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Review article

Cardiovascular compromise in the infection by the human immunodeficiency virus

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ABSTRACT

Human immunodeficiency virus (HIV) infection was associated with increased morbidity and mortality, predominantly for opportunistic infections in the era prior antiretroviral therapy. Patients have experienced increased survival and cardiovascular involvement. The etiology of these clinical conditions could be related to the infection itself, adverse events associated with antiretroviral therapy, or adverse events produced by the combination with other drugs. Some of these conditions have an acute onset, and their rapid recognition is vital for a better prognosis.

Keywords: Human Immunodeficiency Virus; Cardiovascular Diseases; Acquired Immunodeficiency Syndrome (source: MeSH NLM).

Introduction

People living with Human Immunodeficiency Virus (HIV) infection have a higher risk of cardiovascular disease compared to people without this condition. The associated mechanisms are viral infection-dependent factors, the antiretroviral therapy they receive, as well as traditional and non-traditional factors associated with cardiovascular disease [1]. It is known that this infection can generate a profound immunosuppressed state, which predisposes the patient to infections by unconventional agents, malignant neoplasms and progressive dysfunction of different organs and systems [2].

Cardiac involvement in Acquired Immunodeficiency Syndrome (AIDS) patients, which is the most advanced stage of the infection, was described in 1983 by Austran, who reported myocardial Kaposi's sarcoma in a necropsy. Afterwards, several epidemiological studies have been carried out in patients at different stages of disease, hospitalized and managed on an outpatient basis, whether or not they were receiving antiretroviral therapy. In addition, different safety profiles have been established with the use of antiretroviral agents, which are excellent strategies to improve immune system function and reduce viral load but can have some heart or blood vessels adverse events or can be associated with an increase in classic cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, among others [2].

Since 1983, when the first case of AIDS was reported in Peru, a total of 143,732 cases of HIV infection have been reported in

September 2021, of which 46,641 have been diagnosed as AIDS stage. The male/female ratio is approximately 3:1, with 50% of HIV infection and AIDS stage cases in people aged 20-34 years are reported [3].

Below, there is a description of cardiovascular involvement associated with HIV infection, with an initial mention of some local studies.

A prospective comparative study was carried out between 2001 and 2003 at the Guillermo Almenara (EsSalud) and Cayetano Heredia (Ministry of Health, MINSA) hospitals, in which 164 patients in the AIDS stage were evaluated. Although the results showed that there were some population differences in these centers, no differences were found in cardiovascular involvement evaluated by echocardiography. In both centers, left ventricular diastolic dysfunction was found in 26.82% of cases, pericardial effusion in 9.75%, systolic dysfunction in 1.82% and signs compatible with pulmonary hypertension in 2.43% of cases [4].

In addition, a retrospective study was conducted at the Edgardo Rebagliati Hospital (EsSalud) between 1996 and 2002. The authors reviewed 510 medical records of patients with a diagnosis of HIV infection at any stage of the disease who were hospitalized in the infectious diseases department. Cardiovascular involvement was recorded in 26 patients. Eleven of them had cardiac involvement (42.3%) and 15 (57.7%) non-cardiac involvement. The causes of cardiac involvement were pericardial effusion (4 cases), myocardial infarction (3 cases), myocarditis (2 cases), bacterial endocarditis (1 case) and heart failure (1 case). Non-cardiac vascular causes included deep vein thrombosis (6 cases), cerebrovascular disorders (5 cases), pulmonary hypertension (3 cases) and pulmonary embolism (1 case) [5].

1. Cardiac involvement

Cardiac involvement can include different clinical syndromes, the prevalence of which can vary depending on the use of antiretroviral therapy (Tables 1 and 2).

1.1. Myocardial involvement

1.1.1. Dilated Cardiomyopathy

HIV infection has been recognized as a significant cause of acquired cardiomyopathy, which has a low prevalence in the era after the use of antiretroviral therapy, probably due to the reduction in infections by opportunistic agents. In the era prior to antiretroviral therapy, its prevalence was 3.6% in cardiomyopathy patients with different prognostic characteristics, since dilated cardiomyopathy patients have a four-fold increased likelihood of death compared to patients with dilated cardiomyopathy without HIV infection [2,6]. Histopathological features are similar

Table 1. Cardiovascular involvement in HIV infection.

