCAM-1)
Young et al, 2014 ⁴⁰	United states	Randomized clinical trial	PLWH on cART (n=4073), having an average age of 47 years (78% male). Majority of the participants (56%) were of Caucasian ethnicity.	The cART regimen was not disclosed; however, participants were followed-up for 17 months	Inflammatory and coagulation markers such as D-Dimer, hsCRP and interleukin-6 (IL-6) were elevated and associated with reduced cardiac autonomic function
So-Armah et al, 2016 ⁴¹	United States	Observational study	PLWH on cART (n=1521), having an average age of 52 years (58% male), with 50% having controlled hypertension. Majority of the participants (69%) were of African ethnicity.	The cART regimen was not disclosed; however, participants were monitored for 13 months	Inflammatory cytokines and coagulation markers such as IL-6, and monocyte activation soluble cluster differentiation-14 (sCD14) and D-Dimer were consistently elevated.
Dirajjal-Fargo et al, 2017 ⁴²	United States	Observational study	PLWH on cART (n=93), having an average age of 51 (81% female). Majority of the participants (63%) were African American.	The cART regimen was not disclosed; however, participants were on cART for at least 36 months	Inflammatory markers such as IL-6, hsCRP, soluble tumor necrosis factor receptor 1 and 2 (sTNFR-1 and sTNFR-2) were independently associated with endothelial activation as measured by impaired plasma levels of arginine.
Siedner et al, 2018 ⁴³	Uganda	Observational study	PLWH on cART (n=155), having an average age of 51 years (51% male). Participants (100%) were of African ethnicity.	The cART regimen was not disclosed; however, participants were on cART for 84 months	Inflammatory markers such as hsCRP and monocyte activation markers including sCD14 were elevated.

followed by PIs (n=2) and NRTIs (n=2), respectively. Other research reports reported on switching treatment from NRTIs or PIs to using INSTIs.^{14,30} Approximately 47% (n=7) of our included research reports did not disclose the cART regimen used by their enrolled participants. Majority (n=10) of the research reports addressed a cART-exposure duration \leq 12 months (Table 1),^{14,30–38} while the remaining five (n=5) reported on a treatment exposure duration $>$ 12 months (Table 2).^{39–43} Interestingly, an exposure duration $>$ 12 months was associated with elevated inflammatory and endothelial activation markers.

Quality of Evidence and Risk of Bias of the Included Research Reports

Two independent reviewers judged the quality of evidence and the risk of bias of the 15 included research reports employing the adjusted Downs and Black checklist ([Supplementary file 4](#)). Briefly, all the included research reports had an excellent quality of evidence after scoring at least 22 out of 27 possible points. Moreover, all the included research reports obtained an excellent reporting bias with a mean score of 10.73 (10–11) out of 11 points and a moderate rater agreement noted with a Cohen's kappa (K)-value of 0.42. This included external validity with a mean score of 2.53 (2–3) out of 3 point and a moderate rater agreement of K= 0.42, and an internal validity with a mean score of 5.20 (5–7) out of 7 points and a good rater agreement of K=0.63. The selection bias of all the included research reports was classified as being fair with a mean score of 4.60 (4–6) out of 6 points and a fair rater agreement of K=0.21 ([Supplementary file 4](#)). Importantly, all the included research reports had a good reporting power $\geq 80.0\%$ which is representative of no omission errors to their observations, as supported by a mean score of 0.80 (0–1) and K=0.76 ([Supplementary file 4](#)).

Short Term (≤ 12 Months) Effects of cART on Markers of Inflammation and Endothelial Activation in PLWH

Existing literature suggests that PLWH already present with sustained immune activation and chronic inflammation.^{44,45} That is, despite effective viral suppression with cART, chronic immune activation persists, likely due to ongoing low-levels of viral replication, microbial translocation, and co-infections.^{10,12} This persistent immune activation stimulates the production of pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β that are likely to contribute to the sustained activation of immune cells such as monocytes, neutrophils, and T-lymphocytes that may elevate CVD-risk.^{9,12} Indeed, this phenomenon can lead activation of reactive radicals and impairments on the vascular endothelium, likely causing increased CVD-risk.^{9–13} The resulting endothelial dysfunction not only compromises vascular integrity but also contributes to the increased cardiovascular risk observed in PLWH on cART.^{5,10,12}

