THE LONG-TERM ADVERSE EFFECTS OF ANTIRETROVIRALS ON THE HEART

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Abstract

There are medications that aid in the treatment of people living with the HIV virus so that the disease does not progress or may even never develop; these are antiretroviral medications that are part of antiretroviral therapy (ART). The continuous use of these medications may bring a series of long-term side effects, including heart disease. ART contributes to an increase in inflammatory factors and carotid thickening, being associated with atherosclerosis and myocardial infarction; this thickening is directly linked to the use of protease inhibitors (PIs). As a result, first-generation PI drugs were replaced by others with lower toxicity, such as darunavir (DRV) and atazanavir (ATV). Routine cardiovascular assessment is essential in these patients in order to achieve greater control over the development of the disease and thus manage the appropriate choice of ART. Even with the adverse effects developed over the long term, ART would still be the best form of treatment to combat HIV due to its extreme efficacy in preventing the development of the disease.

Keywords: HIV, Antiretroviral Therapy (ART), Cardiovascular Diseases, Protease Inhibitors (PIs), Side Effects.

INTRODUCTION

The long-term adverse effects of antiretrovirals on the heart have been a matter of concern in global health, where the degree of toxicity that some antiretrovirals may cause to the heart of those

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undergoing antiretroviral therapy (ART) has been discussed. Continuous use of this medication may lead to gastrointestinal problems, liver and kidney injury, osteoporosis, diabetes, and hypertension. The most frequent reports highlight cardiac problems. However, if the risk is analyzed in relation to the benefits that ART provides, it is clear that the possible comorbidities developed are far outweighed by the major benefits it produces in the body carrying the virus (Brazil, 2021).

This study on the adverse effects of prolonged use of antiretrovirals on the heart is currently of extreme relevance in health care. With the increase in life expectancy of people living with HIV, heart diseases have become one of the main causes of morbidity and mortality. Understanding how the cumulative toxicity of this drug acts directly on the heart is essential to ensure that the success of virological control is not overshadowed by metabolic complications (Lima, 2019).

The research problem was to verify how the continuous use of antiretrovirals has contributed to the increase in cardiovascular risk and the development of chronic cardiac pathologies.

The general objective was to analyze the scientific evidence currently present in the literature regarding the main cardiovascular complications arising directly from the prolonged use of antiretrovirals in patients with HIV.

The specific objectives were to study the main risk factors and the cardiovascular diseases most frequently reported in users who made prolonged use of antiretrovirals and to verify and describe the mechanism of action of the main antiretrovirals and their direct relationship with cardiac toxicity.

DEVELOPMENT

METHODOLOGY

The type of research conducted was a Literature Review of a qualitative and descriptive nature. The study was not exploratory, experimental, or a case study; it focused exclusively on the theoretical analysis of materials already published on the topic. The search was conducted in renowned scientific

databases, such as Google Scholar, SciELO, and PubMed, aiming to select articles that discussed the adverse effects of antiretrovirals on the heart.

The search period comprised works published in the last 10 years (2016 to 2026), ensuring the currency of the scientific evidence presented. As inclusion criteria, scientific articles, dissertations, and technical books available in full text, in Portuguese and English, were selected.

To locate the material, the following descriptors and keywords were used: “Antiretroviral Therapy,” “HIV,” “Cardiovascular Toxicity,” and “Adverse Effects.” Data analysis was carried out descriptively, through critical reading of the abstracts and, subsequently, the full content of the selected texts, allowing the synthesis of the information necessary to answer the proposed research problem.

Table 1

Articles selected for review.

Authors	Objectives	Methodology	Results	Conclusion
LEITE et al. (2020)	To evaluate inflammatory biomarkers and carotid thickness in patients with HIV receiving ART.	Cross-sectional study with patients at low cardiovascular risk.	The presence of persistent subclinical inflammation was observed even with controlled viral load.	ART and the virus contribute to an inflammatory state that favors cardiovascular risk.
LIMA (2019)	To analyze the adverse effects of ART and the difficulties in adherence to treatment.	Monograph with an integrative literature review.	It identified drug toxicity as the main cause of changes in therapeutic regimens.	Side effects impair adherence, requiring greater clinical support for the patient.
MANSUR (2020)	To analyze the cardiovascular conditions	Clinical review of guidelines on cardiovascular	It identified a high prevalence of	Early monitoring of cardiac risk factors is