Cardiovascular involvement	Associated clinical syndromes
Cardiac	
Myocardial	
Dilated Cardiomyopathy	Heart failure, arrhythmias
Myocarditis	Heart failure, arrhythmias
Myocardial infarction	Heart failure, arrhythmias
Pulmonary hypertension	Heart failure, pulmonary embolism and infarction
Coronary artery disease	Unstable angina, myocardial infarction, arrhythmias
Neoplasms	Arrhythmias, cardiac tamponade
Endocardial	
Infective endocarditis	Septic shock, heart failure, septic embolism
Non-bacterial thrombotic endocarditis	Systemic embolization, disseminated intravascular coagulation
Pericardial	
Pericardial effusion	Cardiac tamponade, arrhythmias, heart failure
Pericarditis	Heart failure
Extracardiac	
Atherosclerotic	Strokes
Thromboembolic	Deep venous thrombosis, pulmonary thromboembolism
Adverse events or drug interactions	Arrhythmias, increased atherosclerosis
Peripheral arterial disease	Arterial ischemia, critical ischemia
Arrhythmias	Strokes, sudden cardiac death, heart failure

Constructed with data from [2,35-37]

Table 2. Effect of highly active antiretroviral therapy (HAART) on the frequency of cardiac events.

Cardiovascular manifestation	Before HAART	After HAART
Pericardial effusion	40% prevalence in AIDS patients. Cardiac tamponade in 5-30% of patients	Very rare
Myocarditis	More than 40% in autopsies	Very rare
Dilated cardiomyopathy	17.7%	Very rare
Pulmonary hypertension	0.5%	0.5%
Peripheral arterial disease	Inconclusive data	Leading cause of death and disability

HAART: highly active antiretroviral therapy.
Constructed with data from 2,35-37

to uninfected patients with evidence of myocyte hypertrophy and degeneration, increased interstitial and fibrillar endocardial collagen, and myocarditis, whereas macroscopic features include cardiac chambers dilatation with endocardial fibrosis and mural thrombi [2-6]. Besides the etiological contribution of HIV infection, it has been proposed that other variables could play a key role, such as selenium, vitamin B12, carnitine, growth hormone and thyroid hormones, in the presence or not, of malabsorption syndromes. Pharmacological cardiotoxicity has also been described (described for zidovudine), which generates a diffuse destruction of cellular ultrastructures and inhibition of DNA replication, which would lead a state of acidosis capable of amplifying this pathological phenomenon [2,6].

Echocardiography is the first option during the diagnostic process to evaluate left ventricular systolic function, segmental motility abnormalities, as well as diastolic function, for differential diagnosis. Cardiac magnetic resonance imaging should be considered as a complementary method since it will allow the evaluation of ventricular morphology and function, myocardial fibrosis, myocardial edema, late gadolinium enhancement and prognosis, as well as data for differential diagnosis. However, histopathological study is the "gold standard" [7,8].

1.1.2. Myocarditis

Myocardial involvement is patchy, with no association between viral load and cardiomyocyte dysfunction. This would occur by other mechanisms, like the presence of *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Toxoplasma gondii*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Herpes simplex*, *Parvovirus*, *Coxsackievirus B3* and *Cytomegalovirus* [2,7,8].

Prior to antiretroviral therapy era, between 40 to 52% of AIDS patients who died were documented in autopsy studies, without a defined etiology in 80% of cases [2,8]. Shaboodien *et al.* compared the prevalence of myocarditis and viral cardiotropic genomes in patients with HIV-associated cardiomyopathy, idiopathic dilated cardiomyopathy and cardiac transplant recipients in 2013, and myocarditis in 44%, 25% and 36% of the groups were found, respectively. Additionally, myocarditis was acute in 50% of patients with HIV-associated and transplant-associated cardiomyopathy, and chronic in all patients with idiopathic dilated cardiomyopathy, and viral cardiotropic infections were also found in all cases of HIV-associated cardiomyopathy and dilated cardiomyopathy, and in 90% of cardiac transplant recipients [7].