Nonetheless, the use of cART has been reported to induce positive effects in viral suppression, sometimes despite elevated levels of inflammation in PLWH.^{17,46} Thus, it has become empirical to decipher the effects of exposure to cART in PLWH, this includes short- and long-term effects. This is aligned with understanding the pathological link between elevated inflammatory and endothelial activation markers in PLWH on cART. [Table 1](#) gives a synopsis of research reports outlining the potential link between raised markers of inflammation and endothelial activation in PLWH, exposed to cART for a short-term period of ≤ 12 months. Here, ten (n=10) of the incorporated research reports addressed the efficacy of various interventions, ranging from CCR-5 inhibitors such as MVC-based regimens, or combinations of NRTIs such as TDF-FTC, or abacavir (ABC)-lamivudine (3TC), and even ritonavir (RTV)-boosted PIs. Others were exposed to a combination therapy containing NNRTIs such as EFV, with other PLWH allowed to switch from 3TC-based therapy to INSTIs such as dolutegravir (DTG) or the NRTI tenofovir alafenamide (TAF) regimens ([Table 1](#)).

A systematic analysis of literature supports a strong correlation between raised markers of inflammation and sustained endothelial activation markers.^{32,35,38} Although such evidence does not appear to be dependent on the type of cART regimen, the results suggested that inflammatory markers like IL-6 and MCP-1 correlated with indicators of endothelial activation incorporating sICAM-1, sVCAM-1, and sE-selectin ([Table 1](#)). However, it was noted that other cART regimens, including RAL-MVC, TDF-FTC, or even the combined use of these drugs with a statin drug such as rosuvastatin could alleviate inflammation and improve endothelial function in PLWH.^{31,33,34} Some of the inflammatory and endothelial activation makers that were positively affected by treatment included IL-6, TNF- α , MCP-1, sVCAM-1, and plasminogen activator inhibitor-1 (PAI-1). However, from some included research reports it was apparent that some external factors like age, gender, and specific type of cART could influence markers of inflammation, together with endothelial function status in PLWH. For example, Leng et al showed that traditional risk factors of CVDs such as age and gender^{47,48} were associated with sustained inflammation status in PLWH.³² Further highlighting the importance of adjusting for external risk factors when reporting on the potential influence of cART on markers of inflammation or to determine the potential link with endothelial activation.

Markers of inflammation or those indicating endothelial activation were further evaluated in patients switching between different cART regimens ([Table 1](#)). For example, it was reported that switching to Bictegravir (BIC)-FTC-

TAF containing cART treatment did not affect inflammatory marker such as IL-6 nor could it influence indicators of immune activation such as monocytes, or CD4⁺ or CD8⁺ T cells.^{14,37} While it was partially demonstrated that switching from 3TC-ABC to FTC-TDF therapy was associated with increased levels of soluble glycoprotein VI, an indicator of platelet-aggregation and immune activation marker.³⁷ Similar findings are seen when administering RAL twice daily, together with a cART backbone consisting of TDF-FTC or ABC-3TC, for 2.5 months did not affect in inflammatory markers like platelet reactivity measured by sP-selectin, fibrinogen, platelet factor 4, betathromboglobulin, and hsCRP in PLWH.³⁶ Although cART remains effective in suppressing the virus or improving the lives of PLWH,³⁰ the current results show little or no evidence supporting the efficacy of cART in alleviating or diminishing markers of inflammation or endothelial activation in these PLWH.

Effects of Prolonged Exposure (> 12 Months) to cART on Inflammatory and Endothelial Activation Markers in PLWH

Evidence exists elucidating the potential role of raised inflammatory markers during the development of CVDs in PLWH, especially through long-term exposure to cART.^{34,39} Table 2 gives a synopsis of research reports outlining the potential link between inflammation and endothelial activation in PLWH exposed to cART for a prolonged period of >12 months. Here, the majority of included literature supports the close association between elevated markers of inflammation and endothelial activation in PLWH on cART. For example, it was reported that PLWH receiving PI or NNRTI based regime for 56 months presented with elevated levels of hsCRP, an inflammatory marker consistent with increased concentrations of endothelial activation indicator like sVCAM-1.³⁹ Others did not specify the type of cART regimen but did show that prolonged exposure of PLWH to treatment was linked with elevated levels of inflammatory markers incorporating IL-6, sTNFR-1, and hsCRP, together with coagulation biomarkers like D-Dimer, and reduced cardiac autonomic function in PLWH.^{40–42} To attain some level of immune activation within these patients, it was also demonstrated that exposure to cART for 84 months was linked with higher levels of monocyte activation (sCD14), corresponding to elevated pro-inflammatory (hsCRP) markers in PLWH.⁴³ The available evidence remains debatable, motivating for future research reports on PLWH looking at prolonged cART exposure on inflammation and endothelial activation with specific focus on different cART-drug combinations.

