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Cardiac Complications of Human Immunodeficiency Virus Infection: An Overview

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ABSTRACT

AIDS caused by an HIV infection tends to lead a person to a diverse range of opportunistic infections, malignant neoplasms, and multi-organ dysfunction. Cardiac disease is being recognized as a complication of HIV infection. This might happen incidentally in a person suffering from AIDS, as a health problem caused because of AIDS, as a consequence of treatment for AIDS, or also as a natural consequence of HIV infection of the cardiovascular system. Patients with cardiac complications of HIV infection have been associated with poorer course of this medical condition relative to the normal population. Medical professionals are required to be informed of the nature of HIV-related cardiac presentations and the different ways of its management. In this review article, the principal HIV-associated cardiac complications will be discussed, with an emphasis on update on its prevalence, pathogenesis, and treatment.

Keywords: HIV, complications, cardiovascular, antiretroviral.

INTRODUCTION

HIV infection is marked by acquired, chronic, deep immunosuppression that prones individuals to multiple opportunistic infections, malignancies and progressive failure of several organs.[1] Cardiovascular disease (CVD) is a major cause of morbidity and mortality in persons with HIV infection. Recorded research shows that the prevalence of cardiovascular disease among HIV-infected patients is enhanced by around 1.5 - 2.0 times compared to the population.[2]

HIV infection has increased incidence of mortality,[3] and a growing body of evidence implicates chronic inflammation that persists despite effective antiretroviral therapy (ART) in the development of vascular dysfunction and accelerated atherosclerosis.[4] Findings of another study present that HIV and possibly antiretroviral therapy cause myocardial dysfunction due to the release of cytokine pro-inflammation, resulting in myocardial fibrosis, apoptosis, and cardiac steatosis.[5] Atherosclerotic vascular disease, especially coronary artery disease, has become the most important cardiovascular complication of HIV infection and has had the most attention directed to its pathogenesis, prevention, and therapy. In resource-limited settings where medical treatment is sparse, limited, or absent, HIV disease and its complications are similar to the disease in the pre-ART era.[6]

Cardiovascular disorder seems to be a major complication of infection with HIV and is now more frequently mentioned. Although there is a growth in the number of reports, the precise prevalence of cardiac participation in patients infected with HIV is unclear. There is a potential danger that HIV infected patients might develop chronic heart diseases like atherosclerosis as they continue to live for a longer period of time. Physicians must be careful in discussing established causes of risk for coronary disease in HIV infected patients and therefore should be familiar with the different cardiac symptoms of HIV infection.[7]

Chronic immune stimulation together with lower CD4 + cell counts linked with chronic inflammation is typical mechanisms for such complications. Treatment of HIV infection health problems usually involve treatment of conventional factors, lifestyle interference, primary introduction of antiretroviral drugs, as well as precise medications for inflammation and immune activation.[8] Deep comprehension of the progression of heart related disorders in individuals infected with HIV might aid in initial detection and suitable interference. The accompanying analysis discusses the cardiovascular problems of HIV infection with an emphasis on occurrence, etiology, detection & treatment.

Cardiac Complications of HIV Infection

HIV infection adversely affects cardiac function. Cardiovascular impairment tends to be a significant complication of HIV infection and more frequently cited.[9] Understanding the frequency of each type of cardiovascular disease in patients with acquired immunodeficiency syndrome (AIDS) is gradually progressing. The cardiac complications may include premature coronary artery disease, dilated cardiomyopathy, left ventricular systolic as well as diastolic dysfunction, pulmonary artery hypertension, infective endocarditis, etc.[10]

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Prevalence Cardiac complications of HIV infection

Cardiac complications of HIV infection tend to occur late in the disease or are associated with related therapies and are therefore becoming more prevalent as therapy and longevity improve.[10] Infection with HIV is accountable in the United States for significant morbidity and mortality. At first, cardiac engagement was believed to be an uncommon expression of the infection, however now it is widely mentioned. Most effective therapy of opportunistic infections, the impact of antivirals, enhanced patient survival, greater symptom comprehension, and timely detection with chest radiography and echocardiography might be the causes for the significant rise in cardiac disease occurrence.[11]