1.1.3. Right Ventricular Dysfunction and Pulmonary Hypertension

The pulmonary hypertension patients' symptoms and prognosis vary according to the hypertension severity, ranging from asymptomatic patients to patients with advanced heart failure and *cor pulmonale*. In general, patients with pulmonary hypertension associated with HIV infection have a shorter survival time compared to those without this condition (1.3 years vs. 2.6 years) [2,9-11].

The accepted prevalence of pulmonary hypertension in HIV-infected patients is 0.5%, considering data from a Swiss cohort of 1200 patients evaluated with transthoracic echocardiography for respiratory symptoms. This prevalence was confirmed in a French study of 7648 patients, also evaluated by echocardiography and postulated that antiretroviral therapy would not modify the prevalence of this condition [12].

The mechanism by which this condition occurs is not fully understood, since there is no data to support that HIV infects pulmonary artery endothelial cells and nucleic acids are found in pulmonary vessels. However, viral proteins can generate vascular remodeling, proliferation of vascular endothelial cells, induction of inflammation, oxidative stress, and dysregulation of apoptosis [12].

Its presentation is indistinguishable from the idiopathic form, the most important symptoms are progressive dyspnea (86%), foot edema (30%), non-productive cough (19%), fatigue (13%), syncope or pre-syncope (12%) and chest pain (7%). Echocardiography may be helpful as a screening method, especially in the subpopulation with risk factors (female gender, cocaine use, intravenous drug use, hepatitis C infection) [12].

When pulmonary hypertension is present, it is an independent predictor of death and is associated with shorter survival. Conventional medication, including phosphodiesterase inhibitors, endothelin receptor antagonists and prostacyclin analogues, is used as a treatment [12].

1.1.4. Myocardial infarction

The atherosclerosis process in people living with HIV should not differ significantly from the rest of the population. The most

Table 3. Most common adverse events of antiretroviral drugs

Drugs	Adverse events
Nucleoside Reverse Transcriptase Inhibitors	
Abacavir	Potential increase in cardiovascular events
Didanosine	Hypertension, myocardial infarction
Emtricitabine	Hypertriglyceridemia
Lamivudine	Possible cardiotoxicity in fetuses
Stavudine	Fat redistribution, dyslipidemia
Tenofovir	Modest reduction in total and LDL cholesterol
Zidovudine	Potential mitochondrial dysfunction / myopathy
Non-nucleoside reverse transcriptase inhibitors	
Delavirdine	Drug interactions with calcium channel blockers, warfarin, beta-blockers, quinidine, corticosteroids, theophylline
Efavirenz	Fatal arrhythmias
Etravirine	Dyslipidemia, atherogenic dyslipidemia
Nevirapine	Hypertension
Protease inhibitors	
Amprenavir	
Atazanavir	
Darunabir	
Fosamprenavir	Hypercholesterolemia, hypertriglyceridemia
Indinavir	Hypotension
Lopinavir/ritonavir	Atrioventricular block
Nelfinavir	Prolonged QT interval
Ritonavir	Increased risk of myocardial infarction
Saquinavir	
Tipranavir	
Integrase inhibitors	
Raltegravir	
Elvitegravir	
Dolutegravir	Weight gain, predominantly dolutegravir and bictegravir (up to 6 kg in 4-years follow-up)
Bictegravir	Neutral effect on lipids
Fusion inhibitors	
Enfuvirtide	Sporadic cases of postural hypotension, angina, heart failure, myocardial infarction
Maraviroc	

LDL: low-density lipoprotein

Constructed with data from [2,35-37]

important processes are endothelial dysfunction of immune and non-immune causes, inflammation, transformation of macrophages into foam cells, and foam cells apoptosis. We must highlight the pivotal role played by monocyte activation (even after antiretroviral treatment), associated with persistent inflammation and immune activation [13-15].

The atherogenic properties of some antiretrovirals; the effect of viral proteins Tat, Nef and gp120; the decrease of smooth muscle proliferation in the inflammatory milieu; the co-infection with cytomegalovirus and even the contribution of bacterial translocation processes at the intestinal level are also known [14]. Thus, the mechanism associated with coronary syndromes in HIV-infected patients would be rupture rather than erosion of the atherosclerotic plaque. Thus, thrombosis and microvascular dysfunction are two associated factors [14].