Authors	Objectives	Methodology	Results	Conclusion
	of patients undergoing HIV treatment.	management in seropositive patients.	dyslipidemia and hypertension in long-term ART users.	necessary to avoid serious events.
MATEUS et al. (2022)	To investigate drug interactions involving antiretrovirals in the treatment of adults.	Integrative literature review in scientific databases.	It identified interactions that potentiate toxicity and reduce treatment efficacy.	Pharmaceutical management is essential to minimize serious adverse events and interactions.
OBARE et al. (2024)	To investigate inflammation in HIV and its impact on atherosclerotic cardiovascular disease.	Clinical follow-up study and analysis of inflammatory markers.	It demonstrated that chronic inflammation accelerates the process of atherosclerosis in patients with HIV.	Control of inflammation should be an integral part of cardiovascular management in HIV.
PONTES et al. (2020)	To identify factors associated with chronic kidney disease in people living with HIV/AIDS.	Cross-sectional study with analysis of clinical and laboratory data.	It found a correlation between prolonged use of certain antiretrovirals and decline in renal function.	Renal function should be continuously monitored together with cardiovascular health.
RIBAS et al. (2020)	To describe the pathologies associated with the use of antiretroviral therapy.	Integrative review exploring various associated comorbidities.	It listed a wide range of secondary pathologies, especially metabolic and bone changes.	Therapy requires constant surveillance regarding secondary pathologies induced by treatment.
SILVA, A. G. et al. (2020)	To evaluate subclinical carotid atherosclerosis in HIV-positive patients.	Observational study applying the DAD score for risk stratification.	Patients on ART presented greater thickening of the carotid intima-media.	Duration of exposure to antiretrovirals is linked to increased risk of atherosclerosis.
SILVA, J. N. et al. (2025)	To analyze the evolution of HIV/AIDS medications in Brazil.	Documentary and historical study presented at a scientific congress.	It traced the evolution of drugs, noting improvement in efficacy and reduction in toxicity.	Pharmacological evolution seeks to reduce adverse effects without losing viral suppression.
SILVA, L. L. G. et al. (2020)	To investigate lipodystrophic syndrome and its associated factors.	Quantitative cross-sectional study with analysis of medical records.	High prevalence of fat redistribution associated with disorders of blood glucose and cholesterol.	Lipodystrophy negatively impacts metabolic health and the patient's self-image.

Authors	Objectives	Methodology	Results	Conclusion
VALIM & EIRA (2020)	To relate cardiovascular diseases to HIV and antiretroviral therapy.	Literature review focused on cardiovascular pathophysiology.	ART, especially protease inhibitors, negatively alters the lipid profile.	Treatment must balance virological efficacy with protection of the cardiovascular system.
VENDRUSCOLO (2016)	To study the adverse effects resulting from the use of antiretrovirals in patients.	Monograph based on a descriptive clinical study in Salvador.	It reported a significant incidence of gastrointestinal disorders and early metabolic changes.	Understanding the local profile of adverse effects is fundamental to the management of care.
VILAÇA et al. (2021)	To identify orofacial lesions and side effects in patients under potent ART.	Clinical follow-up study of patients using HAART.	Metabolic systemic changes were reported in addition to oral manifestations.	Multiprofessional follow-up is vital to manage the side effects of therapy.