Other Factors Potentially Enhancing Inflammation and Endothelial Activation in PLWH on cART

In people living with HIV, age and sex, particularly being male, play significant roles in exacerbating inflammatory and endothelial activation.^{14,39} Thus, with increasing age PLWH are more likely to experience heightened levels of chronic inflammation and immune activation, which can contribute to CVDs and other comorbidities.^{31,32} Nonetheless, our included evidence predominantly associates being male of >45-years-old and HIV-infected with sustained inflammation and endothelial activation.^{14,31,32,39} Leng et al, in a study predominately composed of males with an average age of 47 years, demonstrated that elevated inflammatory markers incorporating IL-6 were linked with age and sex.³² Similarly, two studies on 54-year-old males affirmed the probable link between old age elevated inflammatory markers.^{14,39} However, one of these studies further elaborated that administering INSTI-based cART may suppress inflammation in these persons.³⁹ Thus, addressing these gender and age-specific risks is crucial in managing the long-term health of people living with HIV.

Discussion

It is now well accepted that many PLWH present with chronic inflammation and sustained immune activation despite administering cART.^{12,49} Thus, there is a lot of interest to understand the potential pathological connection between markers of inflammation or immune activation with the development of endothelial activation in PLWH on cART.^{12,50} Indeed, it has been of particular interest whether inflammation over short-term exposure to treatment is beneficial or perhaps prolonged exposure to cART could contribute to increased CVD-risk in PLWH. Here, we selected studies based on a systematic review approach, which provides a validated methodological approach to select studies and critically

discuss them based on their common primary outcomes and covariances of CVDs, inflammation, and endothelial activation in PLWH on cART.

Starting with short-term exposure/treatment with cART (≤ 12 months), it was obvious that predominant markers of inflammation such as IL-6 and MCP-1 were correlated with indicators of endothelial activation such as sICAM-1, sVCAM-1, and sE-selectin (Table 1). Interestingly, both IL-6 and MCP-1 have been associated with the progression of HIV,⁵¹ while IL-6 is known to play an active role in activating peripheral blood mononuclear cells to initiate immune activation and could eventually lead to organ damage.⁵² Increased circulating levels of IL-6 have been reported to be associated with CVD-related events such as diminished cardiac autonomic function.⁴⁰ In addition, circulating levels of IL-6 were also reported to have a positive association with GDF-15, a marker of cardiovascular function.³⁵ These findings may potentially explain the increased risk of developing CVD-related complications in PLWH. Anyway, short-term exposure to cART was associated with elevated markers of endothelial activation such as sICAM-1 and sVCAM-1 in PLWH (Table 1).

It is important to decipher whether prolonged exposure to elevated inflammatory markers could have a profound effect in damaging the endothelium. Research already indicated that endothelial activation may develop due to enhanced adhesion molecules, which correspond to the detrimental effects of oxidative stress as well as activation of cytokine secretion.^{50,53} The systematic analysis of literature did show that prolonged exposure to cART (> 12 months) confirmed that elevated markers of inflammation, including sustained immune response are consistent with the existence of endothelial activation in PLWH (Table 2). Prolonged exposure to cART and its potential influence on the general health of PLWH is a well-investigated phenomenon. Although effective in maintaining lives of PLWH,^{54,55} many questions are raised on whether prolonged exposure to cART could potentially cause increased CVD-risk through enhanced indices of inflammation and endothelial activation.⁵⁰ To supplement information on detrimental effects of sustained platelet activation,⁵⁶ some of the findings within the current systematic review show that markers for monocyte activation such as sCD14 are indeed elevated in PLWH on cART. Even accumulative evidence has closely monitored the potential use of activated monocytes or immune activation markers as a therapeutic target to attenuate vascular inflammation and lower CVD-related complications in people with diverse medical conditions.^{57,58}

