International Journal of Cardiovascular Sciences. 2018;31(5)538-543

REVIEW ARTICLE

# Cardiovascular Complications of HIV

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## Abstract

With the advent of the antiretroviral therapy (ART), people infected with HIV are experiencing a significant increase in life expectancy. However, as this population ages, the morbidity and mortality due to events not related to HIV infection and/or treatment become increasingly clear. Cardiovascular diseases are among the major causes of death, and, thus, understanding the factors that trigger this situation is necessary. This review article will assess how the intrinsic and extrinsic factors related to HIV, ART and the associated risk factors can aid the epidemiological transition of mortality in this population. Moreover, we will present the studies on the epidemiology and pathogenesis of each clinical condition related to HIV-infected individuals, in addition to introducing the major markers of cardiovascular disease in this population. Finally, we will point the main issues to be addressed by health professionals for an adequate prognosis.

## Introduction

Since the first case reported, HIV infection has become a worldwide public health problem. Over 36 million people are estimated to be infected with HIV, and approximately 1.1 million deaths were attributed to that infection in 2015. In addition, by the end of 2015, more than 2.1 million new cases were identified.[1]

Pharmacological strategies have been created aimed at reducing HIV replication in infected individuals. The pharmacological intervention was monotherapy with zidovudine (AZT), which inhibits the action of reverse transcriptase.[2] Later, in the mid-1990s, antiretroviral therapy (ART) was introduced, significantly changing the course of HIV infection, with consequent increase in the life expectancy and quality of life of infected individuals.

Although essential to treat HIV infection, ART is associated with several side effects. The most studied impairments are those related to the metabolism of glucose and lipids, and the lipodystrophy syndrome.[3,4]

This set of changes has affected the mortality of those individuals. Previous studies have confirmed that their causes of death are associated with diseases not related to HIV, but to ART.[5] The major causes are neoplasms and cardiovascular diseases.

This review was aimed at summarizing the studies on cardiovascular diseases and their risk factors in HIV-infected people.

## Keywords

Cardiovascular Diseases; HIV; Acquired Immunodeficiency Syndrome; Acute Retroviral Syndrome/therapy; Inflammation Mediators.

## Cardiovascular diseases in HIV-infected people

Traditional cardiovascular risk factors are known to be directly related to mortality in the general population.[6] In HIV-infected people, some risk factors, such as smoking habit and use of illicit drugs, can be more frequent than in the non-infected population.[7,8] In addition, the infection per se can pose a higher risk of cardiovascular disease because of the adverse effects of the continuous use of ART.[9,10]

One of the major characteristics of the relationship between HIV and cardiovascular disease is the higher carotid intima-media thickness. This condition of subclinical atherosclerosis is directly associated with modifiable risk factors, except for the male sex.[11] One possible explanation for that characteristic is associated with ART effects on the lipid metabolism, with increased LDL-c, triglycerides and total cholesterol.[12]

Regarding the modifiable risk factors and mortality in HIV-infected people, the smoking habit, arterial

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DOI: 10.5935/2359-4802.20180049

Manuscript received June 29, 2017; revised manuscript October 05, 2017; accepted November 17, 2017.

hypertension and diabetes were independently associated with a higher risk for death during ART.[13] Such findings show the immediate need to create resources to raise that population's awareness about those risk factors.

Of the cardiovascular diseases that affect HIV-infected people undergoing ART, ischemic and non-ischemic myocardial diseases stand out.[14,15]

## Ischemic cardiovascular diseases

Regarding the ischemic diseases that affect HIV-infected people, acute myocardial infarction stands out. In addition, the incidence of sudden cardiac death of HIV-infected patients is significantly higher as compared to that of the general population with similar risk factors.[16]

In the D:A:D study, acute myocardial infarction accounted for more than 50% of the causes of death due to cardiovascular diseases, followed by stroke.[13] In addition, as age advantages, the mortality rate due to those causes increases from 0.27 per 1,000 among young people to 16.99 per 1,000 in people aged over 70 years.[17] Corroborating those data, the mortality due to acute myocardial infarction of HIV-infected people was shown to be as much as three times higher than that of people of their same age.[18,19] According to a recently published study, HIV-infected people are at a higher risk for cardiovascular diseases as compared to the general population of the United States. In addition, seropositive males develop a higher risk of cardiovascular diseases throughout life, while women are at lower risk as compared to the general population of the United States.[20]

