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Epidemiology and Management of Antiretroviral-Associated Cardiovascular Disease

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Abstract: Risk and manifestations of cardiovascular disease (CVD) in patients infected with human immunodeficiency virus (HIV) will continue to evolve as improved treatments and life expectancy of these patients increases. Although initiation of antiretroviral (ARV) therapy has been shown to reduce this risk, some ARV medications may induce metabolic abnormalities, further compounding the risk of CVD. In this patient population, both pharmacologic and nonpharmacologic strategies should be employed to treat and reduce further risk of CVD. This review summarizes epidemiology data of the risk factors and development of CVD in HIV and provides recommendations to manage CVD in HIV-infected patients.

Keywords: Antiretroviral therapy, cardiovascular disease, drug interactions, HIV, hyperlipidemia, hypertension.

INTRODUCTION

Following the introduction of antiretroviral (ARV) therapy, treatment and long-term prognosis of human immunodeficiency virus (HIV)-infected patients has significantly changed. As ARV therapy became more available and more widely used, a significant reduction in annual mortality was observed. The median survival for persons with HIV infection was estimated to be 10 years in 1986, whereas now, almost 90% of infected patients are expected to survive at least 10 years [1]. Despite the downward trend in mortality, the number of deaths due to non-HIV-related causes has dramatically increased [2]. This increase in mortality can be attributed to noninfectious chronic illnesses, including hepatic disease, cardiovascular disease (CVD) and cancer. This review will focus on the cardiovascular (CV) manifestations observed in HIV-infected patients.

EPIDEMIOLOGY OF HIV-ASSOCIATED CARDIOVASCULAR DISEASE

The incidence of CVD in HIV-infected patients has been estimated to range from 28-73%, despite effective ARV therapy [3]. Compared to uninfected individuals, HIV-infected patients are at a much higher risk of developing CVD, which remained significantly elevated despite adjusting for traditional CV risk factors [4, 5]. Metabolic abnormalities are common adverse effects of ARV therapy, which may account for some of the higher rates of hypertension, diabetes mellitus (DM), and dyslipidemia that have been observed in this patient population [6, 7]. The incidence of CVD has previously been expected to continue to increase due to a longer life expectancy coupled with higher rates of CV risk factors. However, recent data suggests that HIV-infected patients may not actually be at higher risk for CVD [8]. Proposed mechanisms behind this decline include early initiation of ARV therapy, use of ARV medications with favorable effects on lipids, and employment of risk reduction strategies.

PATHOGENESIS OF HIV-ASSOCIATED CARDIOVASCULAR DISEASE

The inflammatory and prothrombotic changes caused by HIV infection may lead to atherosclerosis and subsequent plaque rupture. Increased levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6, which have been associated with an increased CV risk independent of traditional risk factors, have been found in ARV-naïve HIV-infected patients [9-13].

Coagulation abnormalities and platelet activation are also associated with the development of CVD, and increased D-dimer has been identified in HIV-infected patients despite viral suppression with ARV therapy [9, 14]. Immunosuppression and ongoing viral replication, usually observed in advanced HIV-infection, lead to increased pro-inflammatory biomarkers and abnormal coagulation, including IL-6, D-dimer, and soluble CD14 (sCD14) [15].

HIV-induced inflammation, endothelial cell infection, proinflammatory cytokines, viral proteins, oxidative stress, and HIV infection itself have been described as the pathogenic mechanisms of endothelial dysfunction observed in HIV-infected patients [16]. Increased concentrations of biomarkers associated with endothelial activation, including

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intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, P-selectin, and von Willebrand factor (vWF), have been found in patients with advanced HIV-infection and opportunistic infections compared to uninfected controls [17, 18]. HIV-associated proteins, Tat and glycoprotein 120 (gp120), may also play a role in inducing endothelial dysfunction [19, 20].

HIV replication disrupts of the reverse cholesterol transport pathway, which is essential for regulating cellular cholesterol [21, 22]. Nef, a viral accessory protein, impairs the actions of transmembrane lipid transporters, particularly ATP binding cassette transporter A1 (ABCA1) [23]. This leads to inhibition of cholesterol efflux from macrophages resulting in the formation of foam cells [22].

Monocyte activation, caused by microbial translocation or elevated concentrations of sCD14 and soluble CD163 (sCD163), may result in the release of pro-inflammatory cytokines and atherogenesis [24-26]. Elevated sCD14 concentrations, a serum biomarker of macrophage activation, have been associated with significant increases in carotid intima media thickness (IMT) [27, 28]. Greater measurements and a more rapid progression of carotid IMT were observed in HIV-infected patients compared to controls [29]. Increased levels of sCD163, produced in response to inflammation by activated macrophages, are commonly found in ARV-naïve patients and remain elevated despite low or undetectable HIV-RNA viral loads [26].

Depletion of peripheral CD4+ T-cell counts and a greater degree of immunosuppression has been directly correlated with an elevated risk of CVD [30]. Patients with a CD4 count < 350 cells/mcL were 58% more likely to experience a CVD event compared to those with a CD4 count > 500 cells/mcL [31]. Progression of HIV infection induces T-cell activation despite ARV therapy, and elevated CD8+ T-cell counts are associated with an increased risk of carotid artery plaques and carotid artery stiffness [30, 32]. Ongoing HIV-RNA viral replication has also been theorized to increase the risk of developing CVD; the associated mechanism has been proposed to be the result of chronic inflammation and endothelial dysfunction, which improved after initiating ARV therapy [9, 33]. Concern exists that low-level HIV-RNA replication occurring in patients receiving effective ARV therapy maybe associated with an increased risk of CVD in a similar manner as that observed in untreated HIV-infected patients [30].

TRADITIONAL CARDIOVASCULAR DISEASE RISK FACTORS

In addition to the inherent risk of CVD associated with HIV, an increased prevalence of traditional CV risk factors, including smoking, dyslipidemia, insulin resistance, impaired glucose tolerance, hypertension, and visceral adiposity has been observed in the HIV-infected patient population. This likely contributes to the increased rate of CV morbidity observed in these patients.