Source: Authors, 2026

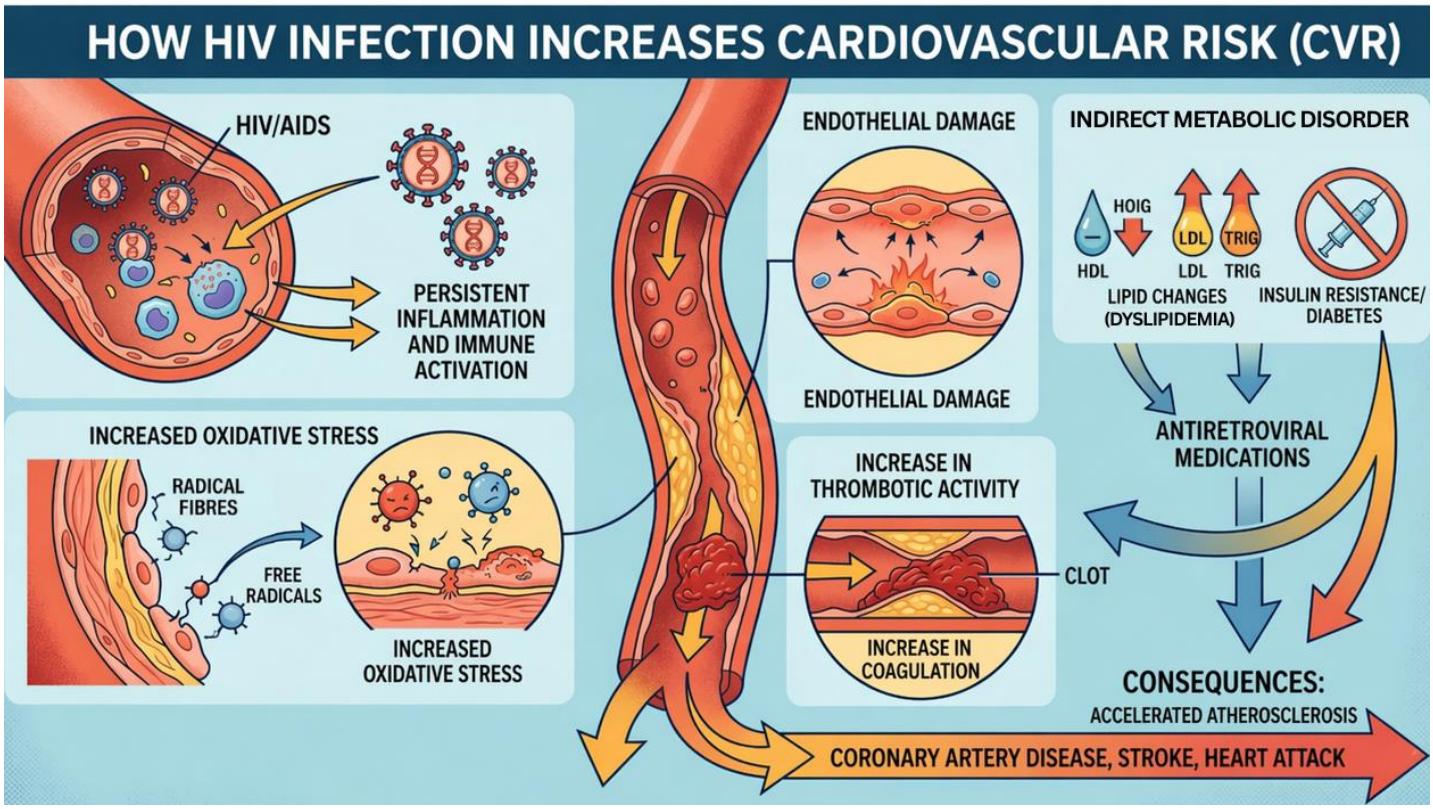
RESULTS AND DISCUSSION

The human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS), a disease that remains a worldwide public health problem to this day. According to the global document AIDS Up Date, in 2017 there were 1.8 million new HIV infections in the world population, totaling 36.9 million people living with HIV worldwide (Vilaça et al., 2021).

HIV infection increases cardiovascular risk (CVR) through persistent inflammation and immune activation, **Figure 1**, as well as greater oxidative stress, endothelial damage, increased thrombotic activity, and indirect metabolic disturbance (Aguiar; Eira, 2020).

Figure 1

HIV: Increased risk of coronary disease



Source: (Adapted). Hsue and Waters, 2019.

Therapy against the HIV virus is quite complex, involving the use of several medications, especially antiretrovirals. Thus, the occurrence of drug interactions becomes common, which may decrease the efficacy of the medication, increase adverse reactions, or cause toxicity to the organism (Bernardes et al., 2021).

The initial treatment protocol consists of the use of three antiretrovirals: two are NRTIs/NtRTIs (nucleoside/nucleotide reverse transcriptase inhibitors) and one from another class, which may be an NNRTI (non-nucleoside reverse transcriptase inhibitor), PI/r (protease inhibitor boosted with ritonavir), or INSTI (integrase inhibitor). Tenofovir and lamivudine are generally used as NRTIs/NtRTIs and dolutegravir as an INSTI (Brazil, 2018).

Dyslipidemia is an important toxicity of antiretrovirals (ARVs), generally arising after 2 to 3 months of use. Associated with the use of PIs, NRTIs, and NNRTIs, increases in triglycerides, HDL, and LDL cholesterol are commonly found, which raises the risk of atherosclerosis and coronary disease. For

its control, non-pharmacological therapeutic measures should begin first (diet, exercise, smoking cessation, etc.) and, depending on severity, the drug class should be changed and/or lipid-lowering drugs added (Vendruscolo, 2016).