Furthermore, the use of PI-r or NNRTIs such as EFV appears to be effective in maintaining immune response by diminishing inflammatory cytokines such as IL-6 and IL-12.³³ Similarly, the use of INSTIs such DTG diminishes acute phase inflammatory proteins such as hsCRP more effectively when compared to PI-r regimen.³⁰ This evidence requires confirmation on whether specific cART-drug classes hold beneficial outcomes in viral suppression subsequently diminishing inflammation, with INSTIs having the most effective drugs. Notably, research has indicated that switching treatment to DTG containing cART regimen may potentially influence inflammatory markers like IL-6 to influence CVD-related outcomes.^{14,59} Similarly, however, O'Halloran et al (2018)³⁷ indicated that switching from 3TC-ABC to FTC-TDF containing cART regimen has no beneficial effects on improving inflammation or alleviating endothelial activation markers in PLWH, further opening avenues for more research to investigate the possible detrimental effects of the participant's prior cART regimen.

There is also scarce evidence supporting an inverse association between elevated inflammatory markers and the development of endothelial activation in PLWH. For instance, Iantorno et al, (2017)³⁴ who reported an inverse association between IL-6 and coronary endothelial function in PLWH. Thus, these observations may evocate that sustained inflammation and endothelial dysfunction in PLWH may be a result of age and sex predispositions. For instance, males infected with HIV, in particular, may face a greater risk of inflammation induced endothelial dysfunction compared to their female counterparts.^{32,55} This sex disparity may be due to differences in immune responses, and lifestyle factors that can impact the vascular system. Studies have shown that older men living with HIV exhibit increased markers of inflammation and impaired endothelial function,^{43,48} which can lead to a higher prevalence of cardiovascular complications. Notably, our reporting presents some bias in that the included studies predominantly consist of male participants than their female counterparts. However, it remains ambiguous to assign such level of bias in influencing the outcomes of these studies because there is no evidence indicating a systematic under-representation of females in clinical studies.⁶⁰ Nonetheless, more evidence is required to clarify the role of inflammation during the pathogenesis of

endothelial activation, in association with other prevailing markers and covariances of CVD in PLWH. This is essentially true to understand potential effects of specific cART regimen combinations.

Strengths and Limitations

This systematic review gives knowledge on the currently existing evidence reporting on the potential link between inflammation and endothelial activation following the manifestation of CVDs. To ensure quality, reliability, and minimum bias of our reporting, the included studies were selected based on a systematic review approach, which provides a validated methodological approach to select studies and critically discusses them based on their findings in relation to inflammation, endothelial activation, and CVDs. All the included research reports reported evidence of excellent quality and risk of bias as determined using the Downs and Black check list, making their research findings accurate and reliable. However, the present systematic review holds some limitations worth considering. Including the retrieval of a few research reports (n=15) reporting on the link between inflammation and cardiovascular outcomes. In addition, the diversity of these research reports hindered us from performing a meta-analysis. It is also important to note that the incorporated studies poorly dined the health status of their participants, which might have had HIV-linked co-infections with the capacity to influence inflammation and endothelial activation pathway. Consequently, influencing the outcomes of our reporting. Our extracted research reports predominately reported on males, which might have impacted the quality of their conclusions. It is also worth mentioning that the reported information by the included studies does not consider a broad spectrum of CVD-related outcomes which may predict CVD-risk in PLWH on cART.

Conclusion

The pathological role of HIV and cART in the manifestation of CVDs is poorly understood. The present review systematically identified and appraised clinical research reports addressing the potential pathological link between elevated markers of inflammation and the development of endothelial activation in PLWH on cART. This was further motivated by existing evidence that PLWH present with persisting inflammation that may be detrimental to cardiovascular health.^{12,61} Our findings highlight that cART exposure enhances immune activation leading to the constant expression of inflammatory markers which potentially contribute to increased CVD-risk via the pathogenesis of endothelial activation in PLWH. This may however be elucidated through various factors incorporating the cytotoxic effects of cART on cells, inducing inflammation and oxidative stress known to cause damage to the vascular wall.^{9,12} An additional factor that could aid in elucidating the persistent expression of inflammatory markers in the presence of long-term exposure to cART, is the ability of the virus to acclimatize to the inhibitory effects of the treatment.^{62,63} All these while taking into consideration individual differences in adhering and responding to cART, as well as HIV-linked co-infections, age, and sex predisposition. Nonetheless, more findings are required to confirm this, especially longitudinal research reports to bridge the gap on cART-mediated inflammation and closely related cardiovascular events.

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Author Contributions

All authors made a significant contribution to the work reported in this study, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or

critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

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