The incidence of cardiovascular disorder in people infected with HIV is not evident; the recorded rate of cardiac participation relies on the examined population and the description of cardiac anomaly. Clinically relevant heart dysfunction was rare in population infected with HIV prior to the introduction of ART and was only identified at autopsy in most cases. Nevertheless, cardiovascular participation seems to be more prevalent than observed earlier in individuals with AIDS. Indeed, in the late 1980s, when echocardiography tested HIV-infected individuals, cardiovascular complications were observed more than anticipated from symptoms and medical examination. While most circumstances are medically dormant, some could lead to disastrous and lethal findings. Among the most frequently cited complications was pericardial effusion and myocarditis, although cardiomyopathy, endocarditis, and coronary vasculopathy were also documented.[12] Several studies have analyzed large clinical databases and cohorts in the United States, Canada, and Europe to compare the occurrence of CVD in HIV positive and HIV negative patients.[13]

While some of such experiments are confined by a small series of events, brief take-up and unfinished evaluations of cardiovascular factors, they repeatedly document a one and a half times increase in the number of cardiovascular events in people infected with HIV in comparison to control group. One of the largest of these studies evaluated California state-sponsored health insurance claims data, which included 28,513 HIV-infected and 3,054,696 uninfected patients.[14] The occurrence of CHD in individuals falling in the age group of 18 to 24 years was low overall but enhanced in the ones who were HIV-infected compared to the uninfected (relative risk of 6.76, 95 percent Confidence Interval 3.36–13.58 for men and 2.47, 95 percent Confidence Interval 1.23–4.95, for women). The relative risk of CHD was the most increased in HIV-infected patients over the age of 45 years compared with uninfected populations.[15]

A study was undertaken to study the common cardiovascular complications in Indian HIV patients and to their association with the CD4+ T-cell count. Prevalence of cardiac abnormality was 24%. The abnormalities included left ventricular diastolic dysfunction (22%), pulmonary hypertension (12%), DCMP (12%), pericardial effusion (7%), left ventricular systolic dysfunction (5%), and right ventricular dysfunction (1%).[10] According to a study done by US it was found that the percentage of deaths due to circulatory CVD among patients infected with HIV in their mid twenty years of age or more rose to 3.8 % from 2.1% and to 4.9 % from 1.9 % among females and males, respectively from 1999 to 2013.[16]

It is expected that the prevalence rate of cardiovascular complications would also improve with the fast increasing incidence of HIV infection as well as AIDS. Myocardial, pericardial and endocardial diseases are some of the cardiovascular disorders associated with individuals suffering from HIV infection. Significant medical disorders mentioned in HIV patients involving the heart are cardiac tamponade, dilated cardiomyopathy, many types of myocardial failure, refractory ventricular tachyarrhythmias, as well as systemic thromboembolic disease.[17] Pericardial participation is common, mostly asymptomatic, and typically presented as a non-specific pericardial effusion, while neoplasms and opportunistic infections might also be observed. Medical professionals must be observant to the higher frequency of cardiac participation in HIV-infected patients, which may influence the medication needed by such individuals.[18]

Noteworthy HIV-associated cardiac complications

Cardiomyopathy and other symptomatic heart diseases associated with HIV infection

Cardiomyopathy is the most common and life-threatening cardiovascular complication of HIV infection. Other less common forms of symptomatic heart disease in HIV-1-infected patients are pericardial effusion with cardiac tamponade, high-grade arrhythmia with sudden cardiac death, and systemic embolization caused by nonbacterial thrombotic endocarditis or infective carditis. The demographic and clinical characteristics of HIV-infected patients who develop cardiomyopathy as well as potential enhancing risk factors are as yet poorly characterized.[19]

According to the latest reports, patients infected with HIV are posed at a greater threat of developing heart failure as well as subclinical impairment of left ventricular mechanics and myocardial defects.

