Abstract
Since the advent of combined antiretroviral therapy, it is clear that the survival of HIV-infected individuals has substantially improved. However, with extended lifespan, there is increasing prevalence of chronic diseases. Cardiovascular disease is currently the leading cause of morbidity and mortality in patients with HIV. Unlike seronegative individuals, HIV-associated cardiovascular disease has unique features and requires a specialized approach that calls into question the usefulness of traditional cardiovascular risk factor assessment tools. HIV infection can manifest as both non-ischemic and ischemic heart disease; a good understanding of the natural history of the disease becomes extremely valuable for the clinician when providing care to the HIV-infected patient with cardiovascular disease.

This review will examine the evidence and provide an update on the current available tools to identify and manage HIV infected patients at high risk of heart disease.

Keywords: HIV; AIDS; Cardiovascular disease

Introduction
Cardiovascular disease is one of the leading causes of morbidity and mortality in patients with HIV [1]. Nearly 36 million people in the world are currently living with HIV. The proportion of individuals having access to combination antiretroviral therapy (cART) has continued to increase, however nearly 42% of HIV infected patients worldwide remain untreated [2]. The advent of cART continues to have a significant impact on life expectancy. Currently, the overwhelming majority of infected individuals on cART achieve near normal life expectancy and are, therefore, at risk for chronic diseases associated with aging such as cardiovascular disease (CVD) [3]. HIV-infected individuals have a 50% greater risk of myocardial infarction (MI) and a fourfold increase in the risk of sudden cardiac death when compared with uninfected individuals [4].

Although, CVD abnormalities in HIV-infected individuals, predominantly concerns ischemic heart disease and accelerated atherosclerotic complications in developed countries, a review of HIV associated non-ischemic cardiovascular disease is also warranted, considering that the large global population remains untreated due to lack of access to cART [2] (Table 1).

Methods
We designed a comprehensive outline covering topics relevant to both ischemic- and non-ischemic cardiomyopathy (NICM) in the HIV infected adult patient. Each individual topic was searched using Google Scholar, PubMed, and EMBASE databases focusing on the terms “HIV”, “AIDS”, “CVD”, “Cardiomyopathy”, “Myocardial infarction”, “Cardiovascular disease”, “pulmonary hypertension”, “Coronary artery disease”, “Heart failure”, “myocarditis”, and “pericarditis”. Only articles published in English were considered. 300 articles published between 1999 and 2016 were extensively reviewed for potential usage. Of the initial review articles, 65 were considered to be highly significant for this paper and were included in this review.

Non-Ischemic Heart Disease in HIV
Cardiomyopathies
Left ventricular diastolic dysfunction: Diastolic dysfunction is an early and common manifestation of cardiac disease in HIV-infected patients. It has been shown that even after adjusting for gender and arterial hypertension; these patients tend to have a higher LV mass when compared to controls. It is estimated that for every 100 CD4+ T-cells drop there will be a 1.3 g increase in left ventricular mass [5]. Also higher rates of myocardial fibrosis, steatosis, and alterations in function, have been noted in HIV-infected subjects [5-7].

Approximately 50% of the newly diagnosed heart failure in HIV-individuals is due to diastolic dysfunction regardless of cART; about 64% of asymptomatic individuals on cART have some degree of diastolic dysfunction when evaluated by echocardiography [6-8]. It is believed that intermittent, low level viral replication in the heart can lead to diastolic dysfunction [6-8].

In the P2C2 HIV multicenter study it was found that an increased left ventricular mass and mild left ventricular dysfunction is associated with higher all-cause mortality in HIV infected subjects, therefore left ventricle hypertrophy is a marker of poor prognosis [9,10]. Given that viral replication has been associated with the incidence of diastolic dysfunction, antiretroviral therapy could potentially slow down the onset of diastolic dysfunction; however, it has been shown that even when undetectable viral loads are achieved, low level myocardial viral replication persists and could translate into diastolic dysfunction in asymptomatic patients. Management therefore focuses on risk factor modulation and early initiation of antiretroviral therapies.