Cigarette Smoking

Despite declining rates of cigarette smoking for the entire U.S. population, the incidence of cigarette smoking has continued to rise among HIV-infected individuals [34]. Among more than 33,000 HIV-infected patients enrolled over a 10 year observation period in the Data Collection of Adverse events of Anti-HIV Drugs (D:A:D) study, 51.5% were classified as current smokers [6]. The risk of death due to smoking in HIV-infected patients is of almost twice that of controls (61.5% *vs* 39.4%), and excess mortality was three times higher in HIV current smokers than in HIV negative population controls classified as never smokers [35, 36].

Dyslipidemias

Reductions in high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) and increases in triglyceride (TGL) and very-low-density lipoprotein-cholesterol (VLDL-C) levels occur early in HIV-infection [37]. These changes in lipids are caused by increased lipogenesis and a reduced rate of VLDL-C clearance, which may promote atherogenesis. Varying rates of dyslipidemia among HIV-infected patients have been reported depending on the methodology and patient population, ranging from 20% to 80% [38].

ARV-induced lipid abnormalities are characterized by increased levels of total cholesterol (TC), LDL-C, VLDL-C, and apolipoprotein B (apoB), in addition to low HDL-C levels, and usually occur within 3 months after initiation of therapy [39, 40]. Analysis of the D:A:D study revealed an increased risk of elevated TC in patients treated with nucleoside reverse transcriptase inhibitor (NRTI)-based regimens combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI), or both compared to untreated patients [6]. Using a univariable logistic model for cumulative exposure to ARV therapy, the odds ratio (OR) for elevated TC was 1.42 for PI (1.38-1.47, $p<0.001$), 1.00 for NRTI (IQR, 0.98-1.02, $p=0.81$), and 1.39 for NNRTI (IQR 1.31-1.47, $p<0.001$), per year of exposure.

PI-based regimens are associated with worsened lipid profiles and are estimated to occur in up to 50% of HIV-infected patients receiving a PI [41, 42]. However, the degree of resulting lipid abnormalities vary with individual PIs and duration of treatment [43, 44]. Greater increases in TGL levels have been observed in patients receiving ritonavir (RTV)-containing regimens, while similar increases in TC occur with all PI-containing regimens [45]. Patients treated with RTV-boosted PI-based regimens were found to have more elevated TC, LCL-C, and TGL levels and lower HDL-C levels compared to untreated patients and those receiving only one PI. Newer PIs, atazanavir (ATV) and darunavir (DRV), appear to have minimal, if any, effects on lipid profiles, even when boosted with RTV [46, 47].

NRTI-induced lipid abnormalities have been observed to occur at a much lower rate and degree than that seen with PIs [48]. ARV-regimens containing tenofovir (TDF) combined with emtricitabine (FTC) or lamivudine (3TC) were associated with reductions in TC, TGL, LDL-C, HDL-C, and non-HDL-C when compared with other NRTI pairs [49]. Increased LDL-C were observed in patients receiving didanosine (ddI)/3TC-containing regimens, whereas TGL levels were the highest in patients treated with stavudine (d4T)/3TC. Addition of TDF to the current regimen of dyslipidemic HIV-infected patients produced a lipid-

lowering effect, evidenced by significant reductions in TC, LDL-C, and non-HDL-C [50]. However, significant improvements were not observed for HDL-C and TGL. Furthermore, TDF significantly decreased lipid parameters, including TC, LDL-C, HDL-C, and TGL in patients switched from abacavir (ABC)- to TDF-containing regimens [51].

NNRTIs may induce lipid abnormalities, but increases in HDL-C have also been reported [52, 53]. Greater increases of HDL-C and resultant decreases in TC:HDL-C ratio were found in patients treated with an NNRTI-based rather than PI-based regimen. Previous studies suggest that both nevirapine (NVP)- and efavirenz (EFV)-containing regimens demonstrate a protective effect against decreased HDL-C. In contrast, analysis of cross-sectional data from the D:A:D study revealed that treatment with NNRTIs lead to significant increases in TGL [42]. Additionally, more elevated TC and TGL were observed with EFV-based regimens than those that contained NVP.

Integrase inhibitors (INSTI) have been associated with favorable effects on lipid profiles [54]. Smaller mean changes in TC, LDL-C, HDL-C, and TGL levels were observed in patients receiving raltegravir (RAL) compared to those receiving EFV, both combined with TDF and FTC [55]. Although elvitegravir (EVG) may produce a favorable effect on lipids, when combined with cobicistat (EVG/c), increases in TC and LDL-C are similar to those seen with RTV-boosted regimens [56, 57]. Compared to EFV, improvements in lipid profiles occurred with EVG/c- and dolutegravir (DTG)-containing regimens [58, 59]. Data from phase IIb and III clinical trials of DTG plus an NRTI backbone confirm its minimal effects on lipid values in ARV therapy-naïve patients [60]. Patients treated with RTV-boosted DRV-containing regimens had greater increases in TC, LDL-C, and TGL compared to those treated with DTG.

Dysglycemias

Abnormalities of glucose homeostasis in HIV-infected patients, manifesting as impaired glucose tolerance and insulin resistance, are estimated to occur in 4.5% to 12% of patients [61, 62]. Limited data exists suggesting an increased rate of impaired glucose metabolism prior to the ARV era, and hyperinsulinemia was observed more frequently among HIV-infected females receiving ARV when compared to uninfected controls [63]. The pathogenesis of insulin resistance is thought to be the result of lipodystrophy, particularly increases in visceral fat and decreases in subcutaneous fat [64]. Associations between insulin-glucose disorders and impaired adiponectin and leptin regulation, as a result of HIV-infection and ARV therapy, have also been put forth as possible mechanisms of insulin resistance [65]. Multiple studies have, however, reported an increased frequency of impaired glucose homeostasis among HIV-infected patients receiving ARV therapy compared to those who are ARV-naïve [66, 67]. Among ARV-naïve patients, 2.6% were reported to have DM, compared to 14% of those treated with ARV [68, 69].