Of the risk factors associated with acute myocardial infarction in HIV-infected people, the following are worth noting: age, male sex, smoking habit, hypertension, diabetes mellitus, dyslipidemia, moderate to high Framingham score, and use of protease inhibitors for at least 18 months.[19,21]

## Disorders of the heart's electrical conduction system

People with HIV infection have a change in the heart's electrical conduction system. The major findings have shown a prevalence of prolonged QT interval on the electrocardiogram ranging from 28% to 65%.[22,23] In addition, regardless of the autonomic dysfunction or ART, there is a greater risk for ventricular arrhythmias and mortality due to prolonged QT interval in HIV-infected patients on combined ART.[24]

Moreover, autonomic cardiac dysfunction has been shown in that population. Individuals infected with HIV undergoing ART have increased sympathetic activity and a consequent increase in heart rate variability, shown by the heart rate values at rest.[25,26] Those data indicate an autonomic system imbalance, in which the sympathetic activity overlaps the parasympathetic activity.

## Pulmonary hypertension

Pulmonary hypertension related to HIV has a conflicting epidemiology. In developing countries, its prevalence ranges from 0.6% to 13%, while in developed countries, it is 0.5%.[27,28] Pulmonary hypertension related to HIV can occur in any stage of the infection and associates with neither CD4+ cell levels nor viral load.[29] The most frequent symptom of pulmonary hypertension is dyspnea, but other symptoms, such as lower limb edema, syncope, fatigue, dry cough and chest pain, can be reported.[30] For individuals classified as NYHA functional class III-IV, the prognosis tends to be unfavorable, with a survival time of three years.[31]

Although there is no cure, the condition can be treated. The options include support treatment, such as oxygen therapy, diuretics and oral anticoagulants, and specific medications for pulmonary hypertension, such as prostaglandins, endothelin receptor antagonists and calcium channel blockers.[30] Special care should be taken regarding the interaction between ART and the medications for pulmonary hypertension, mainly calcium channel blockers.

## Cardiomyopathy

With the advent of ART, cardiomyopathy became frequent in HIV-infected people. The prevalence of systolic and diastolic dysfunction is approximately 8.3% and 43.3%, respectively.[32] In addition, myocarditis and dilated cardiomyopathy are observed in that population. Cardiomyopathy is associated with the increase in mortality caused by heart failure,[33] and is usually associated with socioeconomic status, long use of ART, low lymphocyte count (mainly CD4+ cell), high viral load and low serum level of selenium.[34]

The assessment of HIV-infected individuals with cardiomyopathy should follow the recommendations for the general population. However, factors that can require specific therapies, such as opportunistic diseases, cardiotoxic drugs and coronary artery disease, should be investigated.[35]

## Pericardial disease

Pericardial disease is the most common heart disease among HIV-infected individuals. One of the major risk factors for its development is opportunistic infection, mainly tuberculosis.[36] Pericardial disease can be caused by opportunistic diseases, being used as a marker of progression of HIV infection, because it associates with a shorter survival.[37]

## Markers of cardiovascular diseases in HIV-infected individuals

Some markers that are directly related to cardiovascular mortality in HIV-infected people can be measured and, therefore, used in clinical practice. Regarding inflammation, interleukin (IL)-6 and C-reactive protein stand out.[38] In HIV-infected people, those markers are increased by 50% to 152% as compared to those of non-infected individuals.[39,40] In addition, they are associated with all-cause mortality, including that due to cardiovascular diseases.[41,42]

Of the thrombolytic factors, fibrinogen and D dimer stand out. Those markers are increased by 8% to 94% in HIV-infected people as compared to those in the non-infected population. In addition, they correlate directly with viral load (amount of HIV RNA copies) and all mortality causes.[40,43,44]

The endothelial function is measured by use of the vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM). Those molecules relate directly to the viral load and consequent cardiovascular death, because they affect more than 40% of the arterial lumen of HIV-infected patients.[43,45,46]

Finally, it is worth noting that the HDL-c concentrations, which are reduced by 13% to 21% in HIV-infected people as compared to non-infected people, are inversely related to the viral load and directly related to cardiovascular mortality.[39,47]

## Dyslipidemia

In HIV-infected people, undergoing or not ART, the change in the lipid profile can promote the atherosclerotic process and increase the risk for cardiovascular diseases.[11] Thus, in clinical practice, it is important to understand how the factors inherent in infection and in treatment can trigger changes in the lipid profile.