Left ventricular systolic dysfunction: In the pre-cART era, the annual incidence of symptomatic dilated cardiomyopathy (DCM) in HIV-infected individuals was approximately 28%. This has now improved to approximately 8% [10]. Importantly, the SUN study demonstrated that even while on cART, HIV-infected individuals develop subclinical structural cardiac abnormalities at a higher rate than the matched general population [11]. Notably, most of the cases of left ventricular systolic dysfunction are transient in subjects on cART [6]. The most common reasons for DCM in HIV includes infectious myocarditis (HIV-1 myocardial infection, toxoplasma gondi, coxsackievirus group B, Epstein-Barr virus, cytomegalovirus, adenovirus), autoimmunity (cardiac specific antibodies; anti-α myosin autoantibodies), and metabolic (nutritional deficiency/wasting; Vitamin B12, selenium, carnitine). Other causes include encephalopathy, HIV viral load, cytokines (TNF-α, Nitric oxide, TGF-β, endothelin) and paradoxically antiretroviral therapy [12,13].

The exact mechanism for direct HIV-mediated cardiac myocyte death continues to be a highly debated topic. Several mechanisms have been proposed including HIV replication within inflammatory cells and induction of apoptosis of cardiomyocytes via ligand usage in an extrinsic pathway, as well as direct virus entry with gp120 and Tat-proapoptotic signaling in an intrinsic pathway [14]. HIV can also alter surface antigens on myocardial cells leading to an autoimmune reaction to endogenous epitopes and formation of cardiac specific autoantibodies (CSA) [15]. CSA are more common in HIV infected
Echocardiography is the most commonly employed method to diagnose, monitor, and prognosticate left ventricular dysfunction. Cardiac Magnetic Resonance (CMR) can also be used to further distinguish cardiovascular complications of HIV infection when trying to identify the etiology [19]. Because cardiac MRI has the added value of identifying subclinical myocardial inflammation and fibrosis which both serve as prognostic indicators of HIV related cardiomyopathy. CMR also allows the evaluation of left ventricular global systolic strain patterns, and provides a more accurate assessment of the systolic ejection fraction; When altered, all of these, indicate myocardial damage and are frequently present in asymptomatic HIV infected subjects [20,21]. Management of HIV CM is similar to management of nonischemic cardiomyopathy. Prevention of heart failure with early initiation of cART remains the best strategy.

**Pulmonary arterial hypertension**

The incidence of pulmonary arterial hypertension (PAH) in HIV-infected subjects is 0.5%, which is 6 to 12 times more common than in the general population. This has not changed despite the use of cART [22]. The HIV virus causes plexogenic pulmonary arteriopathy and endothelial remodeling with intimal fibrosis, via indirect activation of secondary messengers such as cytokines, growth factors, endothelin, and viral proteins [23]. Considering that PAH is a diagnosis of exclusion, work up includes both invasive and non-invasive studies ruling out alternative etiologies [24]. Studies have shown benefit with long-term usage of epoprostenol infusions, or bosentan given to estimate the rate of pericarditis while on cART demonstrated a significant reduction in the incidence of pericardial effusions to 0.25% [24]. The HIV-HEART study, a contemporary multicenter cohort designed to study PAH predisposes to the development of pulmonary vascular thrombosis and embolism therefore patients should be also started on anticoagulation [25].

**Pericarditis**

Pericarditis was described as one of the most common cardiac manifestations of HIV infection (up to 49%) in the pre-cART era. The HIV-HEART study, a contemporary multicenter cohort designed to estimate the rate of pericarditis while on cART demonstrated a significant reduction in the incidence of pericardial effusions to 0.25% during a 2 year follow up period [26].

Typically, pericardial effusions occur more frequently in subjects with lower CD4 counts and more advanced disease. The best initial test is an echocardiogram and should be part of the workup for all HIV-infected patients presenting with dyspnea, edema and exercise intolerance.

Pericardiocentesis is indicated when clinical or echocardiographic signs of tamponade are present. It is recommended that all HIV-infected patients with pericardial effusions undergo evaluation for opportunistic infections or malignancies (Lymphoma, Kaposi sarcoma) [10,27].

**Ischemic Heart Disease in HIV**

With the widespread availability of cART in western societies, HIV-infected patients have achieved an extended life expectancy. Consequently, we have witnessed a change in the spectrum of diseases impacting the health of these patients. AIDS-related complications and opportunistic infections have declined in favor of chronic conditions and other illnesses related with aging. Notably cardio metabolic disorders and CVD have now become more prevalent [28]. Cardiometabolic disease is now becoming the most common cause of morbidity and mortality in HIV-infected individuals [29]. Analysis of the Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiological Research (WONDER) database demonstrated that with the advent of c-ART, the annual total mortality in HIV-infected patients decreased from 15,749 in 1999 to 8,660 in 2013. However, cardiovascular mortality increased almost by 30% in that same time period [4].