The prevalence of DM among patients treated with PI-based regimens ranges from 1% and 11%, whereas impaired glucose tolerance occurs more frequently [70]. NRTIs may also induce insulin resistance and DM, with an estimated risk of 8% per year of exposure [71]. The incidence rate of DM in the Women's Interagency HIV Study (WIHS) was reported to be 1.53/100 person-years (PY) for untreated patients, 2.50/100 PY for patients receiving a PI-containing regimen, and 2.89/100 person-years for those treated with a PI-sparing ARV regimen, while a similar incidence rate of 1.96/100 person-years was found among uninfected women [72]. Analysis of the D:A:D study found significant associations between exposure to d4T and zidovudine to the development of DM [73]. Inhibition of mitochondrial synthesis, mitochondrial DNA release, and increased production of reactive oxygen species has been proposed as a potential mechanism for the development of insulin resistance observed with these two thymidine analogs [74].

An increased risk of insulin resistance and DM among HIV-infected patients has not been observed with in patients treated with NNRTI-containing regimens [75]. Additionally, no available evidence suggests that fusion inhibitors, chemokine co-receptor 5 (CCR5) antagonists, or INSTI contribute to the development of impaired glucose tolerance and insulin resistance [75-78].

Hypertension

The incidence of hypertension has been reported to be marginally higher in HIV-infected patients compared to the general population [79]. In a combined analysis of the WIHS and Multicenter AIDS Cohort Study (MACS) cohorts, the prevalence of hypertension among HIV-infected patients < 40 years of age was 12% to 20%, whereas in patients ≥ 41 years of age, the rate was 35% to 41% [80]. Previous studies have suggested that ARV therapy may induce a modest increase in blood pressure, although this association remains unclear as participants also experience weight gain, increases in body mass index (BMI), and other potential factors resulting in the development of hypertension [80, 81]. Risk factors for hypertension among the general population are similar to those observed in HIV-infected patients, including older age, male sex, greater BMI, increased TC, and lipodystrophy. Exposure to any ARV therapy did not result in an increased risk of hypertension; however a significantly lower risk of hypertension was discovered in patients treated with NNRTIs, but this has not been confirmed in prospective, randomized clinical trials [83].

Lipodystrophy

Lipodystrophy syndrome consists of central lipohypertrophy (abnormal central fat accumulation), peripheral lipoatrophy (adipose tissue depletion in the face and extremities), and metabolic abnormalities comparable to metabolic syndrome [43, 82]. Proposed mechanisms include ARV-induced mitochondrial dysfunction, alterations in fatty acid metabolism, abnormal concentrations of adiponectin and leptin, irregular hormone secretion and signaling, as well as immune reconstitution [83]. Lipodystrophy has been observed in up to 80% of HIV-infected patients following treatment with all classes of ARV drugs and may predispose patients to non-insulin-dependent DM, dyslipidemia, or CVD [43, 82]. Clinical findings may include accumulation of abdominal visceral fat, loss of fat in the face or

extremities, increased fat deposition in the dorsocervical fat pad, and gynecomastia. Pathologic findings include fibrotic changes without inflammation, small adipocytes, and diminished vascularity in adipose tissue [84].

The physiology of adipose tissue differs between subcutaneous and visceral adipose tissue (VAT), the anatomical location, and lipodystrophy status of the patient [85]. Reduced adipose tissue mitochondrial DNA (mtDNA) and increased mitochondrial protein concentrations were discovered in VAT and subcutaneous adipose tissue of ARV-treated patients with lipodystrophy [86]. Inhibition of mtDNA replication and transcription has been found in patients receiving NRTI-containing regimens [87, 88].

Risk factors for developing lipodystrophy include increasing age and cumulative ARV exposure, particularly NRTIs and PIs [89, 90]. A significantly higher incidence of lipodystrophy was observed in patients treated with PI-containing regimens compared to PI-naïve patients after a mean of 13.9 months [43]. The metabolic abnormalities associated with lipodystrophy may result in an increased risk of CVD. Findings of premature coronary artery disease (CAD) in HIV-infected patients with few traditional CV risk factors receiving PI-containing regimens have been published [91].

ANTIRETROVIRAL INDUCED CORONARY ARTERY DISEASE

The relative incidence of myocardial infarction (MI) in HIV-infected patients receiving ARV therapy increased by 26% per year of exposure (95% CI, 1.12-1.41; $p<0.001$) in the D:A:D study [92]. Independent predictors of MI observed in the study included increase age, current or former smoker, underlying CVD, and male sex [93].

Increasing rates of CAD have been observed among HIV-infected patients treated with PI-containing ARV regimens [94]. Lipodystrophy, insulin resistance, and increased levels of LDL-C and TGL are estimated to affect up to 60% of patients treated with ARV regimens that include a PI, of which 10% to 20% of these patients may experience severe manifestations [95]. The relative risk of PI-associated MI was 1.16 per year of exposure (95% CI, 1.10 to 1.23) after adjusting for traditional CV risk factors and exposure to other drug classes [96]. A positive correlation was found between the duration of PI therapy and risk of MI [97]. The projected incidence of MI in HIV-infected males who received PIs for < 18 months or for 18 to 29 months was similar (8.2/10,000 PY, [95% CI, 4.7-11.7], and 15.9/10,000 PY, [95% CI, 7.9-23.9], respectively) when compared to the general population, whose incidence was expected to be 10.8/10,000 PY. In contrast, those treated with PIs for > 30 months (33.8/10,000 PY, [95% CI, 15.4-52.1]) had a statistically significant increase in the risk of MI.