Patients living with HIV generally have less plaque inflammation, more likelihood of single vessel involvement, a

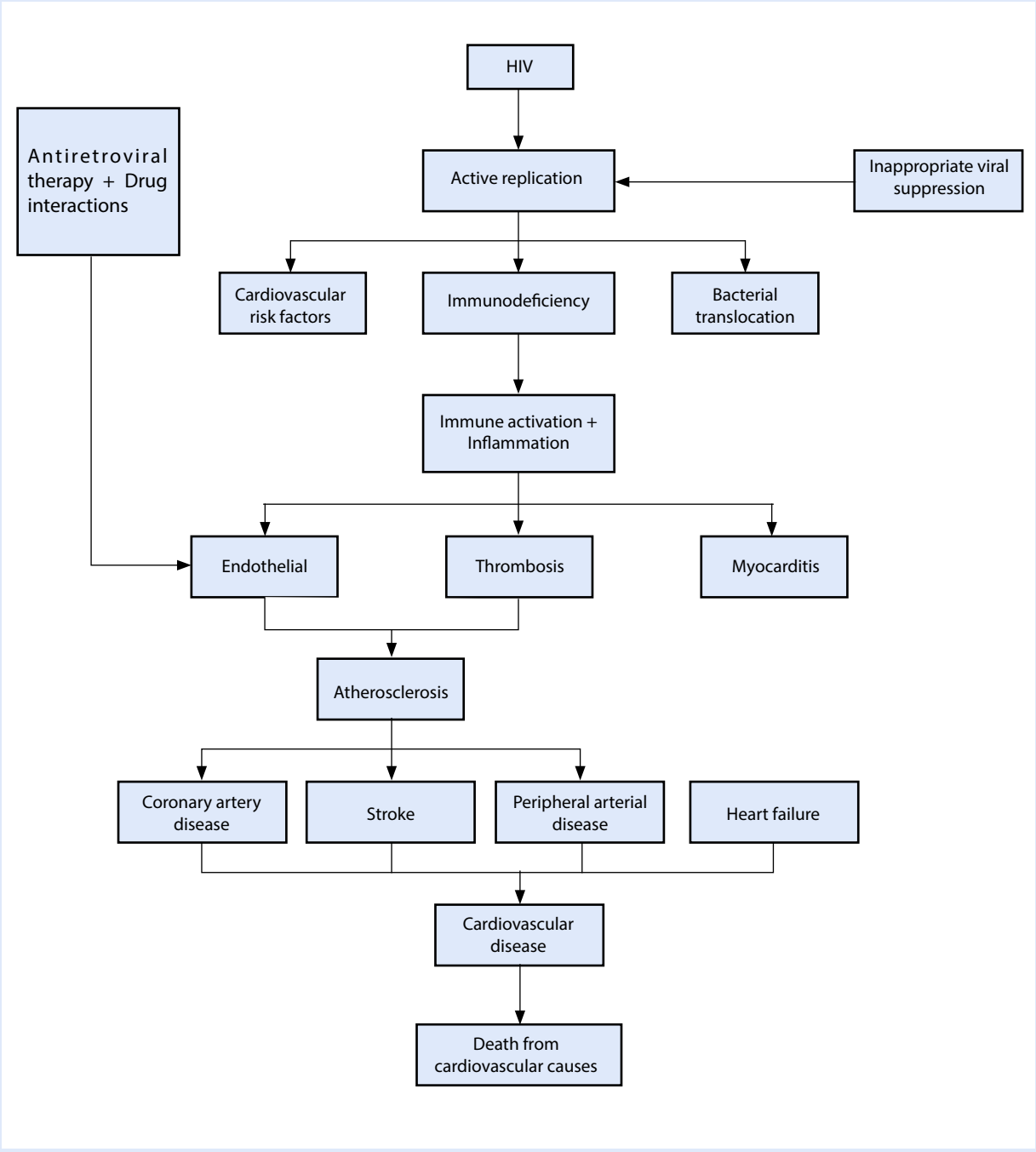

Figure 1. HIV-associated cardiovascular disease.

Modified from reference 1

lower Thrombolysis in Myocardial Infarction risk (TIMI) score, and a higher likelihood of proximal lesions compared to uninfected individuals [16].

