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Cardiovascular challenges in the era of antiretroviral therapy for AIDS/ HIV: A comprehensive review of research advancements, pathophysiological insights, and future directions

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ABSTRACT

Cardiovascular disease, particularly coronary heart disease, is becoming more common among those living with HIV. Individuals with HIV face an increased susceptibility to myocardial infarction, also known as a heart attack, as compared to the general population in developed countries. This heightened risk can be attributed mainly to the presence of effective antiretroviral drugs and the resulting longer lifespan. Some cardiac issues linked to non-antiretroviral medications, including myocarditis, endocarditis, cardiomyopathy with dilation, pulmonary hypertension, and oedema of the heart, may affect those not undergoing highly active antiretroviral therapy (ART). Impaired immune function and systemic inflammation are significant contributors to this phenomenon after initiating highly aggressive antiretroviral treatment ART. It is becoming more challenging to determine the best course of treatment for HIV-associated cardiomyopathy due to new research suggesting that protease inhibitors might have a negative impact on the

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development of HF. Currently, the primary focus of research on ART medications is centered on the cardiovascular adverse effects of nucleoside reverse transcriptase inhibitors and protease inhibitors. This review paper thoroughly evaluates the advancements achieved in cardiovascular disease research and explores the potential implications for prospects. Additionally, it considers the field's future prospects while examining how ART might be altered and its clinical applications.

Introduction

Cardiovascular diseases (CVDs) are a broad category of complicated diseases. Cardiomyopathies, thoracic aortic aneurysms, coronary artery diseases, and HF are among the conditions mentioned above. The intricate situations previously described have a significant impact on global deaths. [1-3] The prognosis for CVDs is still dismal despite substantial advancements in pharmacology and surgery, bettering patient outcomes, and raising survival rates. [4-9] Numerous research efforts have shown the significance of genetic variables and their expression profile modifications as the primary catalysts of genetic components and pathological cardiac events. [10-14]

The human immunodeficiency virus (HIV) is still a significant player in infectious disease research. The turning point occurred in 1985 when it was formally classified as a pandemic, a categorization that a group of scientists quickly confirmed. [15] This pandemic's roots are in a zoonotic infection in Central and West African chimpanzees in the early 1900s. Although unprotected pelvic or anal contact is the most common way for the virus to spread, open cuts or sharing needles with someone who is HIV-positive can also expose a person to the virus. [16, 17] The virus undermines immune function by concentrating on CD4+ T cells and reducing their numbers. If this retrovirus infection is not treated, it might progress to a later stage known as acquired immunodeficiency syndrome, or AIDS. [18] People infected with the HIV/AIDS virus are at increased risk of death from CAD. Cardiovascular disease is more likely to occur in those with compromised immune systems, those who do not get enough of certain nutrients, those who are HIV positive, those who use antiretroviral therapy, and those who have a history of cardiovascular disease [19]. The global population of individuals infected with HIV exceeds 36.7 million, and the annual mortality rate due to AIDS and related HIV diseases varies from 1.0 to 2.0 million. [20]

AIDS, also referred to as the "world plague," is a hazardous infectious disease. The human HIV invades T lymphocytes, leading to a progressive decline in the immune system's functionality. Consequently, the weakened immune system renders the human body susceptible to various opportunistic diseases, ultimately resulting in mortality. Presently, the global population of individuals living with HIV amounts to around 39 million. Fortunately, the development of cocktail therapy specifically designed to target HIV-infected