While metabolic effects are classically associated with PIs, there is some evidence that newer agents may not have as many metabolic effects as older agents. A similar incidence of MI was observed in patients treated with ATV, of which 85% was ATV/r, for > 3 years compared to those who were not [98]. A multivariate analysis was performed that failed to establish a correlation between ATV and the risk of MI. Additionally, DRV/r and ATV/r were found to be relatively free of metabolic changes that plagued older PIs [99]. No significant or clinically relevant differences in lipid profiles, fasting plasma glucose, insulin, or insulin sensitivity were observed after 48 weeks of follow up.

Numerous studies have been conducted evaluating whether treatment with NRTIs were associated with an increased risk of MI. While no significant increase in the incidence of MI was observed in patients receiving ZDV, d4T, or 3TC, patients whose therapy included ABC or ddI either currently or recently (within the past 6 months) had a 90% and 49% higher rate of MI, respectively, compared to those who had never received or who had received these ARV at least 6 months ago [100]. Based on these findings, multiple studies have subsequently evaluated the association of ABC-induced MI with conflicting results. While some studies have confirmed the findings by Sabin *et al.*, others have failed to do so [101-110]. Among these studies, 3 were not designed to test whether an association exists between ABC and an AMI, and therefore may have been underpowered [106-108].

In the Strategies for Management of Anti-Retroviral Therapy (SMART) study, patients receiving ABC or ddI were more likely to be men who required the use of anti-hypertensive and anti-lipemic medications more frequently [102]. Furthermore, a greater percentage of patients treated with ABC were found to have at least 5 CV risk factors compared to those receiving ddI or other NRTIs, 18%, 17%, and 14%, respectively. hs-CRP and IL-6 were also significant elevated in patients exposed to ABC compared to those in the other treatment categories. An 80% increase in the risk of major CV events, including MI, stroke, CAD requiring surgery, and CV death, was observed in patients receiving ABC compared to those who were being treated with NRTIs other than ABC and ddI. A study of the Veterans Health Administration found a 48% increased risk of CVD in patients who were currently or previously, within the past 6 months, treated with ABC [103]. An increased rate of CVD was found in HIV-infected patients randomized to receive ABC/3TC compared to those receiving TDF/FTC in the STEAL study [104].

Three meta-analyses failed to evidence of an increased risk of MI or CVD in patients treated with ABC [107-109]. In contrast, a recent retrospective cohort analysis of patients enrolled in the D:A:D study group concluded that treatment with ABC remains associated with an increased risk of MI [111]. The authors also denounce the hypothesis that the increased risk of CVD observed with ABC may be due to preferentially starting or modifying regimens to include ABC in patients who have an increased a priori risk of CVD, as decreasing rates of ABC have been used in patients with an increased risk of CVD since 2008 [102, 111].

Mechanisms for the association of ABC and MI have been described and include increases in platelet reactivity, abnormal endothelial function, elevated concentrations of inflammatory markers, T lymphocyte hyperactivation, and increases in total cholesterol and LDL-C levels [112-115].

INSTIs do not appear to have negative effects on lipid values and cardiovascular outcomes [116]. Significantly greater increases in fasting lipid values from baseline were

observed in patients treated with EFV than in those receiving RAL [117, 118]. Furthermore, fewer patients treated with RAL started lipid lowering therapy. TC, LDL-C, and non-HDL-C were reduced in patients who switched from RTV-boosted PI- to RAL-containing regimens, which included a shift to a less atherogenic LDL subclass [119, 120]. hs-CRP and IL-6 were also reduced by more than 40%, while endothelial dysfunction remained unchanged [120]. RAL significantly reduced endoplasmic reticulum stress, oxidative stress, inflammatory changes, and foam cell development associated with PI use [121]. To date, no published data exist linking INSTI use to the development of inflammation, endothelial dysfunction, hypercoagulability, atherosclerosis, or CVD.

PREDICTING THE RISK OF CHD AMONG HIV-INFECTED PATIENTS

Although the Framingham risk score equation has traditionally been used to estimate the 10-year risk of developing coronary heart disease (CHD), this equation may not provide an accurate prediction of the risk in HIV-infected patients due to patient age, direct effects from HIV-infection and ARV therapy, as well as variations in traditional risk factors among patient populations [39, 122]. In one study attempting to validate the use of the Framingham CV risk equation in HIV-infected patients, the actual incidence of MI was higher than predicted in patients receiving ARV therapy [123]. A positive correlation was found to exist between both actual and predicted incidence of MI and duration of ARV therapy.

In consideration of the limitations with the Framingham in HIV patients, the D:A:D study group created a CV risk score calculator that includes traditional risk factors for CVD, in addition to exposure to ARV drugs associated with increased risk of CHD [124]. While this risk assessment tool is able to better predict the risk of CHD in HIV-infected patients, it lacks the inclusion of inflammatory and immunologic markers.

REDUCING THE RISK OF HIV-ASSOCIATED CARDIOVASCULAR DISEASE

Due to the increased risk of traditional and HIV-associated risk factors, clinicians should employ strategies aimed to reduce these risks. Baseline assessment for newly diagnosed HIV-infected patients should include laboratory data to identify the presence of DM and dyslipidemia, as well as measurements of blood pressure, waist circumference, and body mass index [125, 126]. Clinicians should inquire about smoking status, diet, current activity level, and any family history of DM, hypertension, or CAD. Routine follow-up of fasting lipid values should be performed within 1 to 3 months after initiation or modification of ARV therapy. Additional monitoring and management of lipid values should follow the recommendations made in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), despite the recent publication of updated cholesterol treatment guidelines due its lack of data regarding the management of dyslipidemia in HIV-infected patients [126-128]. Blood glucose values should be assessed within 1 to 3 months after initiation or modification of ARV therapy, and hemoglobin A1c (HbA1c) should be monitored every 6 months with additional follow-up and treatment based on recommendations provided by the American Diabetes Association (ADA) [129].