Though, the physiological pathways are not well known. A few studies have also shown higher rates of atrial fibrillation and. There are some studies which have reported greater frequencies of AF and cardiac death in people living with HIV. The most regular kind of stroke in post ART period is the ischemic stroke and its physiological pathways are

the ones recognized in coronary artery disease. Analysis of large vessels and peripheral arterial impairment indicate findings that are heterogeneous. Minor pericardial subclinical effusions are normal patients of HIV in post ART period. Pulmonary hypertension appears to be a prospective problem that is not diagnosed correctly and it could also cause death in case of HIV-infection.[20]

Infective endocarditis

Infective endocarditis (IE) is the most severe complication in intravenous drug abusers (IVDAs). HIV infection increases the risk of IE in IVDAs too. IE has special tendency to infect the right-sided heart, with unusual infective aortic valve.[21]

Cardiovascular autonomic neuropathy

HIV infection causes cardiac autonomic neuropathy (CAN). HIV-related cardiac autonomic neuropathy indications were present in 30% of African HIV+ patients without any direct relationship with their immunological condition. Depending on the significance of the issue and the prevalence of CAN symptoms even in recently diagnosed and medication-naïve cases, the researchers suggest that HIV infected patients should always be examined for the existence of the problem, given the potentially serious incidents correlated with the complication.[22]

Thrombosis

Thrombotic events are four times more frequent among HIV-infected patients than among the overall population, and often occur in relatively young patients. At an advanced stage, HIV disease has been reported to be a risk factor for thrombosis. That seems to be related to an increased hypercoagulable state as well as to an inflammatory state, alongside coexisting comorbidities.[23]

Heart failure

HIV-infected individuals have a higher risk of HFpEF, undefined HFpEF, as well as HFrEF relative with uninfected people. HFrEF's elevated risk could present years sooner than expected in an uninfected community.[24] There is framework for studies in patients infected with HIV on prevention, danger stratification and recognition of cardiac failure pathways.

Stroke

According to the findings of latest research, the rate of ischemic stroke among HIV-infected women was greater than among HIV-infected women [incidence rate ratio 2.39, confidence interval (CI) 95 percent, 1.62-3.43]. Infection with HIV was correlated with nearly double the danger of ischemic stroke since modifying for demographics and conventional factors for stroke (hazard ratio 1.93, 95 percent CI 1.31-2.85). HIV involvement with ischemic stroke continued after gender-specific stroke risk indicators were included in the template (hazard ratio 1.89, 95 percent CI 1.28-2.81). Lengthier period of antiretroviral treatment was linked to a lower threat of ischemic stroke (hazard ratio 0.86 per year, 95% CI 0.76-0.96) in individuals infected with HIV.[25]

Pathogenesis of HIV-related cardiac diseases

The underlying cause of the prevalence of HIV-related cardiac presentations is not yet well known. It could be either due to the virus, the actions of anti-retroviral drugs, or the changes in the immune systems involved with the disease. The differentiation or classification of CVD and cardiovascular monitoring appears to be a big problem for today's practitioners especially in case of HIV patients. The cardiovascular abnormalities identified in HIV comprise pericardial disease with effusion and tamponade, myocarditis, dilated cardiomyopathy with left ventricular dysfunction, endocarditis, CAD, pulmonary hypertension, cardiac autonomic dysfunction, and some unusual neoplasms.[27]

HIV infection, along with host heredity and way of living, HIV multiplication with arising immune stimulation, and antiretroviral drugs, could be popular influencing factors for cardiovascular health problems. Calculations of such factors comprise inherent immune stimulation; background of poor nadir CD4 + cell count or small ratio of CD4:CD8; pathogens as well as coagulation abnormalities (e.g., tissue factor expression).8 Unrestrained replication of HIV has been shown to be a major single health risk for modifications in lipids with higher risk of CVD in the wider population, including hypercholesterolemia, high levels of VLDL-C, and TGs as well as decreased measure of HDL-C.[28] The lipid alterations were discovered to be statistically linked with decreased numbers of CD4 + T-cells and increased levels of viral RNA in HIV-infected persons.[29] Additionally, a greater load of virus is associated with endothelial dysfunction, that is also associated with a higher threat to cardiovascular system. Endothelial dysfunction expressing as elevated carotid intima-media thickness (CIMT) is highly associated with typical threat components for atherosclerosis and CVD, particularly elevated plasma concentrations of thrombophilic factor VIII activity and VLDL-Cl and reduced removal of apolipoprotein particles combined with diminished plasma adiponectin levels.[30]