A meta-analysis with data from studies between 2003 and 2015 suggested that after percutaneous coronary intervention, HIV-infected patients have similar mortality, death from cardiovascular causes, and recurrent myocardial infarction at 3-year follow-up. This trend is remained in advanced coronary artery disease patients, who require a myocardial revascularization surgery, with similar short-term mortality, but a slight trend to require a higher proportion of postoperative transfusions and a higher proportion of long-term cardiovascular events [16].

1.1.5. Cardiac Neoplasms

Cardiac non-Hodgkin lymphomas (NHL) are rare in AIDS. Lesions have a macroscopic or more discreetly nodular or even polypoid appearance and usually involve the pericardium and more rarely the myocardium. They are rarely accompanied by inflammation or necrosis. Most lymphomas are high-grade B-cell or Burkitt-type lymphomas [17-22].

Cardiac Kaposi's sarcoma (KS) in AIDS patients ranged between 12 and 28% in autopsy studies in the era prior the use of antiretroviral therapy and associated with systemic visceral involvement [2,17,18]. Lesions are smaller than 1 cm in diameter and can be pericardial or myocardial and, in very rare cases, would be associated with blood outflow tract obstructions, myocardial dysfunction, high mortality and morbidity [2, 20-22].

The introduction of ART has significantly reduced the incidence of cardiac involvement by these neoplasms in particular, probably due to the improvement of the immune status or the suppression of infections by opportunistic agents such as herpes virus type 8 and Epstein Barr virus [20-22].

1.2. Endocardial involvement

1.2.1. Infective endocarditis

The prevalence of infective endocarditis in HIV-infected patients is similar to that of patients in other risk groups, like intravenous drug users. However, individuals with CD4 cell counts below 50 cells/mm^3 and high viral loads (> 100,000 copies/mL) have a four-fold increased risk of developing this condition [17-21].

In developed countries, an important risk factor is the use of intravenous drugs with right-sided heart endocarditis, whereas patients living in developing countries have a history of rheumatic heart disease as a risk factor [23].

Clinical data depend on the valvular involvement's type and location. The most common agent is *Staphylococcus aureus*, mainly methicillin sensitive. On the other hand, it has been described that the rate of negative blood cultures varies from 3.7% to 54%, and it is speculated that this finding would be associated with the use of cotrimoxazole or other antibiotics used as infection prophylaxis [17,23].

The prognosis of this condition is similar to that of patients without infection. However, patients with greater degrees of immunosuppression (lower CD4 lymphocyte counts), and those with left or mixed valvular involvement, have a higher mortality [17,23].

Medical and surgical management should be guided by bacteriological findings and clinical status of the patients, following the recommendations of the guidelines [23].

1.2.2. Non-bacterial thrombotic endocarditis

Patients in the AIDS stage may present another form of endocarditis called marantic: thrombotic, non-bacterial, which is present in 3-5% of AIDS patients, frequently in wasting syndrome patients. Friable endocardial vegetations are friable, smaller than 0.5 cm in size and affect the left-side heart; in spite of this, systemic embolization is rare [17-22].

1.3. Pericardial involvement

Pericardial involvement is one of the cardiovascular involvement forms in HIV infection, with a wide variety of clinical manifestations, including asymptomatic pericardial effusion, pericarditis, cardiac tamponade, and constrictive pericarditis [17,24].

Before antiretroviral therapy, the prevalence of pericardial effusion in HIV-infected patients ranges from 11 to 40%. In the cohort study conducted in Soweto - South Africa between 2006 and 2008, pericardial effusions and pericarditis were the second most common cardiac manifestation (25%). However, the prevalence is low in developed countries [17,24].

1.3.1. Pericardial effusion

Pericardial effusion could serve as a sign of an immune status reduction, probably due to the presence of opportunistic infections such as bacterial infections (e.g., tuberculosis, especially in countries with high prevalence of this disease), *Cytomegalovirus*, *Nocardia*, Cryptococcus, or malignant neoplasms such as lymphomas or Kaposi's sarcoma. An association with hypoalbuminemia has also been suggested, by activation of cytokines generating a "capillary leak syndrome", or by direct invasion of the pericardium or myocardium. On the other hand, in 8% of cases no specific cause is identified [17,23,24].

Patients can present without symptoms when there are small pericardial effusions, whereas in large pericardial effusions, patients can present dyspnea, enlargement of the cardiac silhouette in the chest X-ray, electrocardiographic changes and hemodynamic instability in cardiac tamponade [23,24].