Therapeutic lifestyle modifications including smoking cessation, dietary changes, and exercise should be employed in all dyslipidemic HIV-infected patients [39]. Due to the overwhelming rate of smoking observed among HIV-positive individuals, Triant suggested that smoking cessation may be the most important intervention aimed at modifying the risk of CVD in these patients [130]. Among HIV-positive patients, all-cause mortality was found to be increased > 4-fold in current smokers compared to never smokers [36]. A significantly increased risk of bacterial pneumonia, non-AIDS malignancies, and CVD was also observed in HIV-infected smokers [131].

Some studies have suggested that initiation or modification of ARV therapy in both ARV-naïve and ARV-experienced patients may decrease inflammatory biomarkers, thereby reducing the associated CV risk [132, 133]. Rapid and significant improvements in endothelial function were observed following the initiation of ARV therapy in previously untreated patients [33].

Treatment options for dyslipidemia are limited for HIV-infected patients due to the scarcity of available literature regarding efficacy, drug interactions, and toxicity. Therefore, modification of ARV regimens to include ARV medications with more favorable lipid profiles should be employed in dyslipidemic HIV-infected patients who are considered to be at high risk for CVD when virologic suppression will not compromised. Comparisons of lipid abnormalities associated with ARV drugs are presented in Table **1** [49, 57, 85, 99, 118, 119, 134-142].

Dyslipidemias

Despite ARV therapy and suppressed viral loads, the rate and extent of inflammation observed in HIV-infected individuals still remains significantly elevated compared to those who are HIV-negative. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, commonly referred to as "statins," have anti-inflammatory properties and have been shown to reduce the risk of CVD [144]. Statins lower concentrations of circulating hs-CRP and pro-inflammatory cytokines, decrease the production reactive oxygen species, limit T-cell activation and macrophage infiltration, in addition to stabilizing coronary artery plaque, reducing vascular inflammation, decreasing the risk of thrombus formation, and reversing endothelial dysfunction [145-148].

Statins are recommended to treat elevated LDL-C and non-HDL-C levels above the thresholds prescribed by the NCEP ATP III [149]. Utilization of the 2013 American College of Cardiology/American Heart Association guidelines accounted for some potential risk factors of high risk morphology coronary plaque, but failed to identify those specific to HIV infection [150]. Prior to selecting a statin, clinicians should analyze the patient's ARV therapy regimen to identify any potential drug interactions, as the degree of

Table 1. ARV-induced lipid changes.

	TGL	LDL-C	HDL-C
PIs			
ATV/r [135]	↑	↑	↑/↔
DRV/r [100, 136]	↑	↑	↑/↔
LPV/r [137]	↑↑	↑	↓
FPV/r [138]	↑↑	↑	↓
TPV/r [138]	↑↑	↑	↓
NRTIs			
ABC [139]	↑	↑	↑/↔
FTC [138]	↑	↑	↓
3TC [138]	↑	↑	↓
d4T [138]	↑↑	↑	↓
TDF [49, 140]	↓	↓	↑
NNRTIs			
EFV [86, 141]	↑↑	↑	↑↑
NVP [138]	↑	↑	↑↑
RPV [142]	↓	↑	↑
INSTIs			
RAL [143, 144]	↔	↓/↔	↓/↔
DTG [145]	↔	↓/↔	↓/↔
EVG/c [57]	↑↑	↑↑	↓
Entry Inhibitors			
ENF [139]	↓/↔	↓/↔	↑/↔
MVC [146]	↔	↔	↑/↔

The arrows in the above table specify the degree of change: ↑↑, moderate to large increase; ↑, small to moderate increase; ↔, no change; ↓, small to moderate decrease. *ATV/r* atazanavir/ritonavir, *DRV/r* darunavir/ritonavir, *LPV/r* lopinavir/ritonavir, *FPV/r* fosamprenavir/ritonavir, *TPV/r* tipranavir/ritonavir, *ABC* abacavir, *FTC* emtricitabine, *3TC* lamivudine, *d4T* stavudine, *TDF* tenofovir, *EFV* efavirenz, *NVP* nevirapine, *RPV* rilpivirine, *RAL* raltegravir, *DTG* dolutegravir, *EVG/c* elvitegravir/cobicistat, *ENF* enfuvirtide, *MVC* maraviroc.

hepatic metabolism differs between each individual agent (Table **2**) [151-160]. Pharmacokinetic differences exist amongst the statin drug class, thus allowing certain agents to be used for the treatment of dyslipidemia in HIV-infected patients receiving ARV therapy [161].

Pravastatin is primarily eliminated unchanged through the kidney and liver, leading to a lower risk of drug interactions than some of the other agents [154]. Simvastatin and lovastatin are metabolized through cytochrome P450 (CYP) 3A4, which may result in a higher potential risk of drug interactions when administered with CYP 3A4 inhibitors [152, 168]. In contrast, atorvastatin is less lipophilic, reducing its requirement for extensive hepatic metabolism [152]. However, a significant increase in atorvastatin AUC was observed following concomitant administration of atorvastatin and PIs. Atorvastatin should be started at the lowest dose and titrated to goal lipid values. Caution is advised when the atorvastatin dose exceeds 20mg in HIV-infected patients treated with PI-containing regimens. In contrast, CYP 3A4 inducers (e.g. EFV) may result in decreased atorvastatin serum concentrations. Significant drug interactions with rosuvastatin are not expected to occur because it is not metabolized *via* CYP 3A4 [156, 157]. Pitavastatin, a recently approved FDA medication, appears to have a low risk of drug-interactions with ARV, similar to that seen with pravastatin, atorvastatin, and rosuvastatin, due to its minimal hepatic metabolism [153].

Inhibition of statin metabolism may lead to increased serum concentration of the statin and an increased risk of adverse effects, including myalgias and rhabdomyolysis. Additionally, concomitant use of statin therapy in patients co-infected with HCV did not result in an increased risk of statin-induced hepatotoxicity after 6 months of treatment [162]. Statin therapy was actually found to normalize previously elevated aminotransferase levels in many patients.