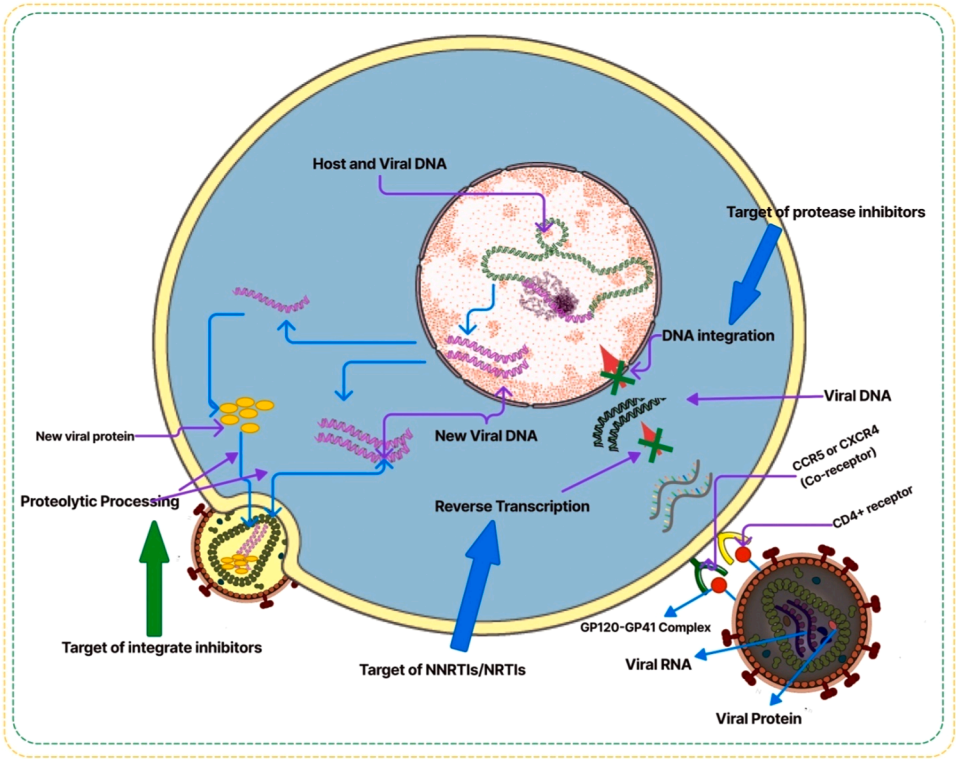

Fig. 1. Various inhibitory mechanisms of ART on the replication of the HIV.

cells has transformed AIDS into a manageable condition in medical settings. This advancement has significantly decreased the mortality rate and alleviated the suffering caused by numerous consequences. [21-23] HIV is an RNA virus with a single strand that invades human T cells through the following procedure [24]. When HIV attaches to particular antibodies on the surface of lymphocytes, the virus is absorbed into the host cell. Viruses rely on the host cell's reverse transcriptase enzyme to replicate itself, which converts RNA into DNA. The viral double-stranded DNA is subsequently integrated into the host cell DNA to enable transcription and protein creation. After a specific packaging phase, the daughter virus strands are discharged from the cell as fully mature viral particles [25] (Fig. 1).

Researchers have discovered that HIV-positive people have an increased risk of developing cardiovascular issues, such as acute myocardial infarction, sudden cardiac death, peripheral artery disease, stroke, and heart failure, regardless of their ejection fraction status. [26] Patients with severe HIV disease and AIDS frequently have HIV-associated cardiomyopathy, which is characterized by systolic dysfunction and left ventricular dilatation. [27, 28] Though the precise causes of HF in young HAART patients remain unknown, several theories have been advanced, including immunological dysregulation, myocarditis, vascular inflammation, HAART toxicity, and chronic low-grade inflammation. Atherosclerosis develops in part because of the chronic, moderate inflammation caused by HIV infection, which occurs through several mechanisms. Patients living with HIV have an increased risk of atherosclerotic plaque rupture due to the increased likelihood of non-calcification in these plaques. [29, 30]

ART is specifically designed to hinder the several mechanisms by which HIV infiltrates cells effectively. Due to its ability to target multiple processes, it is commonly referred to as cocktail therapy. The primary components of backbone medicines consist of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs). NRTIs have a structure that closely resembles nucleosides and is derived from dideoxynucleosides. Upon entering the cell, these drugs undergo phosphorylation to create analogues of dideoxyriboside triphosphate. These analogues can then competitively bind to viral reverse transcriptase alongside cell kernel glycosides. This binding targets the inhibition of the viral reverse transcription process and ultimately stops the synthesis of viral DNA double strands. Protease inhibitors (PIs) hinder the function of proteases, which are responsible for producing and packaging the proteins necessary to assemble viral particles. [31, 32] The conventional cocktail entails the amalgamation of a minimum of three antiretroviral medications to mitigate HIV replication and decelerate the advancement of the sickness. [33, 34] Utilizing ART medication, particularly during the initial phases of HIV infection, can significantly diminish death rates. Nevertheless, although ART has effectively managed the progression of AIDS, it has resulted in evident consequences for patients, including cardiovascular impairment. [35-38]

Moreover, research indicates that the administration of antiretroviral therapy medications to individuals with HIV may potentially

