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Current pharmacotherapy for the treatment of dyslipidemia associated with HIV infection

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Abstract

Introduction: Cardiovascular disease is an important cause of morbidity and mortality in persons with human immunodeficiency virus (PWH). The risk of atherosclerotic cardiovascular disease (ASCVD) is higher in PWH compared to uninfected persons. Dyslipidemia is a critical link in the pathogenesis of ASCVD in PWH. Chronic inflammation associated with HIV infection may drive both dyslipidemia and ASCVD.

Areas Covered: The authors review the evidence for using lipid-lowering therapy in PWH and includes an overview of the utility and complexity of using statins in PWH, in particular, drug interactions, safety and efficacy. In addition, data covering alternate therapies like omega 3 fatty acids, fibrates, niacin, ezetimibe and PCSK-9 inhibitors is reviewed.

Expert Opinion: Dyslipidemia is a common problem in PWH. The risk of ASCVD is higher in PWH. Lipid-lowering therapy reduces the risk of ASCVD but clinical endpoint trials are lacking in PWH. Statin therapy is the mainstay of primary prevention for ASCVD. The timing of when to initiate primary prevention with statins in PWH is unclear. Beyond statins, there is limited data that other lipid-lowering agents have utility in PWH. Ongoing trials like the REPRIEVE trial will inform the community about the optimal approach to lipid-lowering therapy in PWH.

Keywords

Dyslipidemia; HIV; HMG-CoA Reductase Inhibitors; Statins; PCSK-9 Inhibitors

1.0 Introduction

Infection with the human immunodeficiency virus, type 1 (HIV) leads to disorders of lipid metabolism characterized by lowering high-density lipoproteins (HDL-C), higher triglycerides, lower total cholesterol, lower low-density lipoprotein (LDL-C) and an

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Declaration of Interest

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atherogenic phenotype [1-2]. The prevalence of dyslipidemia is particularly high in persons with HIV (PWH), affecting 67.3% of women and 81.2% of men in a study composed of 3,166 PWH [3]. By comparison, 21% of adults in the United States were diagnosed with dyslipidemia [4]. Many of the antiretroviral agents used to control HIV replication also induce disorders of lipid metabolism including elevation of both low-density lipoproteins and triglycerides. Furthermore, chronic inflammation is an important feature of HIV infection resulting in a host of abnormalities that promote dyslipidemia and atherogenesis. Collectively, these abnormalities result in higher risk of atherosclerotic cardiovascular disease (ASCVD) in persons with HIV infection. Indeed, PWH have nearly two-fold increased risk for myocardial infarction (MI) [5]. The purpose of this article is to describe the risk of dyslipidemia and ASCVD in PWH and evaluate lipid-lowering therapies available to treat dyslipidemia and lower ASCVD risk.

1.1 Lipid disturbances in untreated HIV infection and Polygenic Influences

In untreated HIV infection, particularly those with advanced disease, HIV results in elevated TG, lower LDL-C, lower HDL-C and an atherogenic phenotype [6]. Riddler et al demonstrated that initiation of antiretroviral therapy in the men with known date of HIV seroconversion reversed some but not all the lipid abnormalities in persons with HIV [7]. In that study, HDL-C levels remained below pre-HIV seroconversion levels despite suppression of HIV replication with antiretroviral therapy. There are a number of purported mechanisms to explain the abnormalities in lipid metabolism including mitochondrial defects, interference with dietary disposal of triglycerides, reduction in reverse cholesterol transport function and a myriad of inflammation induced changes in the composition and size of lipid particles [8-9]. Grunfeld et. al, hypothesized that disturbances in lipid metabolism may be due, in part, to elevated interferon alpha levels observed in persons with AIDS [10]. Elevated levels of interferon-alpha, were associated with decreased TG clearance. Reed and colleagues confirmed increased secretion of VLDL-TG and decreased plasma VLDL-TG clearance, during both fasting and fed conditions [11] There are likely multiple mechanisms that lead to dyslipidemia in PWH.