Greater reductions in TC, LDL-C, TGL, and non-HDL-C levels were observed in patients receiving atorvastatin 10 to 20mg per day or rosuvastatin 5 to 10mg per day rather than pravastatin 20 to 40mg per day at 1 year follow up [125]. NCEP LDL-C goals were more frequently achieved in patients treated with atorvastatin or rosuvastatin, while only those treated with rosuvastatin were observed to reach non-HDL-C goals. Addition of rosuvastatin 10mg per day to dyslipidemic patients treated with PI-containing regimens resulted in significant decreases in TC, TGL, and LDL-C, while increases in HDL-C were also observed [163]. Compared to other statins, rosuvastatin has been found to be more efficacious in reducing TGL and increasing HDL-C [164]. Preliminary outcomes suggesting greater LDL-C reductions with pitavastatin are to be expected as the lipid-lowering potency of pitavastatin 4mg per day is greater than pravastatin 40mg per day [153, 154]. Despite dose titrations, the relative potency of statin therapy utilized in many of these studies remain disproportionate, and therefore results should be interpreted with caution.

Hypertriglyceridemia results in an increased risk of CAD and pancreatitis, and should be managed with a fibrate. In a retrospective review, the addition of either a statin or fibrate to HIV-infected patients resulted in significant reductions in both TC and TGL levels, while significantly greater reductions were observed in patients who were treated with both a statin and fibrate [165]. No drug interactions have been described between ARV medications and fibrates (Table **2**) [159].

The use of niacin is usually limited due to the potential risks of insulin resistance, worsening of previously controlled DM, and hepatotoxicity in the general population and even more so in HIV-infected patients [166-168]. Significant decreases in TGL and TC, as well as significant increases in HDL-C were observed in HIV-infected patients treated with niacin similar to those seen in uninfected patients treated with niacin. Abnormalities of glucose metabolism were considered to be transient and not result in long-term consequences, while only minimal rates of hepatic impairment occurred.

Table 2. Drug interactions between antiretrovirals and commonly used lipid lowering therapy.

	ABC	FTC	3TC	TDF	ZDV	EFV	ETR	NVP	RPV	ATV/r	DRV/r	FPV/r	LPV/r	SQV/r	DTG	EVG/c	RAL	MVC	ENF
HMG-CoA Reductase Inhibitors																			
Atorvastatin [154]	↔	↔	↔	↓	↔	↓	↓		↔	↑	↑	↑	↑	↑	↔	↑/↑↑	↔	↔	↔
Lovastatin [155]	↔	↔	↔	↓	↔	↔	↓	↓		X	X	X	X	X	↔	X	↔	↔	↔
Pitavastatin [156]	↔	↔	↔	↔	↔	↓	ND	ND	ND	↑	↔	ND	↑	ND	↔	ND	↔	↔	↔
Pravastatin [157]	↔	↔	↔	↓	↔	↓	↔	↔	↔		↑		↑	↓	↔	ND	↔	↔	↔
Rosuvastatin [158-160]	↔	↔	↔	↔	↔	ND	↔	↔	↔	↑	↑	↔	↑	↔	↔	↑	↔	↔	↔
Simvastatin [161]	↔	↔	↔	↔	↔	↓	↓	↓	↔	X	X	X	X	X	↔	X	↔	↔	↔
Fibric Acid Derivatives																			
Fenofibrate [162]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Gemfibrozil [162]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Cholesterol Absorption Inhibitor																			
Ezetimibe [163]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

The arrows and letters in the above table describe the drug interaction and its severity: ↑, potentially increased exposure of non-ARV drug; ↓, potentially decreased exposure of non-ARV drug; ↔, no significant interaction; ↑↑, potentially increased exposure of the ARV; ↓↓, potentially decreased exposure of the ARV; X, contraindicated; ND, no data available.
ABC abacavir, *FTC* emtricitabine, *3TC* lamivudine, *TDF* tenofovir, ZDV zidovudine, *EFV* efavirenz, *ETR* etravirine, *NVP* nevirapine, *RPV* rilpivirine, *ATV/r* atazanavir/ritonavir, *DRV/r* darunavir/ritonavir, *FPV/r* fosamprenavir/ritonavir, *LPV/r* lopinavir/ritonavir, *SQV/r* saquinavir/ritonavir, *DTG* dolutegravir, *EVG/c* elvitegravir/cobicistat, *RAL* raltegravir, *MVC* maraviroc, *ENF* enfuvirtide.

Administration of either 3g of fish oil twice daily (4.86g/day of EPA and DHA) or 160mg of fenofibrate once daily in patients treated with ARV therapy with TGL > 400mg/dL and LDL-C < 160mg/dL was found to significantly reduce serum TGL levels [169]. Very few patients achieved TGL< 200mg/dL with either therapy alone, but combination therapy with fish oil and fenofibrate resulted in a 65% reduction in TGL.

Ezetimibe reduces cholesterol by limiting its absorption at the brush border of the small intestine [160]. Ezetimibe is not metabolized by CYP 3A4, but is glucoronidated *via* UGT1A1, UGT1A3, and UGT2B15, thus making it an attractive agent due to a lack of significant drug interactions (Table **2**). A cross-over study evaluating the effect of ezetimibe monotherapy compared to placebo found a mean reduction in LDL-C of 5.3% while treatment with placebo resulted in a 5.5% increase in LDL-C after 8 weeks [170]. Ezetimibe results in only modest reductions in LDL-C, but may be useful as monotherapy in patients who cannot tolerate statins or in combination with other lipid lowering medications for patients who cannot achieve treatment goals.

Dysglycemias

Traditional risk factor modification, such as dietary changes and increased rates of exercise, in addition to modifications of ARV regimens to exclude thymidine analogue NRTIs or some PIs, may represent useful pathways in treating glucose disorders in HIV-infected patients [85]. Reasonable considerations could include substituting a PI for NNRTI, or selecting ATV when a PI is necessary, as an association with the development of insulin resistance has not been established [171].