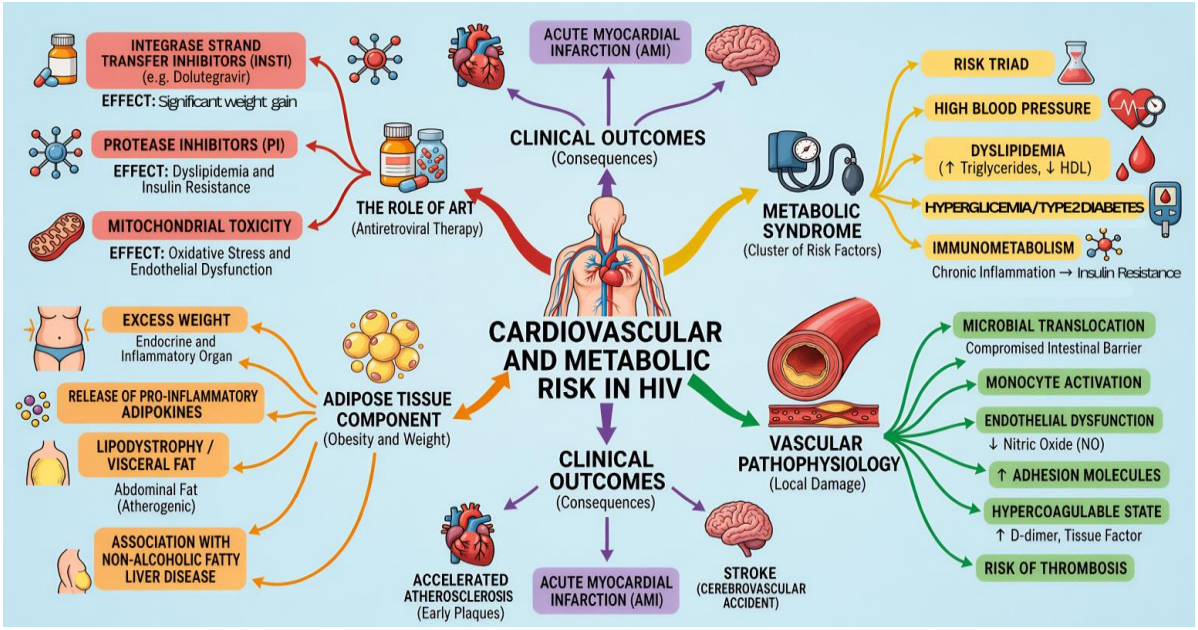
However, people living with HIV have come to present elevated risks of developing comorbidities (cardiovascular, hepatic, and renal diseases) as a consequence of the complex association between immunodeficiency, chronic inflammation, aging, and antiretroviral toxicity (Pontes et al., 2020).

Antiretroviral therapy (ART) is associated with oxidative stress, infiltration of oxLDL through arterial walls activating adhesion molecules, and increased monocyte-platelet aggregation in endothelial cells, which leads to lipid accumulation and altered vascular permeability that further contribute to the formation of atherosclerotic plaque (Aguiar; Eira, 2020).

In addition, other studies have also demonstrated the presence of excess weight in this population as a worrying finding, since the use of ART associated with overweight and fat accumulation predisposes these patients to the development of metabolic syndrome and cardiovascular diseases (Silva et al., 2019).

Figure 2

The risk of metabolic syndrome in an HIV patient



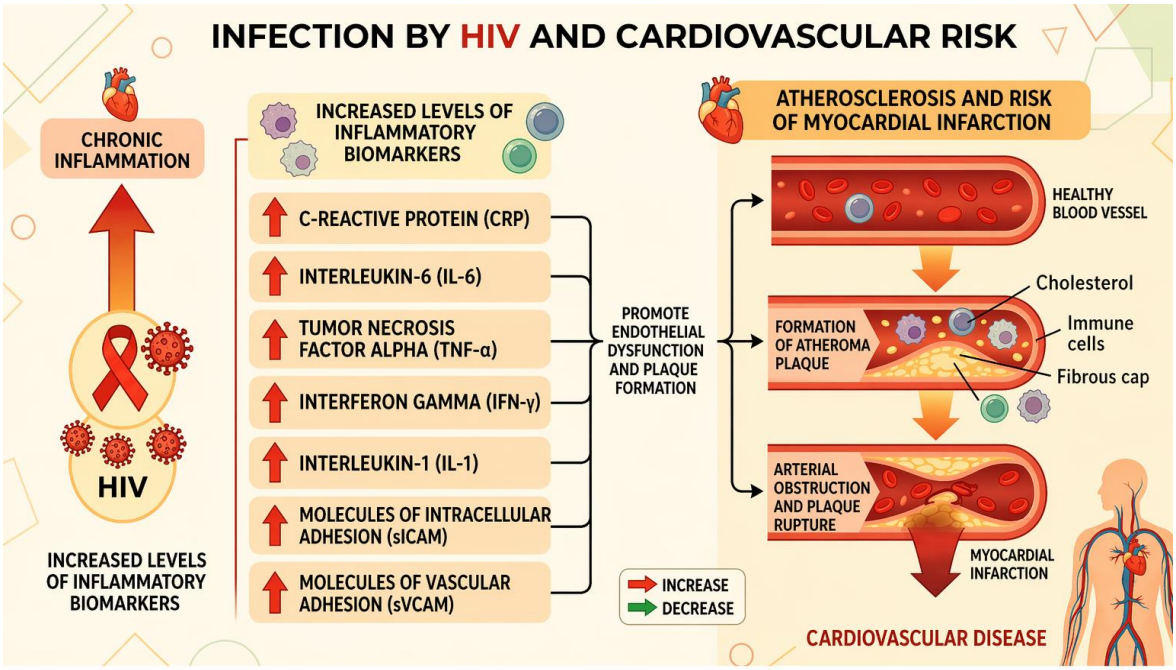
Source: (Adapted). Silva et al., 2019

Cardiovascular diseases emerged as an important cause of morbidity and mortality. Data from the DAD study (Data Collection on Adverse Effects of Anti-HIV Drugs), published in 2014, indicate that 11% of deaths among HIV-positive patients are caused by cardiovascular diseases. Patients infected with HIV have a risk twice as high as the general population of suffering myocardial infarction and four times as high a risk of sudden death. In addition to the increased risk, people living with HIV experience cardiovascular events, on average, approximately 10 years earlier than the general population (Silva; Paulo; Silva-Vergara, 2019).