**Molecular and metabolic derangements**

HIV infection causes multiple metabolic disorders. Importantly, alterations in lipoprotein metabolism in HIV-infected subjects not on cART typically present as low levels of LDL and HDL cholesterol. Despite low LDL-cholesterol reducing the risk for cardiovascular diseases, low HDL-cholesterol levels overpower this positive effect and contribute to accelerated atherosclerosis in HIV-infected individuals [30,31]. It has been shown that HIV, via Nef production, impairs the function of ATP-binding cassette transporter A1 (ABCA-1). This inhibits reverse cholesterol transport and traps cholesterol inside macrophages [30]. Consequently, HDL-cholesterol catabolism increases and serum levels fall. HIV has direct effects on macrophages, endothelial cells and smooth muscle: gp-120 leads to activation, migration, and foam cell formation in a pro-inflammatory and pro-atherogenic environment [31]. All of these lead to increase atherosclerosis despite low plasma lipid levels.

Furthermore, recent studies have demonstrated the association of altered metabolic pathways with plaque inflammation in coronary artery disease [32] and untreated HIV infection [33,34]. It has been shown that HIV infection up regulates GLUT-1 [35], and promotes a glycolysis predominant metabolism. These changes along with an expanded intermediate monocyte/macrophage CD4+CD16+ subset increase intracellular production of reactive oxygen species (ROS) resulting transcription of inflammatory cytokines (IL-1β, IL-6 and TGF-β) via metabolic intermediates [32,24]. Insights on these mechanisms have uncovered multiple potential therapeutic targets for the management of CAD in HIV infected patients.

Importantly, combined antiretroviral therapy has been shown to

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**Table 1: HIV worldwide statistics**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of new HIV infections worldwide</th>
<th>Number of people receiving ART worldwide</th>
<th>Coverage of people receiving ART worldwide</th>
<th>Number of AIDS related death worldwide</th>
<th>Number of People living with HIV worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>2 200 000 [1 900 000 - 2 400 000]</td>
<td>10 935 600</td>
<td>32 [29 - 34]</td>
<td>1 400 000 [1 200 000 - 1 600 000]</td>
<td>34 500 000 [31 900 000 - 37 400 000]</td>
</tr>
<tr>
<td>2013</td>
<td>2 100 000 [1 900 000 - 2 400 000]</td>
<td>12 936 500</td>
<td>37 [34 - 40]</td>
<td>1 300 000 [1 100 000 - 1 500 000]</td>
<td>35 200 000 [32 600 000 - 38 100 000]</td>
</tr>
<tr>
<td>2014</td>
<td>2 100 000 [1 900 000 - 2 400 000]</td>
<td>14 977 200</td>
<td>42 [39 - 45]</td>
<td>1 200 000 [990 000 - 1 400 000]</td>
<td>35 900 000 [33 300 000 - 38 900 000]</td>
</tr>
<tr>
<td>2015</td>
<td>2 100 000 [1 800 000 - 2 400 000]</td>
<td>17 023 200</td>
<td>46 [43 - 50]</td>
<td>1 100 000 [940 000 - 1 300 000]</td>
<td>36 700 000 [34 000 000 - 39 800 000]</td>
</tr>
</tbody>
</table>

*Adapted from UNAIDS: AIDSinfo
attenuate but not terminate the vascular inflammatory process by decreasing viral replication. Nevertheless, some antiretrovirals have also been shown to be pro-atherogenic. These drugs interfere with nitric oxide synthase (NOS); down regulate LDL-receptors, and cause dyslipidemias, glucose intolerance and lipodystrophy, which also predispose to atherosclerotic vascular disease. Clear understanding of the pathophysiological mechanism by which inflammation and cardiometabolic dysfunction induce CVD in HIV-infected patients has not been completely elucidated. The potential to identify early vascular changes in these patients is currently a clinical need [30,31,36].

Clinical presentation

The first clinical presentation of CVD for many HIV-infected patients is with an acute coronary syndrome (ACS). Most specifically, up to 64% of cases present with an ST-segment elevation myocardial infarction (STEMI); 48% with a non ST-segment elevation myocardial infarction (NSTEMI) and 46% with unstable angina (UA) [28]. The association between myocardial infarction and HIV-infected subjects has been consistently demonstrated, and therefore demands for a more aggressive management of both traditional and non-traditional risk factors [37].