While insulin is very attractive given its minimal pharmacokinetic modifications in patients with hepatic or renal dysfunction, anti-inflammatory effects, and relatively few drug interactions with ARV, the drawbacks of use may force clinicians to utilize oral anti-diabetic agents first, such as metformin [172, 173]. Metformin, a biguanide antihyperglycemic agent, increases insulin sensitivity, decreases hepatic gluconeogenesis, reduces intestinal absorption of glucose and increases glucose uptake and utilization by peripheral tissues [174]. The reductions in CVD and all-cause mortality observed in uninfected patients treated with metformin have not been mirrored in those infected with HIV [173]. In HIV-infected patients treated with metformin, studies have been published describing improvements in insulin resistance, reductions in body weight, decreased rates of endothelial dysfunction, improvements in coronary artery calcium, and beneficial effects on lipid profiles [175-180].

Thiazolidinediones, which include rosiglitazone and pioglitazone, bind to peroxisome proliferator-activated receptor-gamma (PPAR-γ) resulting in increased insulin sensitivity and glucose utilization in adipose tissue, skeletal muscle, and the liver, as well as reducing hepatic gluconeogenesis [180]. Improvements in insulin sensitivity have been observed with both of these agents in HIV-infected patients, but each is associated with the risk of weight gain and fluid retention [181].

In 2010, the FDA restricted use of rosiglitazone as evidence accumulated suggesting treatment with rosiglitazone resulted in an increased risk of CV events in HIV-uninfected patients, but limited evidence exists linking any increased CV risk with rosiglitazone in HIV-infected patients [182, 183]. However in 2013, the FDA removed the restrictions following a failure to establish a definite association between rosiglitazone and an increased risk of CV events [184]. Contrary to outcomes observed in HIV-negative patients, carotid IMT, pro-inflammatory markers, and endothelial activation were not worsened in HIV-infected patients with lipoatrophy treated with rosiglitazone

[185]. Compared to rosiglitazone, treatment with pioglitazone has been associated with an improvement in lipid profiles [186].

Glucagon-like peptide-1 (GLP-1) analogues, including formulations of exenatide and liraglutide, increase glucose-dependent insulin secretion, decrease gluconeogenesis, promote β-cell proliferation and differentiation, decrease gastric emptying time, and reduce food intake [187]. Substitution of exenatide for insulin in combination with metformin and repaglinide in ARV-treated HIV-infected patients resulted in weight loss, improved insulin sensitivity and β-cell function [188].

Dipeptidyl peptidase-IV (DPP-IV) inhibitors slow the degradation and prolong the activity of incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), through the inhibition of DPP-IV [189]. Contrary to previous concerns of worsened immunodeficiency and increased risks of infections due to the use of DPP-IV inhibitors in HIV-infected patients, a recent report of non-diabetic HIV-infected patients given sitagliptin found no immune or virilogic effects [190].

Identification of potential drug interactions should be performed when designing an antidiabetic regimen to be used in combination with ARV therapy. Clinically significant drug interactions include an increased risk of hypoglycemia as a result of inhibition of the metabolism of sulfonylureas, thiazolidinediones, or DPP-IV inhibitors by boosted-PIs [85]. NNRTIs may also induce the metabolism of the aforementioned antidiabetic medication classes resulting in poorly controlled blood glucose and episodes of hyperglycemia.

Hypertension

Endothelial inflammatory changes and direct effects of ARV therapy have been proposed as the mechanism for the development of hypertension in HIV-infected patients [191, 192]. Uncontrolled hypertension, even among the HIV-infected patient population, leads to an increased risk of CVD events, renal dysfunction, and blindness. Prompt screening and management of hypertension should be employed and should follow the recommendations for the general population [193]. Clinicians must also take into account the direct effects of ARV drugs on hypertension and potential drug interactions (Table **3**).

Diuretics, including thiazide diuretics, thiazide-like diuretics, loop diuretics, and potassium-sparing diuretics, inhibit sodium reabsorption at various locations in the renal tubule [194]. Most of these diuretics are not metabolized or are metabolized outside the CYP450 system, so concomitant administration of diuretics and ARV agents is unlikely to yield pharmacokinetic drug interactions.

β-blockers inhibit β1- and β2- adrenergic receptors to various degrees based on pharmacokinetic properties of each individual agent, which also determines the primary route of elimination [195]. Propranolol and metoprolol are hepatically metabolized *via* CYP2D6. Coadministration with PIs or EFV, CYP2D6 inhibitors, may lead to increased serum concentrations of metoprolol or propranolol, potentially prolonging their therapeutic effect and increasing the risk of adverse effects [196-199]. Hydrophilic β-blockers, such as nadolol and atenolol, are primarily excreted in the urine as unchanged drug [195, 196, 200, 201]. Most β-blockers are eliminated through both renal and hepatic routes, primarily CYP2D6, and therefore potential interactions with NNRTIs, CYP3A4 inducers, are not thought to exist [195, 196].

Calcium channel blockers (CCB), which include phenylalkylamines (verapamil), benzothiazepines (diltiazem), and dihydropyridines (amlodipine, nifedipine, etc.), relax coronary vascular smooth muscle and cause coronary vasodilation by inhibiting the transmembrane calcium ion flow through voltage-gated L-type channels [202, 203]. All CCBs undergo CYP3A4 mediated hepatic

Table 3. Drug interactions between antiretrovirals and commonly used antihypertensive therapy.