HIV affects and eventually reduces CD4 + lymphocytes, progressing to extreme immunosuppression, leading to their eventual decline. Recent studies suggest that HIV might have a heart tropism. Most specifically, in acquired immunodeficiency syndrome (AIDS) patients' cardiovascular symptoms may be compromised with other pathogens like viruses, fungi, and protozoa. Cardiovascular disorder in patients suffering from AIDS can be induced by any of the following difficulties: (i) contagious or neoplastic problems of AIDS and their medications, (ii) any of the known

leads of heart disease (iii) or probably by myocardium HIV infection itself.[31]

Incidence of pericardial effusion is increasing among HIV-infected individuals, often from TB-coinfection.[32] Infection with HIV as well as its management, even with effective viral suppression, results in a massive depletion of CD4+ cells throughout the gastrointestinal tract, increases intestinal permeability and bacterial translocation, may drive immune activation, enhances systemic inflammation, changes coagulation mechanisms, induces irregular vascular activity, and facilitates plaque development and eventual destabilization, everything leading to increased incidence of ischemic and non-ischemic CVD. Other potential contributors to ongoing inflammation include low-level HIV replication during antiretroviral therapy and viral coinfection, particularly with cytomegalovirus, hepatitis B or hepatitis C virus.[33] [Figure 1]

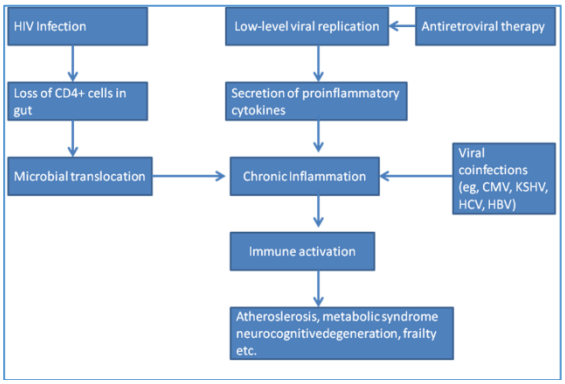

Figure 1: The developing positions of chronic immune excitation as well as inflammation in people infected with HIV in the aetiology of cardiovascular disease.36 CMV=cytomegalovirus, HBV=hepatitis B virus; HCV= hepatitis C virus, KSHV= Kaposi sarcoma–associated herpesvirus.

Table 1: The threat level for various cardiovascular diseases in a population with HIV-1

Cardiaovascular Disorders	Risk with HIV-1 infection	Possible Causes and Associations
Pericardial Disease	11-17%/year	HIV, Prolonged acquired immunodeficiency, Kaposi's sarcoma, Malignant lymphoma, Staphylococcus, Streptococcus, Proteus, Nocardia, Pseudomonas, Klebsiella, Enterococcus, Listeria, Mycobacterium tuberculosis, herpes simplex virus, Cytomegalovirus, Hypothyroidism etc.
Myocardial Disease	1.6% HIV patients	HIV, opportunistic infections, vasculitis, hypoxia, excess of catecholamine, deficiencies in nutrition and many more.
Infective Endocarditis	5-20% of hospital admission in HIV	A common complication among injecting drug users.[38]
Coronary artery disease	6-15% of all the deaths occurred in patients with HIV infection	Protease-inhibitor–induced metabolic and coagulative disorders; arteritis etc.
Hypertension	20-25% prevalence	HIV-induced endothelial dysfunction, protease inhibitor-induced insulin resistance with increased sympathetic activity and sodium retention, HAART-secondary atherosclerosis, large vessel aneurysms with affected renal artery flow, etc.
Pulmonary Hypertension	0.5% HIV patients	Microvascular pulmonary emboli due to thrombus or drug injection, recurrent bronchopulmonary infections, pulmonary arteritis, plexogenic pulmonary arteriopathy, mediator release from endothelium etc.
Thromboembolism	2% of HIV patients	HIV
Dilated cardiomyopathy	15.9 patients in 1000 asymptomatic HIV-infected persons before the introduction of HAART.39	HIV, toxoplasma gondii, coxsackievirus group B, Epstein-Barr virus, cytomegalovirus, adenovirus, cocaine, nucleoside analogues, IL-2, doxorubicin, interferon, Nutritional deficiency (selenium, B12, carnitine), thyroid hormone, growth hormone, adrenal insufficiency, hyperinsulinemia, cytokines, nitric oxide, endothelin-1, hypothermia, hyperthermia, autonomic insufficiency etc.
Kaposi's sarcoma	12%–28% of AIDS patients before the introduction of HAART	HIV
Non-Hodgkin lymphomas	Mostly limited to case reports before the introduction of HAART	HIV