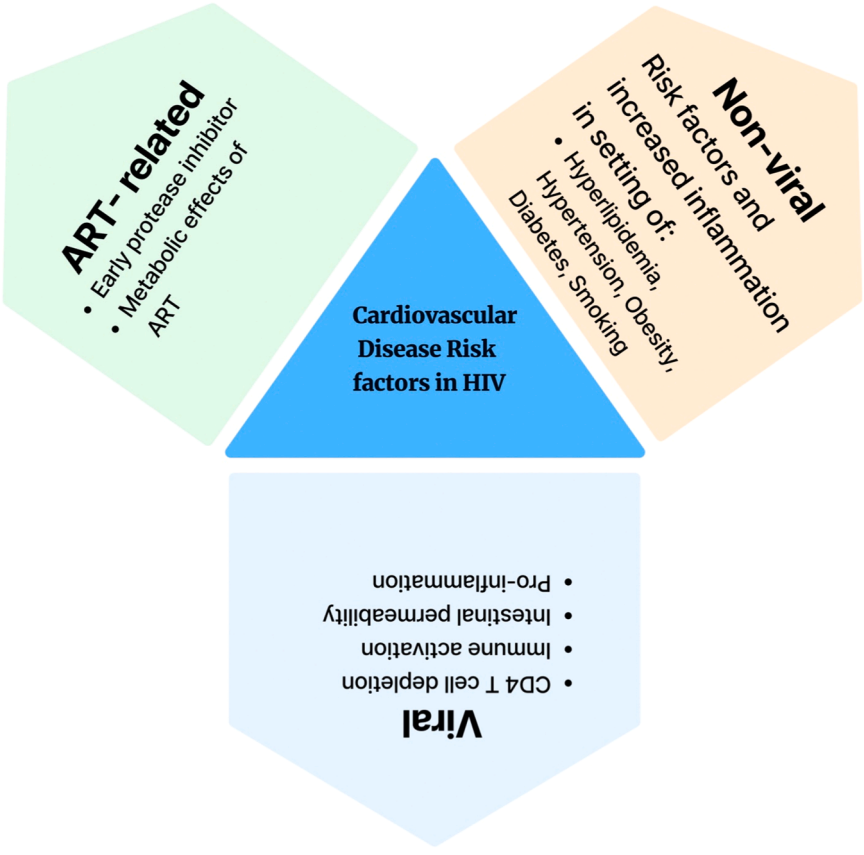

Fig. 2. Graphic demonstrating possible processes of cardiovascular disease related to HIV

lead to heart-related issues. [39] Although individuals with HIV who are receiving treatment and have successfully suppressed the virus are present, the number of new cases of HIV infection is still increasing. Comprehending the mechanisms responsible for HIV-related atherosclerosis, precisely identifying individuals who are susceptible to it and offering efficient treatments to reduce this risk continue to be significant hurdles for cardiologists and HIV healthcare doctor. This article aims to provide an overview of the current scientific advancements in ART in the context of cardiovascular disorders.

HIV-related cardiac disorders: causes and pathophysiology

The progression of cardiac disease in patients with HIV is characterized by an intricate and diverse pathophysiology. [40, 41] Numerous variables, including infections, dietary issues, drug toxicity during HIV-1 therapy, and direct HIV-1 infection of the heart tissue (either alone or in conjunction with myocarditis), are possible contributors. [42, 43] Several different things, including toxic exposure, smoking, substance misuse, and some HIV treatments like NRTIs and protease inhibitors, can bring on heart problems in HIV patients. [44, 45]

Etiological factors of cardiac effects in HIV-associated conditions

Heart problems caused by HIV infection, opportunistic infections, the side effects of highly active antiretroviral therapy (HAART), and the impact of HIV transmission routes, such as intravenous drug use and comorbid diseases, are essential considerations in the area of cardiovascular health in people living with HIV. A thorough comprehension of these characteristics is necessary for developing strategies to decrease the likelihood of cardiovascular complications, enhance the efficacy of treatment, and improve the general health of HIV-positive patients. [46, 47]

Many factors can initiate or exacerbate cardiac issues in HIV-positive individuals and those utilising antiretroviral medications. Several HAART medications may accelerate the development of cardiomyopathies associated with HIV. An elevated risk of cardiovascular events and cholesterol is a prominent adverse effect of HIV protease inhibitors. According to a new study, prelamin A cardiomyopathy may be caused by the buildup of prelamin A, a protein in ageing people's smooth muscle cells of the vascular system and linked to premature senescence. [48] This buildup could be caused by suppressing zinc metallopeptidase STE24 function, which these inhibitors hinder. The current literature goes into further detail about additional relevant factors [49] as show in Fig. 2.