According to some studies, the virus and antiretroviral therapy (ART) are factors that favor the increase of inflammatory factors and carotid thickening. Individuals infected with HIV present high levels of C-reactive protein, associated with atherosclerosis and myocardial infarction. Levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin-1 (IL-1), intracellular adhesion molecules (sICAM), and vascular adhesion molecules (sVCAM), which increase in the progression of cardiovascular disease, are also elevated in this population, Figure 3 (Leite et al., 2020).

Figure 3

HIV infection and cardiovascular risk



Source: (Adapted). Leite et al., 2020

These findings contribute to the assessment of patients on successful HIV therapy and once again emphasize the achievements of contemporary comprehensive clinical care for patients, probably including therapeutic counseling on cardiovascular risk factors such as smoking, hypertension, dyslipidemia, and diabetes (Mansur, 2020).

Initially, the risk of the emergence of cardiological illnesses is attributed to protease inhibitors (PIs), due to the lipid alterations caused by them. The most plausible explanation among these factors is that the introduction of PIs interferes mainly in the exogenous pathway of lipid metabolism, responsible for an increase in cardiovascular risk (Ribas et al., 2020).

Linked to the class of protease inhibitors (PIs) are metabolic changes that include dyslipidemia, defined by increased serum cholesterol and triglycerides, insulin resistance, and even diabetes mellitus, all of which promote greater risk of cardiovascular diseases in these patients. The antiretrovirals with adverse reactions directly linked to the heart are from the class of NRTIs (stavudine, abacavir) and PIs (lopinavir) (Lima, 2019).

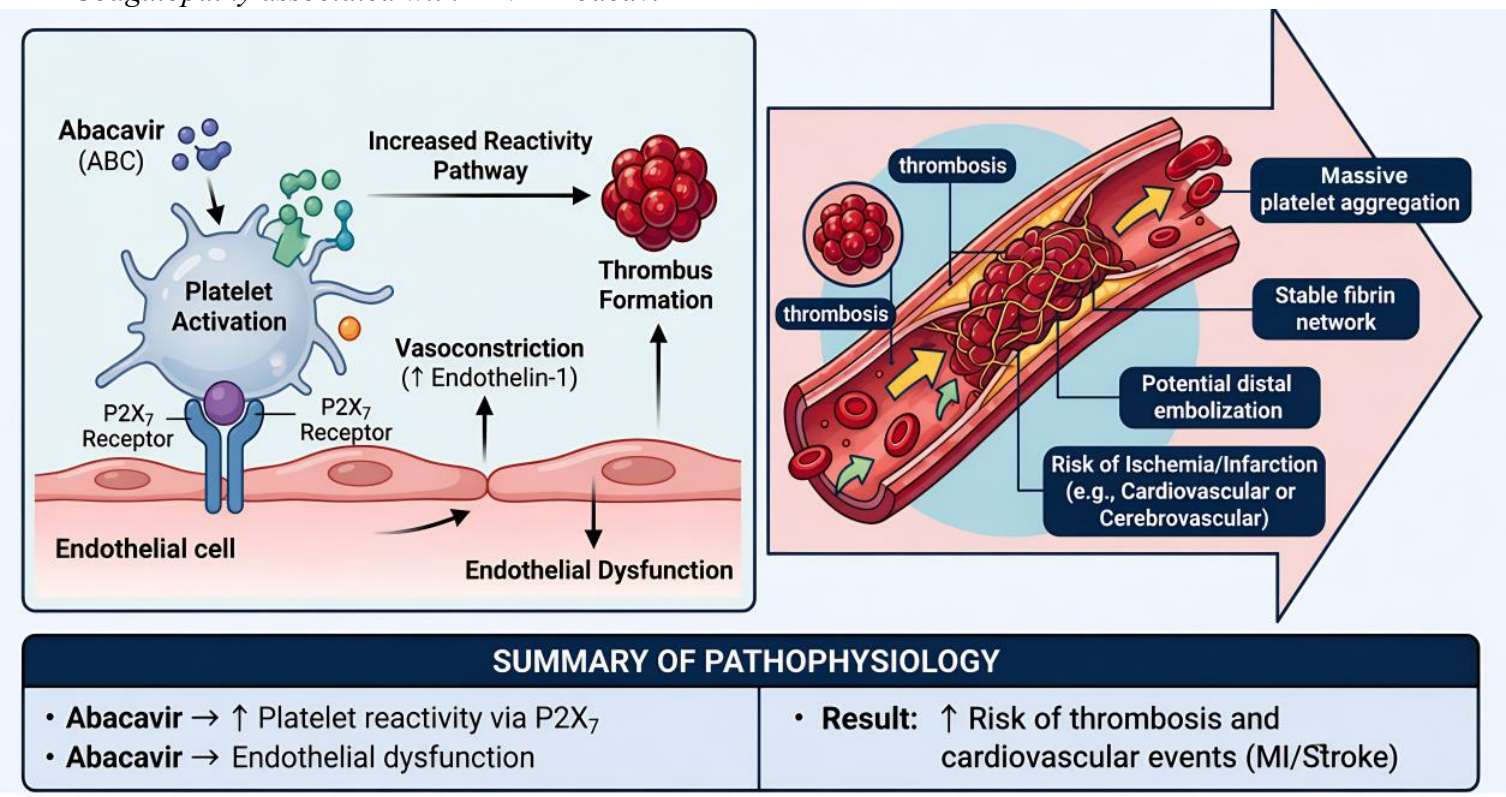
Some authors demonstrated increased carotid intima-media thickness (CIMT) and its progression (a subclinical marker of atherosclerotic disease) in an observational study of patients treated with ART, particularly when using protease inhibitors (PIs). Both HIV infection and ART promote cardiovascular disease (CVD) through the induction of dyslipidemia and pro-inflammatory cytokines with oxidative stress, endothelial damage, and hypercoagulability. Some ARVs such as ritonavir (RTV), indinavir (IDV), lopinavir (LPV), zidovudine (AZT), and NRTIs may induce metabolic effects, endothelial dysfunction, oxidative stress, and provoke an inflammatory response (Aguiar; Eira, 2020).