Usually, HIV-infected individuals have reduced TC, LDL-C, and HDL-C along with elevated TGs.. ART (antiretroviral treatment) or HAART (highly active antiretroviral treatment) leads to significant increments in total cholesterol, low density lipoprotein cholesterol and triglycerides and greater amount of tiny, thick low density lipoprotein particles, while high density lipoprotein cholesterol stays reduced in count. Current inhibitors of protease, inhibitors of non-nucleoside reverse transcriptase or inhibitors of integrase influence the metabolism of lipoproteins to a smaller degree. Antiretroviral treatment also decreases sensitivity to insulin and furthers the progress of hypertension and dispersal of fat in the body, which leads to risk of CVD. Individuals infected with HIV are prone to a greater threat for CVD in comparison with uninfected individuals [RR 1.61 (95% CI 1.43, 1.83)], whereas antiretroviral threatment (typically older inhibitors of protease) additionally elevates this threat, to two-folds [RR 2.00 (95 percent confidence interval 1.70, 2.37)]. Even after alterations for conventional risk elements, the threat of cardiovascular disease continues to rise. Antiretro-viral treatment can speed up the occurrence of CAD-related episodes in chain smokers suffering from dyslipidemia.

An early indication of the potential effects of inflammation on CVD came from findings in the SMART (Strategies for Management of Anti-

Retroviral Therapy) trial, in which more than 5000 participants were randomly assigned to receive continuous antiretroviral therapy or to discontinue antiretroviral therapy (drug-conservation arm) when the count of CD4+ cells was greater than three hundred and fifty per micro liters and then resume therapy when it fell below 250/μL.[34,35]

Some have suggested an autoimmune method as the likely explanation of myocarditis and cardiomyopathy. While ZDV was correlated with myopathy, several medications used for the management of HIV infection were reported to cause cardio-toxicity.[37]

Diagnostic evaluation

Myocarditis, myocardial necrosis, cardiomyopathy, arteriopathy, endocarditis, pericarditis, pericardial effusion, and cardiac neoplasm were documented in individuals with HIV infection. Medical analysis frequently fails to detect these disorders, although echocardiographic and autopsy findings have identified them in 40-50 percent of cases.[40]

Normally, individuals suffering from HIV/AIDS must get a baseline echocardiogram as well as electrocardiogram (ECG), as many patients are asymptomatic. Patients with low CD4 counts, those receiving zidovudine, and intravenous drug users must be further evaluated. Most patients with symptomatic effusions have a potentially treatable cause (neoplasm or infection), and a full workup must be initiated; however, small asymptomatic effusions often can be observed and followed by serial echocardiography. Doctors need to be more vigilant about cardiac intervention in HIV patients. Initial monitoring is required, which can result in timely care and treatment.[41]

A number of CVD risk calculators are available, although the most commonly used have generally not been validated for use in HIV-infected individuals. CVD risk calculators include the American Heart Association (AHA)/American College of Cardiology (ACC) 2013 pooled cohort risk calculator, the Framingham Risk Score, and the D:A:D 5-Year Estimated CVD Risk Equation, which is specific for HIV infection, but has not been validated for use outside of the dataset from which it was derived. CVD risk stratification tools for the general population are generally not validated for use in people infected with HIV. It is reasonable to use the Framingham Risk score or AHA/ ACC pooled cohort risk calculator for HIV-infected individuals and to consider HIV infection a risk factor, as suggested by the National Lipid Association.[2] In the extremely active age of antiretroviral drugs, some CVD modalties like heart failure, peripheral artery disease, and stroke need little more consideration in the sense of infection with HIV.[42]

CD4+ and CD8+ cell counts, D-dimer and interleukin (IL)-6 could be taken as the biomarkers. Such findings show once again the relative value of the ratio of CD4+:CD8 + as an indicator of course of the disease and point out that there cannot be one biomarker which could describe a significant part of the medication impact.43 Single assessments of the coagulation marker D-dimer and the inflammation marker interleukin (IL)-6 have been reported to predict severe non-AIDS cases or deaths in people infected with HIV over a decade.44 Radiologists have a significant function in the primary observation and diagnosis of such medical complications.