HIV's influence on cardiac disorders

HIV's affects on the heart cause an irregular and structural heart, which puts patients at risk for conduction, pericardial, vascular, and myocardial diseases. [50, 51] Comprehensive studies including a large group of individuals show a notable rise in the probability of experiencing a heart attack in people with HIV compared to those who are not infected. The risk of developing CAD is 1.5 to 2 times higher in this group. [52, 53] HIV and HIV-associated myocarditis can result in cardiac failure and cardiomyopathy. HIV can directly infiltrate cardiac myocytes, causing inflammation and compromised heart function at the later stages of infection. [54, 55] Cardiovascular magnetic resonance imaging (CMR) shows that untreated patients who have HIV/AIDS (PLWHA) have abnormalities in their heart muscles, including inflammation, increased levels of lipids inside the heart muscle, and reduced heart function. [56, 57] Additional research indicates that persons undergoing Highly Active Antiretroviral Therapy (HAART) develop myocardial fibrosis and cardiac steatosis, which can be detected using cardiovascular magnetic resonance (CMR) imaging. [58, 59] Within individuals living with HIV/AIDS who are undergoing ART, the presence of myocardial fibrosis and myocardial steatosis are contributing factors to diastolic dysfunction. [60, 61] Individuals with perinatally-acquired HIV (PHIV) have higher levels of markers indicating cardiac fibrosis. Myocarditis is a common cause of mortality in AIDS patients. Mycobacterium avium-intracellulare, Cryptococcus neoformans, and Toxoplasma gondii are frequently found in patients with left ventricular failure and severe disease stages autopsies. Diastolic dysfunction was observed in 48% of the 802 HIV-positive individuals. This condition was most prevalent in individuals over 55, with a rate of 85.6% [62, 63].

Nutrient depletions

People living with HIV may get ventricular dysfunction due to nutritional deficits. Essential nutrients like selenium, vitamin B6, and growth and thyroid hormones can be lost due to HIV-related malabsorption and diarrhoea. Cardiomyopathy and left ventricular failure have been associated with these factors.[64, 65] An essential part of the cellular damage seen in AIDS is thought to be caused by the "oxidative stress" hypothesis. The pathophysiology of dilated cardiomyopathy and abnormal left ventricular failure includes selenium insufficiency. Selenium insufficiency, which is associated with the Chinese cardiomyopathy called Keshan disease, is observed in individuals with HIV-1 infection. [66, 67] In Rwanda, researchers looked at 416 people who tested positive for HIV. Cardiomyopathy was almost twice as likely in people whose blood selenium levels were lower, according to the study. A statistical method known as multivariate analysis was used to discover this correlation. [68, 69] As a possible solution, selenium salts have been suggested by some. Current research out of Scotland indicates that the majority of HIV/AIDS patients and their families are deficient in selenium, antioxidant vitamins, and glutathione peroxidase. That being said, we need further studies to prove that oxidative stress is a cause of HIV-related muscle disease. [70-72]

Clinical cardiovascular disease associated with antiretroviral therapy drugs

The United States National Institutes of Health (NIH) has announced that HIV patients have a high rate of cardiovascular illness and has established a specific research program to fund studies in relevant fields. [73, 74] Several variables, including the inflammatory response and prolonged immune system activation produced by HIV, contribute to the development of HIV-related cardiovascular disorders [75, 76]. Additionally, the adverse effects of ART medicines have garnered increasing attention [77, 78]. Currently, it is well accepted that ART medications primarily contribute to HIV-related cardiovascular illnesses through two main mechanisms: firstly, by inducing metabolic disorders through alterations in lipid metabolism, and secondly, by directly harming tissues through the effects of individual drugs. [79, 80]

Several clinical studies have indicated that protease inhibitor (PI) medicines used in ART can have a considerable impact on dyslipidemia in individuals with HIV, leading to the redistribution of body fat, insulin resistance, and other related symptoms. [81, 82] As an illustration, the findings from the AIDS clinical data survey conducted at Vienna Central Hospital in Australia revealed that the levels of plasma cholesterol and triglycerides in HIV-positive patients increased after a 3-month treatment with PI medications. Although the TGs and low-density lipoprotein cholesterol (LDL-C) levels were much more significant, the amount of HDL-C in plasma was significantly lower. [83, 84]

However, over six years, 157,921 HIV-positive patients at 212 designated AIDS medical points in the US, Australia, and other countries were monitored by the international research group of ART drug side effect data analysis in Europe as part of their investigation into the relationship between NRTIs and cardiovascular disease. The prevalence of heart attack rose by 49% and 90% in HIV-positive individuals who initiated treatment with the NRTI medications abacavir and didanosine, respectively, in comparison to HIV-positive individuals who did not receive these two medications. [85, 86] Furthermore, the British Tropical Medicine Research group performed a statistical examination of clinical data obtained from the HIV Treatment Center Hospital in Limbe, Cameroon. Their study revealed a direct correlation between the administration of ART medications and the occurrence of hypertension in patients. [87, 88] The statistical analysis revealed that the administration of ART medicines increased the occurrence of hypertension in HIV-positive patients by two-fold in comparison to those who did not get ART drugs. [89, 90]