The HIV infection per se causes changes in the lipid profile. The HIV viremia increases the serum concentrations of triglycerides and LDL-c.[48] Studies on the mechanisms of how HIV causes dyslipidemia are scarce. However, factors, such as an exacerbated inflammatory profile, reduced lipid clearance and increased hepatic vLDL-c synthesis, can be an explanation.[49,50]

Another triggering factor of dyslipidemia in HIV-infected people is the use of ART. The drug increases the concentrations of triglycerides, LDL-c and total cholesterol. Although initially associated with the use of protease inhibitors, some studies have shown that nucleoside analog and non-nucleoside analog reverse transcriptase inhibitors can trigger that condition.[51-53] The mechanisms of how the ART causes dyslipidemia have not been totally clarified, but the binding site seems to have high affinity with the catalytic site of the HIV protease, thus, binding and inhibiting the homologous protein involved in the lipid metabolism, inducing an increase in the blood concentrations of that substance.[54]

## Metabolic syndrome

Metabolic syndrome (MS) is characterized by the presence of hyperglycemia or diabetes mellitus, altered blood pressure or systemic arterial hypertension, abdominal obesity and dyslipidemia.[55,56] Metabolic syndrome has been reported to relate to morbidity and mortality worldwide, mainly because of complications involving the cardiovascular system.[57,58] Epidemiological studies have shown that the incidence of MS in HIV-infected people ranges from 18% to 50%.[59-61]

Some factors are known to be fundamental for the diagnosis of MS in HIV-infected people. Conditions related to the infection, ART, adipose tissue distribution and dyslipidemia seem to stand out.[62-64]

One of the major side effects of ART is the lipodystrophy syndrome, characterized by lipoatrophy (reduced adipose tissue) of the upper and lower limbs and face, with lipohypertrophy (increased adipose tissue) in the central and cervical regions. As a consequence, the waist circumference increases, but for HIV-infected patients this criterion seems not to be fundamental for the diagnosis of MS.[65] Finally, the adipose tissue accumulation in the central region of the body can lead to other disorders, such as insulin resistance and cardiovascular diseases.

## Glucose metabolism disorder

Diabetes mellitus is a systemic disease caused by an insulin and/or glucose metabolism disorder. Although the

risk factors for its development in HIV-infected people are similar to those in the general population, epidemiological studies have reported a prevalence of type 2 diabetes mellitus in HIV-infected people ranging from 3% to 14%.[66-70] In addition, 35% to 63% have insulin resistance.[71-74]

Diabetes mellitus can relate to the development of other diseases in HIV-infected people, such as neurocognitive changes, kidney failure and albuminuria.[75] In addition, it associates with an increased risk for cardiovascular diseases and consequent mortality.[76]

The mechanisms leading to type 2 diabetes mellitus in HIV-infected people remain to be explained. However, type 2 diabetes mellitus is known to be directly related to the accumulation of adipose tissue, an increase in proinflammatory cytokines (mainly TNF-alpha), and, thus, insulin resistance.[77,78] Therefore, physical exercise and/or dietary reeducation programs become important to prevent and treat that condition.

## Future perspectives

Based on that information, programs of cardiovascular disease prevention are required. A recent study has suggested the use of cardiovascular disease stratification and prevention programs.[79] Thus, multidisciplinary care should be encouraged to significantly reduce the side effects of ART, and, consequently, ART-related mortality.[80]

## Conclusion

The risk factors for cardiovascular diseases of HIV-infected people are similar to those of the general population. However, because of HIV infection and its treatment, those individuals are at higher risk for cardiovascular morbidity and mortality. In addition, the mechanisms by which HIV and ART lead to cardiovascular diseases are yet to be explained. Finally, prevention should be the first step to reduce the incidence of that type of disease in that population.

## Author contributions

Writing of the manuscript: Zanetti HR, Roever L, Gonçalves A, Resende ES. Critical revision of the manuscript for intellectual content: Zanetti HR, Roever L, Gonçalves A, Resende ES.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This article is part of the thesis of Doctoral submitted by Hugo Ribeiro Zanetti, from Universidade Federal de Uberlância.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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