The abacavir (ABC) combination from the NRTI class increases platelet reactivity, **Figure 4**. INSTIs, on the other hand, have been related to beneficial effects on these processes. One of the hypotheses raised is that some ARVs may cause cardiac dysfunction through mitochondrial toxicity. The protease inhibitors LPV and atazanavir (ATV) may be associated with QT interval prolongation and subsequent arrhythmias. Efavirenz (EFV), from the NNRTI class, promotes adhesion of leukocytes to

endothelial cells and prolongs the QT interval; the presence of this alteration on the electrocardiogram warns of a predisposition to the emergence of polymorphic ventricular tachycardia torsades de pointes, which may lead to sudden death, **Figure 5.** PIs are related to atrioventricular block (AVB) and left bundle branch block (LBBB). Observational data suggest that LPV and IDV modify the size of LDL particles and cause insulin resistance, which would increase the risk of CVD (Aguiar; Eira, 2020).

Figure 4

Coagulopathy associated with ARV – Abacavir



Source: (Adapted). Aguiar., 2020.

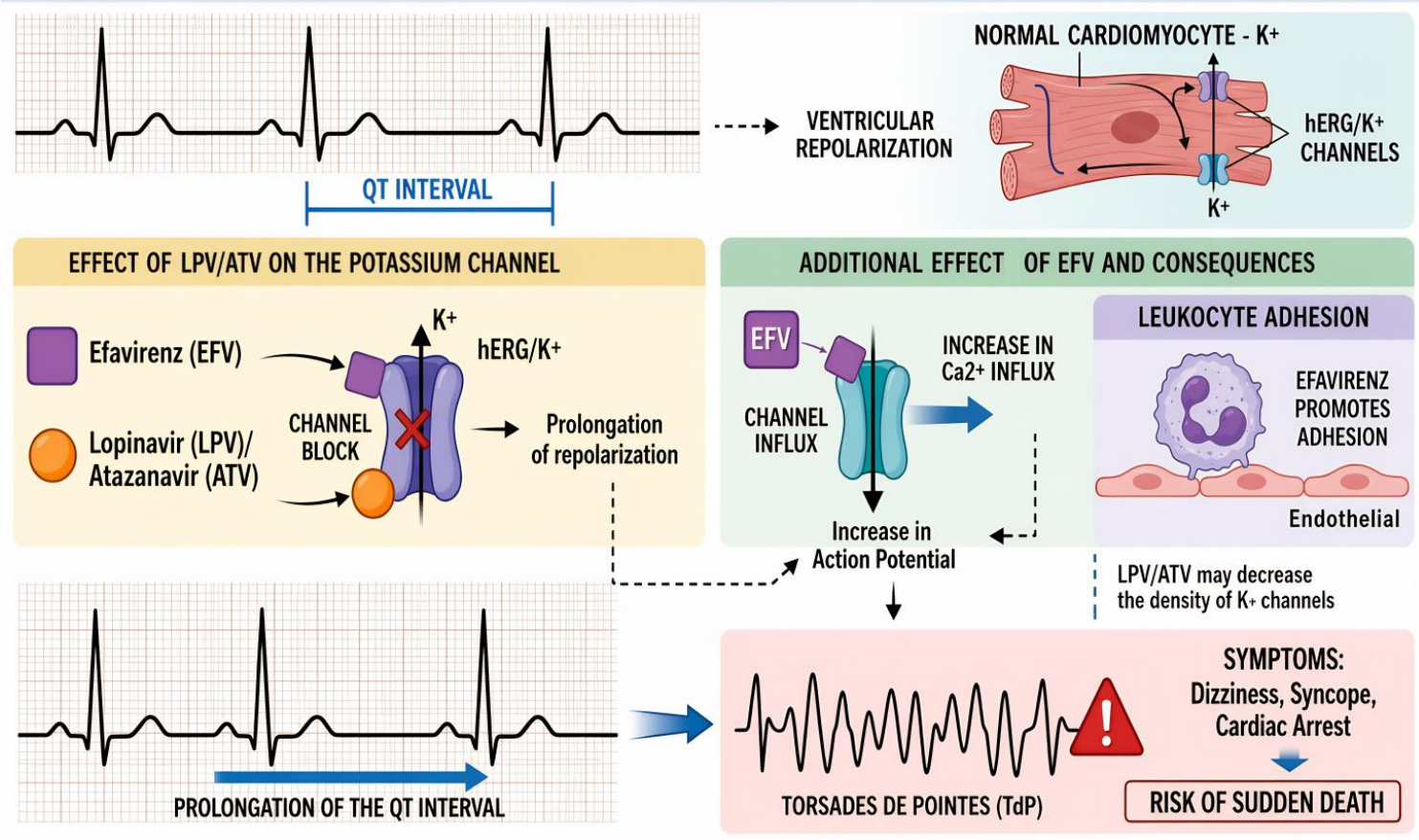
Switching from boosted PIs to raltegravir or dolutegravir results in a better plasma lipid profile and changes in biomarkers associated with cardiovascular events than continuing boosted PI therapy (Obare et al., 2024).

In order to detect and adequately manage early signs of CVD, routine cardiovascular evaluation should be performed in these patients, allowing guidance in the management of risk factors and the choice of ART, particularly among higher-risk individuals (Aguiar; Eira, 2020).

In addition to the direct effects of HIV, plasma cytokines and chemokines also stimulate the endothelium, leading to persistently elevated levels of sVCAM-1 (vascular cell adhesion molecule-1) and sICAM-1 (soluble intercellular adhesion molecule-1). Notably, sVCAM-1 levels decrease with antiretrovirals. Despite the reduction in sVCAM-1 levels, PLWH on ART with effective viral suppression still present higher levels of endothelial inflammation compared with people without HIV. This is confounded by data that implicate ART in endothelial dysfunction, adding complexity to the understanding of the underlying mechanisms in PLWH; endothelial dysfunction among PLWH on therapy has also been associated with monocyte activation (Obare et al., 2024).