Impacts of antiretroviral therapy drugs on arteriosclerosis

Arteriosclerosis is when the arterial wall thickens and hardens, resulting in a loss of elasticity and a narrowing of the artery's lumen. It is a non-inflammatory lesion that encompasses degenerative and proliferative changes. Atherosclerosis, a prevalent form of arteriosclerosis, is the primary factor behind myocardial infarction and cerebral infarction. [91, 92] The aberrant multiplication and movement of vascular smooth muscle cells primarily cause arteriolar media thickening. Under the influence of zidovudine (a type of NRTI drug) or Indian that wei (a type of PI drug), the co-culture of vascular smooth muscle cells and endothelial cells damages the endothelial cells. This damage leads to the endothelial cells' secretion of a growth factor called endothelin-1 (ET-1). Subsequently, endothelin-1 stimulates the proliferation of vascular smooth muscle cells. [93, 94] Arteriosclerosis is typically not detected until it has advanced to a point where it causes severe infarctions. However, numerous ways are available to measure and assess the extent of arteriosclerosis. Intima-medium thickness (IMT) and cross-sectional area (CSA) are universally acknowledged as reliable techniques for identifying arteriosclerosis without evident clinical manifestations. [95, 96] This technique is also extensively employed for assessing the condition of the carotid artery in individuals who are HIV-positive. [97, 98] Administration of zidovudine and Inavir in a mouse model resulted in an augmentation of both the intima medium thickness and the transverse area of the artery. Corroborating clinical observations, the rise in intimal media thickness caused by ART medications in mice was primarily due to neointimal hyperplasia. This involved accumulating many pathogenic vascular smooth muscle cells in the expanded intima. [99] According to research into the causes of arteriosclerosis associated with ART, the main culprit is the arterial wall REDOX balance disturbance. Mice administered ART treatment had significantly elevated Reactive oxygen species levels and immunofluorescence staining of oxidised or reduced glutathione in their vascular tissue. The glutathione there was a significant drop in the glutathione REDOX ratio (GSH/GSSG).

Simultaneously, following the identification of cholesterol, triglyceride, and 8-isoprostaglandin F2α, the final byproduct of lipid peroxidation in mouse plasma, it was observed that ART substantially elevated the levels of cholesterol and 8-isoprostaglandin F2α in mouse plasma. However, there was no alteration in the level of triglyceride. Maintaining a balanced REDOX status is crucial for the body's stability. [100] The body has several mechanisms to eliminate too many ROS to protect itself from oxidative stress. Observing the GSH/GSSG ratio can provide insight into the efficacy of REDOX within the body. An increase in ROS levels in the body is correlated with a decrease in the GSH/GSSG ratio. [101] Elevating cholesterol levels in mice significantly promotes the onset of arteriosclerosis, with the generation of ROS and oxidative stress also contributing factors to arteriosclerosis. Another hypothesis suggests that the damage to the endothelial cells induced by ART increases the ability of platelets to stick together, resulting in their activation and the subsequent release of platelet-derived growth factor. This process ultimately stimulates the formation of new tissue within the inner layer of blood vessels, known as neointimal proliferation. [102]

Correlation of antiretroviral therapy drugs with vascular endothelial disorders

The primary biological occurrence during the initial phase of vascular disease is an abnormality in endothelial cells. Endothelial cell diseases encompass the activation of vascular endothelial cells, leading to increased production of endothelial cell adhesion molecules and the impairment of normal physiological processes, such as the attenuation of vasoconstriction and vasodilation. [103] There is ample evidence to demonstrate that ART medications directly increase the expression of adhesion molecules in endothelial

cells, such as VCAM-1, ICAM-1, and E-selectin, leading to chronic vascular inflammation. The receptors of inflammatory lymphocytes, such as monocytes and macrophages, identify these adhesion molecules. [104] This recognition leads to lymphocyte rolling, adhesion, and migration on the vascular endothelium. As a result, inflammatory cells invade and accumulate in the vascular wall, causing the proliferation of the vascular intima. [105] Research has demonstrated that ART can induce dysfunction in mouse arterial endothelial cells in a live organism, impair the ability of artery endothelial cells to relax blood vessels, and elevate the levels of ET-1, a prominent indicator of endothelial disorders in mouse plasma. [106]

Similarly, the level of ET-1 in aortic endothelial cells treated with ART in a laboratory setting showed a substantial increase. Conversely, in laboratory trials when ART medicines are applied to endothelial cells, it has been discovered that these treatments can impede the production of endothelial oxide synthase (eNOS), thereby diminishing the levels of nitric oxide catalyzed by eNOS. eNOS, or endothelial nitric oxide synthase, is primarily accountable for the production of nitric oxide in vascular endothelial cells. Nitric oxide is a compact, lipid-soluble gas molecule that primarily controls the function of vascular endothelial relaxation. As a result, it regulates vascular tension and maintains cardiovascular system homeostasis. ART-induced endothelial problems are characterized by reduced availability of nitric oxide while simultaneously promoting vascular inflammation and impaired control of blood vessel constriction and dilation.