The diagnostic process should consider the region's epidemiology and the clinical presentation. Pericardiocentesis with pericardial fluid analysis, including cytology, biochemistry, and bacterial cultures (especially for tuberculosis) may be useful. In addition, pericardioscopy and pathological study, including molecular biology studies may also be useful [23,24]. The pericardial effusion diagnosis is associated with reduced survival. In AIDS patients, six-month mortality was nine-times higher than in those without pericardial effusion [23,24].

Treatment depends on severity and etiology. Small effusions do not require treatment but do require follow-up. In patients with hemodynamic instability and cardiac tamponade features, emergency pericardiocentesis is indicated. The combined effect of oral prednisolone and *Mycobacterium indicus pranii* has been studied and no association with lower mortality has been found. In this study, oral prednisolone was found to be associated with a reduced risk of constrictive pericarditis, but with a three-fold increased risk of cancer [24].

2. Extracardiac vascular involvement

2.1. Vascular atherosclerotic involvement

2.1.1. Cerebrovascular disorders

The epidemiology of cerebrovascular involvement can be altered considering the longer survival of patients, the increase in cardiovascular risk factors, the extensive use of antiretroviral therapy and the decrease in infections by opportunistic agents [25].

Although it is true that, in the era before antiretroviral therapy, people affected by this condition were young people who were in the AIDS stage [16,19,20], current studies have shown a greater incidence of the cerebral vascular disease risk in the infected population compared with the uninfected. According to the study carried out by Rasmussen and collaborators in Denmark, the incidence rate is 1.6 (95% confidence interval [CI] 1.32-1.94), and the

meta-analysis carry out by Gutiérrez found hazard ratio intervals of 1.53-2.16 [25].

Seemingly, there would be a greater predominance in non-elderly women, compared to men, and especially in people living in low-income countries. The following are described as risk factors: advanced stages of immunosuppression, use of protease inhibitors (darunavir has been identified), and traditional risk factors (hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation and age). It is necessary to consider the presence of infections by opportunistic agents such as tuberculous meningitis, neurosyphilis, Varicella Zoster virus vasculitis, or even space-occupying lesions such as central nervous system toxoplasmosis, tuberculomas or brain abscesses [16,19,20,25].

The clinical presentation would be the sudden onset of a focal neurological deficit, although there can be altered mental status symptoms, acute loss of consciousness, fever, subacute onset of symptoms in hours or days, or even subclinical presentations. Cerebral infarcts are more frequent than hemorrhages (some series report that 90-95% of cases presented cerebral infarcts and 5-10% cerebral hemorrhages) [25-27].

When cardioembolism is suspected, we must remember that these patients are at increased risk for atrial fibrillation, and they can develop cardiomyopathy in the uncontrolled infection context, or can have valvular disease, even with added infectious disease. Management is similar to that of the general population, with good responses with the use of tissue plasminogen activator (tPA), and control of risk factors in secondary prevention [25].

2.2. Thromboembolic involvement

2.2.1. Deep vein thrombosis

}Venous thromboembolic disease can present as deep vein thrombosis or pulmonary embolism. Venous thrombi are a consequence of frictional stress and are red blood cells and fibrin-rich, with low platelet levels. Virchow's triad includes three factors present in patients' group: hypercoagulability, endothelial injury and blood stasis [22].

In general population, venous thromboembolic disease occurred with an annual frequency from 1 to 2 events per 100,000 person-years (0.1%-0.2%), which increases with age. The incidence varies depending on the study population (0.19%-7.63%) [16,22].

The causes of this syndrome are complex, and can be related to coagulation disorders, such as increased levels of fibrinogen, interleukin-6 (IL-6), C-reactive protein (CRP), D-dimer, tissue-type plasminogen inhibitor type 1, plasminogen activator antigen or a protein S deficiency [16-21].

2.3. Peripheral arterial disease

}The prevalence of peripheral arterial disease in HIV-infected patients ranges from 2 to 27%, depending on the technique used for its diagnosis, predominantly through the ankle-arm index, and considering different cut-off points, including after physical exercise. The associated variables in some studies are male gender, dyslipidemia, advanced age, smoking, CD4 count lower than 200 copies/mL, or active disease [28].