There may also be polygenic influences on dyslipidemia. Dyslipidemia can be influenced by an accumulation of both rare and common genetic variations and polygenetic risk scores may estimate the proportion of dyslipidemia resulting from these factors [12]. Indeed, single nucleotide polymorphisms (SNPs) associated with dyslipidemia have been documented via genome-wide association studies in PWH pre- and post-initiation of ART. Of 727 genotyped individuals, several SNPs were found to both effect LDL-C and HDL-C in combination with specific ART regimens [13]. Several SNPs in apolipoprotein B were associated with elevated levels of LDL-C in PWH while SNPs in genes ABCA1/LIPC/CETP were associated with higher HDL-C levels in the setting of NNRTI use. Finally, in a study of PWH even those with well controlled HIV replication had higher levels of Lp(a) and atherogenic allele specific apolipoprotein a [14]. Thus, a combination of genetic and environmental factors may explain alterations in lipid levels in PWH and the effects of selected antiretroviral agents.

1.2 Antiretroviral effects on lipids

There are multiple classes of medications used to treat HIV infection. Many have class effects but within each class there are differential effects on lipid metabolism. The entry inhibitors like the CCR5 receptor antagonist maraviroc or the fusion inhibitor enfuvirtide do not appear to alter lipid metabolism [15-16]. Similarly, the integrase inhibitors do not affect lipid levels [17]. There is limited information on lipid metabolism with newer classes such as the maturation or capsid inhibitors. In contrast, three classes of antiretrovirals have profound effects on lipid metabolism including the non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), nucleoside/tide reverse transcriptase inhibitors (NRTIs) [18]. Current treatment of HIV infection typically requires a combination of 2–3 antiretroviral agents, usually from distinct classes. Thus, an important paradigm is that there are differential and sometimes additive effects from these combinations of agents on lipid metabolism. Moreover, longitudinal study of individual agents in PWH is not available because of the frequent emergence of resistance with the use of single antiretrovirals to treat HIV infection. Thus, most of the evidence of the effects of antiretrovirals comes from studies where combination antiretroviral therapy is used.

Table 1 lists the effects of different combinations of classes of antiretrovirals on lipid levels [17-24]. Amongst the NRTI class, zidovudine (AZT) and other less commonly used thymidine analogues induce modest changes in lipids [18]. Tenofovir disprovoxil fumarate tends to lower TC, LDL-C and HDL-C while tenofovir alafenamide has no clear effects on lipid metabolism [21, 25]. Two of the most commonly used NRTIs, emitricitabine and lamivudine, have not been well studied. Finally, abacavir, a guanosine analogue, has fewer direct effects on lipid metabolism but may alter ASCVD risk through alterations in coagulation [26]. In the NNRTI class, efavirenz has the most profound effects raising TC, LDL-C, TG and HDL [27-28]. Finally, most of the protease inhibitors alter lipid metabolism particularly those that require pharmacologic boosting with either ritonavir or cobicistat [18, 29].

Current guidelines for the use of antiretroviral therapy recommend regimens that tend to minimize the risk of alterations in lipid metabolism [30]. Most guidelines recommend or suggest clinicians consider switching older regimens to avoid specific toxicities like dyslipidemia. The USPHS Guidelines generally recommend the use of an integrase inhibitor in conjunction with 1–2 NRTIs as first line therapy for most patients [30]. Although lipid alterations are not common with many of these regimens, some recent studies have noted weight gain with the use of integrase inhibitors though not all [31-32]. The mechanism behind weight gain observed in persons taking integrase inhibitors is not clear. However, obesity is a well-known risk factor for dyslipidemia. Initiation of therapy with any of the antiretrovirals typically results in modest increases in most lipid levels, typically felt to be related to a reduction in HIV induced dyslipidemic changes (see Table 1). Many of the older antiretrovirals that often led to more pronounced dyslipidemic changes are in less common use. However, treatment failure remains a common problem with the use of antiretrovirals and requires switching to different classes to suppress HIV replication. Thus, many PWH continue to use antiretrovirals known to alter lipids directly or indirectly.