Vascular endothelial cells possess unique characteristics compared to other cell types in the body, with notably lower mitochondrial content relative to other cell types. Endothelial cells primarily utilize glycolysis, rather than mitochondria-dependent oxidative phosphorylation, to metabolize glucose and produce heat for their life processes. Consequently, a significant portion of mitochondrial function in endothelial cells is dedicated to maintaining the homeostasis of these cellular activities. Hence, the endurance of mitochondria dictates the endurance of vital functions in endothelial cells. The present investigation revealed that ART medications induced mitochondrial harm in endothelial cells within a minimal timeframe of 6 hours.

Furthermore, there was a decrease in cellular oxygen consumption and mitochondrial membrane potential. Reactive oxygen species are excessively released from the mitochondrial electron transport chain when ART interferes with the regular operation of mitochondria in vascular endothelial cells. This upsets the delicate balance of REDOX regulation and raises intracellular ROS levels. Many disorders affecting vascular endothelial cells begin with an overabundance of ROS in the blood vessels and the subsequent oxidative stress response. Studies conducted in living organisms have demonstrated that the administration of MnTMPyP, a stable reactive oxygen species scavenger in combination with ART, alleviated neointima hyperplasia in mice. Simultaneously, there was a notable reduction in the ROS levels in the artery endothelial cells of mice. Hence, another factor contributing to vascular dysfunction induced by ART drugs is the elevation of oxidative stress in endothelial cells, resulting in impairment of ENOS-mediated vasodilation, stimulation of ET-1 secretion, and ultimately disrupting the equilibrium of vascular endothelial homeostasis, leading to the development of vascular diseases. [107]

Impacts of antiretroviral therapy drugs on cardiomyopathy

HIV-positive patients commonly suffer from cardiomyopathy, which is the most prevalent form of cardiac disease. [108, 109] The cause of AIDS-related cardiomyopathy is yet unknown. Several factors contribute to the development of cardiomyocyte damage, including HIV infection, opportunistic infections, inflammatory response, cytokine effects, and the direct toxic effects of ART medicines, mainly nucleoside reverse transcriptase inhibitors (NRTIs). [110] Cardiomyocytes have a plentiful amount of glycogen particles and mitochondria to support the ongoing rhythmic contractile actions of the heart adequately. [111] Empirical evidence from clinical and fundamental research has demonstrated that NRTI medications can induce mitochondrial problems in cardiac tissue. [112] Observations were made of mitochondrial DNA loss and reduced copy number of human cardiomyocytes following extended treatment with low-concentration NRTI medicines. Due to the striking similarity between the structure of DNA polymerase γ in mitochondria and HIV reverse transcriptase, NRTI medications hinder the functioning of mitochondrial DNA polymerase γ in cells, thereby impeding both the activity of HIV reverse transcriptase and mitochondrial DNA replication [113]. Therefore, the removal of mitochondrial DNA results in the removal of peptides encoded by mitochondrial DNA that are important in oxidative phosphorylation, ultimately leading to the malfunction of mitochondria in cardiac cells. [114] Cardiomyocytes experience energy depletion due to malfunctioning mitochondria, resulting in decreased mitochondrial respiratory oxygen consumption and respiratory control rate. This is accompanied by a decline in the ratio of fatty acid oxidation and the accumulation of triglycerides. [115, 116]

Furthermore, the identification of cardiac markers in mice administered NRTI medicines indicated that these treatments induced oxidative stress in mitochondria, resulting in the development of cardiomyopathy. Studies on mechanisms have discovered that NRTIs stimulate the mitochondria of cardiomyocytes to generate excessive mitochondrial ROS by disrupting mitochondrial SOD2 (superoxide dismutase 2). This surpasses the ability of the mitochondria's oxygen-free radical scavenging system to eliminate them, resulting in functional abnormalities and programmed cell death (apoptosis) of cardiomyocytes.