2.4. Arrhythmias

HIV-infected patients can present atrial fibrillation, which is associated with a higher frequency of cardiovascular events. The presentation of autonomic dysfunction with reduced cardiac variability, associated with sympathetic predominance in relation to the progression of the infection is also frequent [29].

On the other hand, sudden cardiac death is the third cause of death in HIV population, being 4.5-times more frequent than general population. Patients can also present long-QT syndrome and twisting of the points, associated with hydroelectrolytic disturbances or the use of some antiretroviral drugs (protease inhibitors such as atazanavir, lopinavir and saquinavir are the best described), or their interactions with other drugs such as macrolides, pentamidine, antifungals, fluoroquinolones or methadone [29].

3. Antiretroviral medication and cardiovascular risk

Some antiretrovirals and antiretrovirals classes have been associated with increased cardiovascular risk (Table 3). Whether immediate initiation of antiretroviral therapy reduces cardiovascular risk can still not be determined. However, data are available from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, which found that each cumulative year of protease inhibitor use was associated with an increase of 10% in myocardial infarction, despite adjusting for cholesterol values [16,30].

It has also been reported that ritonavir-boosted darunavir (but not atazanavir), which belong to the protease inhibitor class, was associated with increased cardiovascular risk and altered carotid intima-media thickness. Regarding the therapeutic class of reverse transcriptase inhibitors, the use of abacavir has been associated with a greater number of cardiovascular events [16,31,32].

Cardiovascular risk assessment in the HIV-infected population is recommended, considering the traditional risk factors: age, diabetes mellitus, smoking, hypertension, dyslipidemia, and the effect of the infection itself, as well as that of the medication.

Any scale can be used as in the general population (US-based pooled cohort equations (PCE), Framingham Risk Score, Europe-based Systematic Coronary Risk Evaluation (SCORE)) or the specific one for this population (D:A:D) study, considering that all of them tend to underestimate cardiovascular risk in this population) [33,34].

A second validated scale has recently been developed for the HIV-infected population, using the analysis of a retrospective cohort of 1,914 patients between March 2012 and January 2017. This scale includes the following variables: gender, ethnicity, chronological age, age at diagnosis of infection, peak viral load, lowest CD4 lymphocyte count, hypertension, hyperlipidemia, diabetes, chronic kidney disease, and smoking. With these eleven variables, the logistic regression model had an area under the curve of 0.957 (CI: 0.938-0.975), for the prediction of cardiovascular events at 10 years [35].

An enormous opportunity is medical education for those who care for people living with HIV, who only recognize some antiretroviral drugs as possible causes of increased cardiovascular risk and identify only a few cardiovascular risk factors. In addition, they assess the cardiovascular risk of their patients "always" in 7% and "sometimes" in 21%. They also evaluate cardiovascular risk factors inappropriately, since blood lipid measurements are very sporadic: once a year (39%), twice a year (46%), three times a year (7%), four times a year (4%) and never (4%) [36].

In Peru, the prevalence of some cardiovascular risk factors in this population is known. The most recent report was the evaluation of 305 patients, who were receiving antiretroviral therapy for more than 6 months, in five hospitals in Lima and Callao. Dyslipidemia was found in 51.5%, overweight in 41.6%, obesity in 11.1%, diabetes mellitus in 7.2%, hypertension in 8.9%. Physicians prescribed pharmacological treatment in 91.3% of patients with diabetes and hypertension, but only 29.3% of patients with dyslipidemia [37].

In this day and age, there are few effective strategies to prevent cardiovascular disease in HIV-infected patients, but it seems that statin therapy would be effective, pending the official publication REPRIEVE study's results. The modulation of the inflammatory process has also been studied using methotrexate and colchicine, but without improvement in endothelial function and the monoclonal antibody canakinumab with a decrease in systemic markers of inflammation and aortic inflammation, measured by positron emission tomography. On the other hand, there are positive data on evolocumab, a PCSK9 inhibitor, which improved coronary endothelial function in only 6 weeks of treatment, and there are more than 70 clinical studies in progress, focused on the prevention and treatment of cardiovascular disease in this at-risk population [38].

Author contributions

GVR participated in the conception of the article, visualization, writing and approval of the final version.

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