Angiographic characteristics: Review of the available data, demonstrates that the majority of HIV infected patients presenting for emergency angiography have single vessel disease (35-56%) with the left anterior descending branch of the left coronary artery being the most commonly affected (42-82%) [28].

It has been demonstrated that HIV-infected patients are at high risk of developing recurrent acute coronary syndromes (ACS). A study determined a hazard ratio for recurrent ACS of 6.5 (95% CI, 1.7-23.9) [38,39]. Importantly, these patients are not only at risk for clinical restenosis and target vessel revascularization but more so for the novo acute coronary syndrome requiring urgent percutaneous coronary intervention (PCI) [38,39]. Small single center randomized control trials have demonstrated the superiority of drug eluting stents in HIV-positive patients undergoing PCI [40,41].

Risk Factor Calculators

With increased survival and longevity from cART, traditional cardiovascular risk factors such as cigarette smoking, hypercholesterolemia, diabetes and hypertension are higher in HIV infected patients [42]. Importantly, non-traditional risk factors such as substance use, coinfections with viral hepatitis and the pro-inflammatory state associated with HIV, need to be taken into account when assessing cardiovascular morbidity and mortality. More specifically, cocaine has been shown to promote silent coronary artery disease [43]. The effects of Hepatitis C; on the other hand are much debated with conflicting results, an analysis of the D:A:D cohort adjusting for confounding variables failed to show an association between viral hepatitis infection and cardiovascular events in HIV-infected individuals [4]. Low-income levels and elevated BMI have also been shown to contribute in the predicted risk of coronary heart disease [45].

Extension of pre-existing risk factor calculators such as The Framingham cardiovascular risk score tends to underestimate the actual CAD risk in HIV-infected patients [28,46]. Classically, HIV is accompanied with accelerated progression of coronary artery disease that occurs in younger individuals with low Framingham risk scores. Therefore, to better estimate cardiovascular risk in HIV-infected individuals, it is critical to also include non-traditional risk factors [28,47]. There is currently only one other model, gathered from the D:A:D cohort. This model includes age, gender, systolic blood pressure, smoking status, family history of CVD, diabetes, total cholesterol, high density lipoprotein, CD4 count, exposure to protease inhibitors, NRTI and use of abacavir [48]. Although this assessment tool is promising it remains to be validated with large sample prospective studies.

Combined Antiretroviral Therapy and Cardiovascular Risk

Initially, the Data collection on adverse events of anti-HIV drugs (D:A:D) study demonstrated the association of myocardial infarction with long term combination antiretroviral therapy specifically with the use of older generation protease inhibitors [49,50]. This trial showed that unlike indinavir and lopinavir-ritonavir, nelfinavir and saquinavir were not associated with a significantly increased risk of myocardial infarctions in HIV-infected individuals. More generally, the FHHD ANRS cohort CO4 concluded that except for saquinavir, all other PIs were associated with increased risk of MI, particularly Amprenavir/ fosamprenavir which was found to have the strongest association with clinical CAD with an odds ratio of 1.53 (95% CI, 1.09-1.61)[51,52].

These same trials also demonstrated that exposure to abacavir and didanosine was also a risk factor for developing acute coronary syndromes [50].

Moreover, factors such as length of exposure to PI or NNRTI was also found to be positively correlated to fatal and non-fatal major adverse cardiac events.

Considering the potential adverse effects that cART entails, multiple models for therapy administration have been suggested. The strategies for management of antiretroviral therapy (SMART) study group hypothesized that administering intermittent cART based on CD4 counts would reduce therapy related adverse effects. The trial demonstrated that episodic antiviral therapy was inferior to continuous therapy and resulted in a higher all cause mortality, serious opportunistic infections and major cardiovascular disease [53]. The results of the more recent INSIGHT START study did not demonstrate a significant difference between immediate as opposed to deferred cART initiation on cardiovascular events endpoint, however, the composite primary endpoint (including AIDS-related events and all-cause mortality) favored early initiation of cART for asymptomatic patients with HIV [54,55]. The benefits of starting cART outweigh the risks of cardiovascular disease. Preventive measures should therefore be undertaken promptly.

Newer agents currently used as part of highly antiretroviral therapy regimen, have been shown to have cardiovascular neutral effects. Currently, novel formulations of nucleoside reverse transcriptase inhibitors making up the “backbone” of cART have been found to be promising. Trials have shown that the use of tenofovir alafenamide as opposed to tenofovir disoproxyl fumarate decreases proteinuria and proximal tubular dysfunction which could translate into cardiovascular neutral effects. This, however remains to be proven on randomized controlled trials [56].