Limitations

When examining this analysis, it is crucial to consider specific limitations that apply to many conducted and presented studies. The methodology and evidence-based criteria for HIV management drugs are continuously modified to improve the health outcomes for People Living with HIV (PLHIV). Therefore, the best approach, which involves using the most efficient pharmacological combinations while minimizing the risk of adverse effects, undergoes periodic modifications. The dynamic nature of these medications makes it challenging to track the effects on people living with HIV over time, as healthcare providers continuously modify their treatment plans. The intricacy increases when people living with HIV (PLHIV) receive simultaneous treatment for other pre-existing or subsequent

illnesses, especially cardiovascular disorders.

Moreover, the presence of diverse characteristics among individuals living with HIV (PLHIV), which are shaped by social, economic, and genetic factors, can hinder the comprehensive examination of the lasting impacts of HIV antiretroviral therapy if not adequately taken into account throughout the research. Considering the changing nature of treatments, it is essential to recognize the lack of information regarding the interactions between new HIV therapeutics and the present medication regimens routinely used for treating cardiovascular problems. Research in this field is necessary as therapy advancements continue to develop. On the other hand, people with HIV frequently have additional illnesses and risk factors that can make the occurrence of cardiovascular issues more complex. PLHIV commonly exhibit weakened immune systems, dyslipidemia, and atherosclerosis, which increases their susceptibility to a more significant occurrence of cardiovascular comorbidities and poorer health outcomes. This exacerbates the association between HIV and cardiovascular illnesses. Furthermore, the data's precision might be impaired due to sample mistakes arising from