Figure 5

Mechanisms of QT interval prolongation caused by antiretrovirals and cardiac risks



Source: (Adapted). Aguiar., 2020

Although treatment with the more recent and highly active ART generally improves low HDL cholesterol, it does not fully normalize the lipid profile in treated PLWH. Notably, several ART classes

have also been implicated in altered lipid metabolism and increased oxidative stress in PLWH, potentially contributing independently to elevated cardiovascular risk (Obare et al., 2024).

Analyzing the risk versus benefits promoted by the use of such medications, it is evident that the comorbidities developed during treatment are minimal when compared with their benefits (Ribas et al., 2020).

There is still much to investigate with the recent introduction of new medications into clinical practice that are not yet available in our country, such as tenofovir alafenamide (TAF) and bictegravir (Aguiar; Eira, 2020). The results of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) provided evidence to support specific recommendations for statin therapy as primary prevention of CVD in people with HIV aged 40 to 75 years in the United States. The REPRIEVE results now provide clear evidence to inform the use of statin therapy as primary prevention among people with HIV aged ≥ 40 years, on continuous antiretroviral therapy, and with low to intermediate ASCVD (atherosclerotic cardiovascular disease) risk (Silva; Silva; Santos, 2025).

These discussions should take into account the benefits together with side effects, costs, potential for drug interaction, and other patient-centered factors. For people with low 10-year ASCVD risk who may experience a more modest absolute benefit from statin therapy, it is particularly important to weigh the potential benefits for the individual against the risks. The REPRIEVE results that reported greater absolute benefit from statin therapy among people with HIV aged 40 to 75 years with higher ASCVD risk informed the panel's decision to recommend the use of at least moderate-intensity statin therapy, with a strong recommendation for those with a 10-year ASCVD risk score >5% to <20% (Silva; Silva; Santos, 2025).