It is also important to consider the potential pharmacological interactions of once daily, single pill cART regimens might have in subjects already being treated for baseline cardiac conditions. Such is the case of Cobicistat which is commonly used as a booster in HIV regimens; by working as an enhancer of P-glycoprotein (P-gp) and also having inhibitory properties of the renal multidrug and toxin extrusion-1 transporter (MATE-1), it’s co-administration with substrates of either P-gp and MATE-1 result in multiple interactions. Dabigatran, one of the novel anticoagulants, is a clear example of this as its effect on thrombin time are accentuated when concomitantly taking cobicistat and therefore increasing the risk of bleeding [57].

Prevention

Lipid lowering agents

Expert opinion recommends the use of lipid lowering agents,
particular statins to lower cardiovascular risk in HIV positive patients. Although, specific agent use and dosing regimens remain undetermined. Important factors need to be taken into account prior to starting statin therapy: Most HIV drugs undergo metabolism via cytochrome P450; PI and NNRTI particularly are metabolized through CYP 3A4 and may interact with other drugs sharing this same pathway [10].

PLs reduce CYP 3A4 metabolic activity whereas Efavirenz induces it [58]. Most statins use this same pathway for their metabolism; therefore a variation in their pharmacokinetics is to be expected for most statins. Atorvastatin and rosvastatin are particularly metabolized via CYP3A4. It is recommended that these drugs be started at a low dose, and with progressive dose increments closely monitoring side effects.

Pitavastatin and pravastatin are metabolized by glucuronidation and therefore have more predictable pharmacokinetics [59]. Some trials have suggested that HIV-infected patients at low risk of CVD would benefit from high intensity lipid lowering therapy [60,61]. The ongoing NIH funded REPRIEVE trial will try to determine effectiveness of pitavastatin for cardiovascular event reduction in HIV-infected patients at low to moderate risk of cardiovascular disease, results however will not be available until 2020 [62].

**Screening Recommendations**

The IDSA recommends obtaining fasting glucose, hemoglobin A1c levels, and a fasting lipid profile prior to and within 1 to 3 months after starting cART. For patients on antiretroviral therapy, the IDSA recommends obtaining a fasting lipid profile, a fasting glucose and/or A1c every 6 to 12 months [59]. Routine comprehensive history and cardiac examination are fundamental for initial CAD risk assessment. As it was discussed earlier, the clinical manifestations of ischemic cardiomyopathy in HIV may be as a first ACS, importantly, are also associated with fatal outcomes. Some studies suggest that systematic echocardiographic monitoring could be of benefit for the timely detection and treatment of significant and accelerated coronary artery disease due to HIV. These observations indicate that the threshold for the use of coronary assessment testing should be lower in HIV patients on cART [63].

Carotid media-intima thickening (CIMT) has been established as a promising tool for predicting atherosclerotic cardiovascular disease development. HIV-infected patients display an accelerated CIMT progression when compared to matched HIV-negative subjects. Progression has also been shown to be positively correlated with rising inflammatory markers such as hsCRP [64,65]. Other tools such as flow mediated dilatation of the brachial artery, PET scan and coronary MRI are currently being evaluated as potential tools to help identify HIV-infected patients at risk for CVD.

**Conclusion**

The importance of cardiovascular disease in HIV-infected individuals has been well established. Both disease progression and highly active antiretroviral therapy have been associated with accelerated atherosclerosis and early onset manifestations of coronary artery disease. More aggressive preventive measures would therefore be suitable in this patient population; however, clinicians are lacking accurate risk stratification tools that would help identify HIV-infected individuals at higher risk for major cardiovascular events. Moreover, indiscriminate pharmacological interventions could potentially lead to major drug to drug interactions with ongoing antiretroviral therapies. The sum of these factors makes management of cardiovascular disease in HIV an extremely complex matter. More evidence is needed regarding appropriate preventive measures and management of cardiovascular disease in HIV infected individuals.

**References**


randomized, Double blind comparison of Tenofovir alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF). Each coformulated with Elvitegravir, Cobiscistat and Emtricitabine (E/C/F) for initial HIV-1 Treatment: Week 96 Results. J Acquir Immune Defic Syndr. 72: 58-64.


62. National Institute of Allergy and Infectious Diseases. Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults (REPRIEVE). In progress; clinicaltrials.gov NLM Identifier: NCT02344290.