Management of Cardiac Complications in HIV infected patients

In the last ten years, there has been a transformation in the management as well as the course of this medical condition in long-term for HIV infected patients. With the introduction of extremely effective antiretroviral therapy (HAART) HIV infection has become a relatively manageable medical condition.[45]

Lately, the findings of the Strategies for Management of AntiRetroviral Therapy (SMART) report underlined the advantages of HAART in the fatal and non-fatal events demonstrating that periodic anti-retroviral therapy dependent on CD4 + cell count-guided drug conservation was corelated with considerably higher progression of the disease and risk of mortality compared to persistent anti-retroviral therapy. Moreover, for the individuals who prolonged HAART until CD4 + T-cell counts dropped below 250 cells/mm3 there was a seven-fold increased risk of a severe non-AIDS disease and the threat of fatal/ non-fatal opportunistic disease or severe non-AIDS disease was five-fold greater when they had a follow-up at an average period of one and a half years.[90] In comparison to the patients who delayed treatment, those with persistent medication had over two times the follow-up with a CD4 + count more than 500 cells/mm3.[46]

Congestive heart failure (CHF) carries a poor prognosis and is best treated with traditional therapy.[47] Once myocardial failure develops, it has a poor prognosis despite the observation that patients often respond to traditional heart failure therapies.[48] There is no document regarding the clinical trials on the management of heart failure in patients infected with HIV. Viremia regulation with effective and long-lasting therapies can help decrease the threats. Therefore, active control of replication of virus and control of common risk factors along with the traditional ways provides the best method to reduce overall cardiovascular risk in HIV infected patients. While there is confirmation that HAART could have adverse effects on the serum lipid profile, these would be minimal as well as the cumulative cardiovascular risk involved with HAART is low and could be controlled with therapies widely used in the common population. Alterations in lipid might not be addressed by swapping the antiretroviral agents and must be considered carefully, taking into

account the small yet possible risk of virological failure. Determining the total risk of coronary heart disease in individual patients using the Framingham score or other global risk calculators could provide useful information for patient care and medication scheduling.[46]

The effects of antiretroviral therapy on lipid profiles and the potentially increased risk for cardiovascular events must be taken into account when selecting treatment for HIV-infected individuals.2 In patients suffering from HIV and dyslipidemia, lipid mitigation medication (predominantly statins) must be regarded to accomplish the LDL-C objective as described for high-risk subjects (CLASS IIa, Level C). It is hoped that HAART regimens, by improving the clinical course of HIV disease, will reduce the incidence of pericardial effusions and myocardial involvement of HIV-associated malignancies and co-infections. Nevertheless, absolute CVD risk increase with ART is moderate and should be put into perspective with the benefits of HIV treatment. Statins are effective, but drug interactions with ART need to be considered. Statins metabolized in the liver via the CYP3A4 or CYP2C9 are susceptible to drug interactions with protease inhibitors and the NNRTI efavirenz. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore a preferred statin in HIV-infected individuals. Preferred statins include atorvastatin, fluvastatin, pitavastatin and rosuvastatin, although caution should be exercised.[49]

CONCLUSION

Cardiac abnormalities in HIV are common. HAART has dramatically improved the life expectancy for HIV-infected patients. Long-term complications of both HIV-infection and antiretroviral agents are therefore of increasing concern. Chronic immune activation and inflammation, including chronic inflammation linked to lower CD4 + cell counts, are typical mechanisms for these abnormalities. Treatment and prevention of HIV infection risks may include the management of conventional risk factors, behavioral changes, early introduction of antiretroviral therapy, and possibly effective medicines for inflammation and immune activation. Clinicians should be more alert to cardiac involvement in patients with HIV. Earlier surveillance is warranted and may lead to earlier treatment and supportive care.

Yet more studies need to be done to establish these diseases ' epidemiology and clinical significance and to develop appropriate diagnostic and therapeutic protocols for such a group. Studies on Cardiovascular Disease risk in patients diagnosed with HIV may provide perspectives into the comprehension of the role of inflammation in the manner CVD develops in a common group of people. The evaluation of threat of Cardiovascular disease in HIV continues to be a difficult job, however, latest research into emerging biomarkers could provide additional perspectives.

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