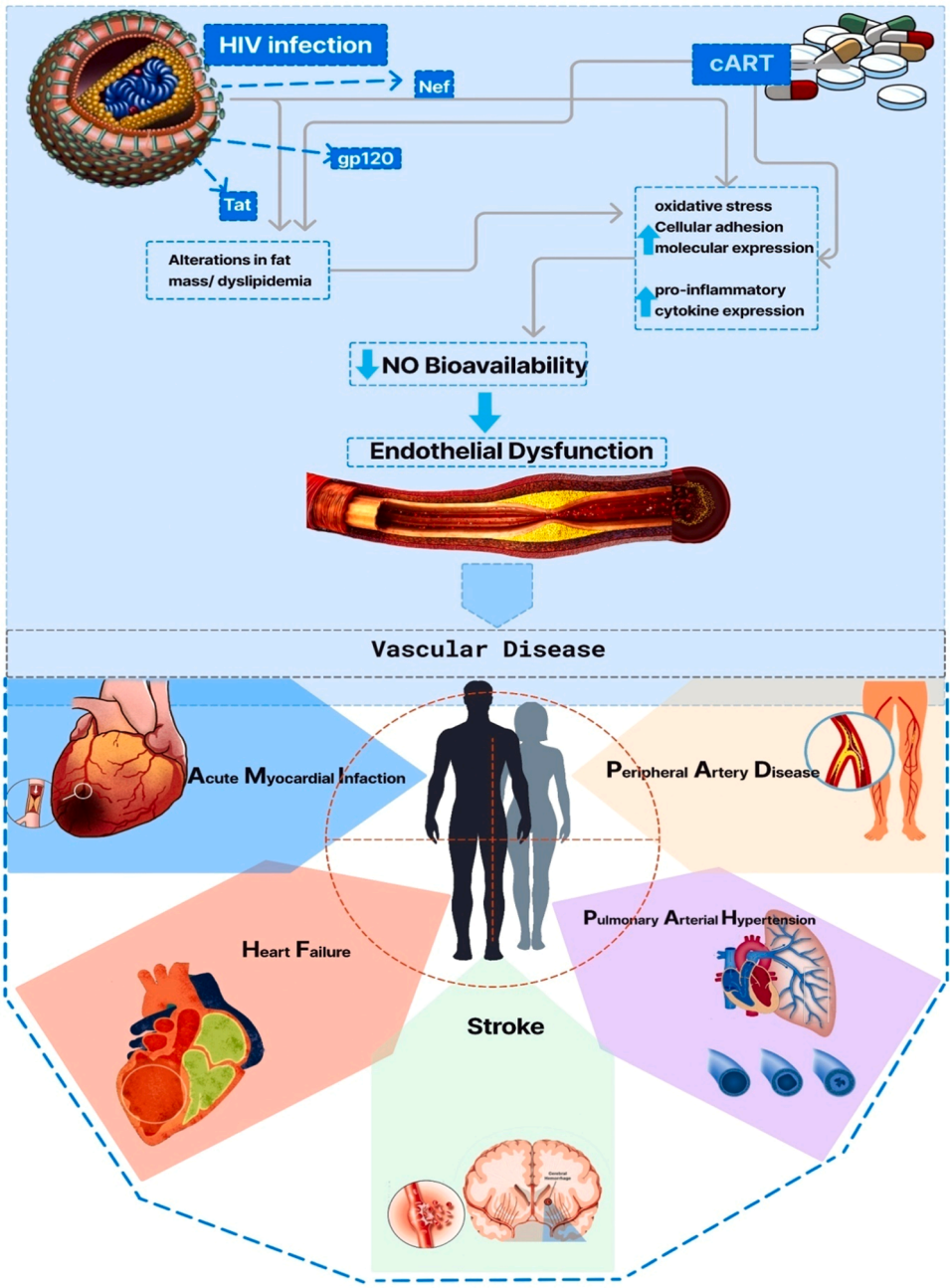

Fig. 3. Diagram showing the possible pathways by which antiretroviral medication in combination with viral infection may cause vascular disease in HIV-positive patients.

populations with diverse socioeconomic levels.

Regions with low socioeconomic status and poverty have a higher prevalence of HIV. This is due to limited access to healthcare and education, which leads to riskier health behaviours and increased rates of HIV infections and other diseases, particularly cardiovascular conditions and related comorbidities. Therefore, it is crucial to carefully analyse research results, taking into consideration these various elements.

Given the multifaceted nature of CVDs, the elevated presence of traditional risk factors in HIV patients, and the strong evidence that CVD is the top cause of death among HIV patients on combination antiretroviral therapy (cART), our knowledge of the underlying causes of CVD is limited. Evidence from clinical and experimental studies establishes that cART and viral proteins have distinct effects on endothelial dysfunction. Modifying metabolic function and fat distribution is likely the mechanism by which this process is accomplished. It also includes persistent immune system stimulation, which causes nitric oxide to be less available and causes blood vessel dysfunction (Fig. 3).

Conclusion and future perspectives

To summarize, HIV-associated cardiomyopathy continues to be a significant worry for those who have HIV/AIDS, even though there has been significant progress in HIV treatment with the use of Highly Active Antiretroviral Therapy (HAART). The increased susceptibility to cardiomyopathy and HF among people living with HIV/AIDS (PLWHA) remains present, even after taking into account well-known cardiovascular risk factors. The presence of atherosclerosis in individuals with HIV infection remains a notable health obstacle, with potential consequences for mortality, significantly as this group of patient's advances in age. Although it has been twenty years since the first reports of heart attacks in people with HIV, there is still a significant lack of understanding regarding the root causes of HIV-related cardiovascular illness characterized by the buildup of plaque in the arteries. Furthermore, there is a continuous requirement to create therapeutic approaches focused on diminishing the likelihood and improving the management of cardiovascular illness in those who have HIV.

Consequently, this poses substantial challenges in clinical investigation and research. Furthermore, due to the multifactorial nature of HIV-related cardiovascular illness, it remains uncertain how the numerous causes interact with each other and the relative contribution of each cause. Consequently, investigating the clinical and molecular basis of cardiovascular illness resulting from ART therapy has emerged as a new area of research in the treatment of AIDS. A thorough and precise comprehension of the pathogenesis of cardiovascular diseases resulting from ART therapy will significantly facilitate the enhancement of ART drugs and the advancement of adjunct drugs for ART therapy to minimize the adverse effects of ART therapy and enhance the efficacy of AIDS treatment. However, ART medicines, particularly protease inhibitors (PI), have been discovered to efficiently manage the progression of Kaposi's sarcoma (KS) by triggering programmed cell death of tumour cells and inhibiting the formation of new blood vessels in tumours [117]. Hence, ART medicines are expected to possess promising antitumor properties.

Focusing on efforts to find accurate biomarkers for HIV-positive patients that can serve as stand-in indicators for cardiovascular disease is essential to advancing HIV research. To learn all they can about the metabolic and cardiovascular complications of HIV infection and therapy, researchers are trying to set up an interdisciplinary clinical research network. An essential goal of this study is to determine whether and how host and virus-related factors, such as genetics and lifestyle, contribute to the onset of cardiovascular disease in people living with HIV. Research into the intricate mechanisms behind HIV-related heart failure is also ongoing, as is an examination of the potential impact of antioxidant and anti-inflammatory medications on endothelial dysfunction brought on by HIV and ART. The primary objective of these collaborative research initiatives is to expand our comprehension of cardiovascular problems in individuals with HIV and make valuable contributions to the advancement of more effective techniques for prevention, diagnosis, and treatment. [118] Further investigation into the underlying mechanisms, mainly into what causes gender differences in the incidence of CVDs, is required in the future.

Compliance with ethical standards

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The authors declared that they have no competing interests among them.

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