Antihypertensive Class	Specific Classes/Agents	Drug Interactions	Notes
Diuretics [194]	thiazides, thiazide-like, loop, potassium-sparing	Unlikely to occur	Metabolized outside CYP450
β-blockers [195-201]	Hepatically metabolized: propranolol, metoprolol	PIs, EFV	Increased concentrations of β-blockers: prolong effect, increase risk of adverse effects
	Hydophilic: nadolol, atenolol	Not thought to exist	Excreted in the urine
Calcium channel blockers (CCB) [202-204]	Verapamil, diltiazem, amlodipine, nifedipine	PIs, NNRTIs	PIs: increased concentrations of CCB, prolonged effect NNRTIs: reduced bioavailability of CCB
Angiotensin-converting enzyme inhibitors [205-208]		Not expected to occur	Metabolized outside CYP450
Angiotensin II receptor blockers [209-216]	Losartan	CYP2C9 inhibitors, PIs	CYP2C9 inhibitors: Decreased losartan efficacy PIs: increased losartan serum concentrations
	Candesartan, irbesartan	Not thought to exist	Undergo hepatic metabolism, do not require biotransformation
	Eprosartan, olmesartan, telmisartan, valsartan	Not thought to exist	Metabolized outside CYP450

PIs protease inhibitors, *EFV* efavirenz, *NNRTIs* non-nucleoside reverse transcriptase inhibitors, *CCB* calcium channel blockers.

metabolism. Additionally, verapamil, diltiazem, nicardipine, and nifedipine may also inhibit CYP3A4. Concomitant administration of PIs and CCB may result in increased or prolonged therapeutic effects of CCB secondary to PI-mediated CYP3A4 inhibition [204]. The bioavailability of CCB may be reduced when combined with NNRTIs, CYP3A4 inducers.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) decrease the stimulation of angiotensin II receptors *via* inhibition of angiotensin II formation [205]. The majority of ACE inhibitors, except captopril and lisinopril, are prodrugs and are required to undergo hydrolysis to be active [206, 207]. ACE inhibitors do not undergo CYP450-mediated metabolism and are primarily eliminated renally [208]. Concomitant administration with ARV agents are not expected to yield any significant pharmacokinetic drug interactions.

Angiotensin II receptor blockers (ARBs) also reduce the activation of angiotensin II receptors by blocking the binding of angiotensin II to the angiotensin I receptor [209]. Losartan requires CYP2C9-bioactivation to form its active metabolite, and therefore when administered with CYP2C9 inhibitors, may result in decreased efficacy [210]. Subsequently, losartan undergoes metabolism *via* CYP3A4, leading to potential increases in serum concentration when used with PIs, which are CYP3A4 inhibitors. Additionally, candesartan and irbesartan undergo varying degrees of CYP2C9-mediated hepatic metabolism, but do not require CYP-mediated bioactivation [211, 212]. Eprosartan, olmesartan, telmisartan, and valsartan are not metabolized *via* CYP450, and are not thought to cause potential drug interactions when used with ARV agents [213-216].

Lipodystrophy

Numerous pharmacologic interventions have been implicated in the treatment of HIV-associated lipodystrophy as a result of a poor understanding of the pathophysiology. Although it may not be completely reversible, reductions in limb fat have been reported following modifications of patient's ARV regimens, which have included discontinuing thymidine analogue NRTIs or switching to an NRTI-sparing regimens [217]. Compared to other PIs, unboosted DRV and unboosted ATV were not associated with abnormal adipocyte differentiation or lipid metabolism [218, 219]. Impaired adipogenesis and pro-inflammatory cytokine synthesis has been observed *in vitro* with EFV and rilpivirine (RPV), but not with NVP [220, 221]. Available data has not shown that treatment with INST or CCR5 antagonists result in adipose tissue dysfunction [222, 223].

Reductions in visceral adipose tissue (VAT) have been observed following treatment with recombinant human growth hormone (GH) in HIV-infected patients with lipodystrophy [224]. These findings subsequently led to the FDA approval of recombinant human GH for AIDS-related wasting. Unfortunately, the doses required to achieve reductions in VAT led to the development of impaired glucose metabolism, arthralgias, and peripheral edema [225].

A novel therapeutic approach was employed, growth hormone releasing hormone (GHRH), to restore natural physiologic GH secretion [226]. In November 2010, tesamorelin (Egrifta ™), a synthetic analogue of human GHRH, was FDA approved for the reduction of excess abdominal fat as a result of HIV-associated lipodystrophy [227]. Tesamorelin, a daily subcutaneous injection, binds to and stimulates GHRH receptors in the pituitary somatotroph cells to produce and release endogenous GH. The anabolic and lipolytic effects observed are the result GH binding to chondrocytes, osteoblasts, myocytes, hepatocytes, and adipocytes.

Two large randomized clinical trials revealed significant decreases in VAT in patients with HIV-associated central fat accumulation treated with tesamorelin for 26 weeks [228, 229]. Following completion, patients were re-randomized to tesamorelin or placebo for an additional 26-week extension [229, 230]. Significant reductions in VAT were sustained in patients treated with tesamorelin. However in patients switched to placebo, VAT was noted to reaccumulate to baseline levels. Although well tolerated, long-term safety data is lacking on optimal duration of therapy.

CONCLUSION

The incidence of traditional and HIV-induced CVD risk factors will continue to rise as the lifespan of HIV-infected patients increases. Control of HIV-RNA viremia with potent and effective ARV regimens has led to a significant reduction in all areas of CVD except CAD. Evidence suggests that some ARV medications appear to have a deleterious effect on serum lipid profiles, so clinicians should focus on interventions aimed at reducing the risk of HIV-associated CVD, which include therapeutic lifestyle changes, smoking cessation, and pharmacotherapy. Switching ARV agents or regimens is reasonable and may lead to improvements in glucose metabolism and lipid profiles; however, caution is advised due to the potential risk of virologic failure. Additional options include managing these traditional risk factors with medications commonly used in the general population, including lipid-lowering medications such as statins, fibrates, and cholesterol absorption inhibitors. Anti-diabetic medications, such as metformin, sulfonylureas, thiazolidinediones, GLP-1 agonists, and DPP-IV inhibitors, should be utilized in the management of glucose abnormalities. Initiation of any additional medications should be done cautiously, due to the increased risk of ARV-drug interactions, which may include to myalgias, rhabdomyolysis, or hypoglycemia. Management of CVD in HIV-infected patients remains a significant challenge and many questions remained unanswered, but early recognition and treatment of these diseases is critical to significantly reduce the morbidity and mortality observed from cardiac involvement.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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