Initiation of statin therapy should be delayed until after pregnancy for people with HIV and ASCVD risk, and statin therapy should be discontinued if pregnancy occurs in the context of HIV. As in the general population, breastfeeding is not recommended during statin therapy. In REPRIEVE, pitavastatin was chosen in part due to the lower potential for drug interaction with certain ARV drugs

compared with other statins. Although there are no comparative efficacy trials of clinical outcomes analyzing different statins among people with HIV, some studies support the treatment effect of other moderate-intensity statins for lipid reduction or reductions in inflammation and immune activation, as well as a treatment effect on surrogate measures of CVD (Silva; Silva; Santos, 2025).

Pitavastatin, atorvastatin, and rosuvastatin are all associated with greater reductions in LDL among people with HIV than pravastatin. In addition, pitavastatin (4 mg), rosuvastatin (10 mg), and high-dose atorvastatin (80 mg) have demonstrated reductions in inflammatory disease, monocytes, and biomarkers of T-cell immune activation among people with HIV. In two separate placebo-controlled randomized phase 2 trials of statin therapy in people with HIV, atorvastatin (initiated at 20 mg per day) was associated with reductions in non-calcified coronary plaque by computed tomography angiography, and rosuvastatin (10 mg) was associated with slower progression of common carotid artery intima-media thickness, **Table 2** (Silva; Silva; Santos, 2025).

Table 2

Comparison of Statins in the Context of HIV

Statin	Cited Dosage	Impact on LDL	Inflammatory and Immunological Markers	Vascular Effect / Clinical Outcome	Interaction Considerations (ART)
Pitavastatin	4 mg	**High**: Superior to pravastatin.	Reduces monocytes (sCD14) and T-cell activation.	35% reduction in major cardiovascular events (REPRIEVE Study).	**Minimal: It is not metabolized by CYP3A4; ideal for those using Protease Inhibitors.**
Rosuvastatin	10 mg	**Very High**: One of the most potent for LDL reduction.	Significant reduction in biomarkers of immune activation.	Reduction in progression of carotid intima-media thickness.	**Low interaction, but doses >20 mg require caution with some ART regimens.**
Atorvastatin	20 mg to 80 mg	**Very High**: Dose-dependent.	Reduction of inflammatory disease (especially at high doses – 80 mg).	Reduction of **non-calcified coronary plaque** (vulnerable plaque).	**High**: Metabolized by CYP3A4. Strongly interacts with Ritonavir and Cobicistat (requires dose adjustment).
Pravastatin	Generally 40 mg	**Moderate**: Inferior to the three mentioned above.	Limited impact on systemic inflammation compared with newer generations.	Less effective in plaque stabilization in PLWHIV.	Low interaction, but less potent for high-risk patients.

Source: (Adapted). Silva; Silva; Santos., 2025

These data motivated the panel's recommendation for the use of at least moderate-intensity statins to include pitavastatin 4 mg per day, atorvastatin 20 mg per day, or rosuvastatin 10 mg per day. The recommendation for which statin agent to select and the intensity of therapy is based on the person's overall risk profile. However, it should also be noted that the magnitude of LDL lowering is variable in clinical practice. Mild increases in liver enzymes are observed in some individuals, although they are generally transient without clinical complications. Nevertheless, the overall clinical benefits of statin use outweigh the overall risks of adverse effects, especially for people with higher estimated 10-year CVD risk (Silva; Silva; Santos, 2025).

CONCLUSION

The research confirmed that prolonged use of Antiretroviral Therapy (ART) establishes a direct correlation with increased cardiovascular risk. Although ART remains the indispensable pillar for controlling viral load and patient survival, the metabolic consequences over the years have become evident. The increase in cardiac vulnerability stems from a multifactorial mechanism involving the intrinsic toxicity of the drugs, persistent inflammatory processes, and profound metabolic disorders, such as dyslipidemia and insulin resistance. Such pathologies do not emerge immediately but become consolidated as deleterious long-term effects that require constant clinical attention.

The main limitation observed lies in the difficulty of isolating pharmacological variables from extrinsic factors, such as lifestyle, suggesting that the cardiac impact may be even more complex than current models describe. In view of this, it is imperative that the clinical management of the seropositive patient transcend virological control. The implementation of continuous follow-up protocols that prioritize cardioprotective diets and regular physical exercise is recommended. The central challenge for contemporary medicine lies in balancing the efficacy of viral suppression with the preservation of cardiovascular integrity, reaffirming that, despite metabolic challenges, ART continues to be the gold-standard intervention and the safest option for maintaining life.

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