2.0 Risk Assessment and Screening

A higher incidence of ASCVD has been reported in a number of cohorts with HIV [5, 33-35]. Most cohorts consistently report a 1.5–2.0 fold higher risk of CVD events compared to HIV uninfected controls [33-35]. In addition to the clinical outcome data, there are several groups noting that subclinical coronary plaque is more common in PWH. Lo and colleagues demonstrated that HIV-infected men had a higher prevalence of coronary artery plaque than uninfected men (59% vs. 34%, P=0.02) [36]. Similarly, Post and colleagues reported that PWH compared to uninfected controls had more significant associations with any plaque or noncalcified plaque even after adjustment for other known ASCVD risk factors (P=0.005) [37]. Numerous studies of PWH identify higher rates of dyslipidemia, glucose intolerance, and tobacco use [38]. Thus, factors associated with the development and progression of atherosclerosis and cardiovascular events like MI, coronary revascularization, stroke and sudden cardiac death (collectively known as MACE – Major Adverse Cardiovascular Events) are more common in PWH.

Screening for ASCVD risk assessment tends to follow recommendations designed for the general population. The updated unified guideline on the management of blood cholesterol recommends fasting or non-fasting plasma lipids and counseling on lifestyle in young adults age 20–39 years [39]. Feinstein and colleagues assessed risk of ASCVD outcomes in the CNICS cohort [40]. They confirmed that the use of 2013 Pooled risk equation estimated ASCVD events better than other available equations and that screening for dyslipidemia should occur in PWH. Most HIV guidelines generally recommend assessment of risk factors and a fasting lipid level before the initiation of antiretroviral therapy [30]. HIV treatment guidelines recommend annual lipid level testing and re-assessing ASCVD risk after initiating or switching ARVs [30]. General population guidelines suggest screening lipids every 3–5 years [39]. What remains unclear is whether more frequent screening in PWH will improve MACE outcomes.

3.0 Treatment of Dyslipidemia

The overall approach to lowering ASCVD risk is to address lifestyle changes improving diet, encouraging exercise, managing elevated blood pressure, eliminating the hazard of tobacco use and controlling lipid disturbances. The mainstay of management of lipid disorders has been the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (Statins) that have demonstrated a reduction in mortality from ASCVD [41]. A number of other approaches have been demonstrated to lower cholesterol but have not consistently demonstrated a reduction in clinical events or mortality. A newer class of lipid-lowering agents, PCSK-9 inhibitors, have recently demonstrated lowering of MACE [42-43].

3.1 Statin Overview

Lowering LDL-C with statins for primary prevention of ASCVD reduces the risk by 26–30% in the general population [44]. In addition to lowering LDL-C, statins have pleotropic effects that reduce inflammation, immune activation, and oxidative stress [45]. However, the main effect of statins is directly linked to the ability to lower LDL-C with an average 1% reduction in risk for clinical events for every 2 mg/dL lowering of LDL-C [44]. A number of

studies of statins demonstrate that are effective in lowering lipids in PWH [46-54] Furthermore, statins also demonstrating improvements surrogate markers of ASCVD with reductions in atherosclerotic plaque and immune activation [55-61]. However, no study has demonstrated a reduction in clinical endpoints (MACE) with statin use in PWH. The REPRIEVE trial is a large, randomized, blinded study of pitavastatin versus placebo in more than 7500 PWH [62]. The trial is fully enrolled with results anticipated in the next 2–3 years. This trial should answer the question of whether primary prevention with a statin in PWH at relatively lower risk of ASCVD will have a reduction in clinical endpoints. The primary endpoint with compare the rate of MACE endpoints in those randomized to pitavastatin or placebo. This trial is unique in that the 2013 pooled risk equation was used as inclusion and exclusion criteria along with the level of LDL-C, thus providing an opportunity to assess statin benefits in those with higher and lower ASCVD risk. In addition, there is an embedded mechanistic sub study of 800 participants who will have computed tomographic angiography performed at baseline and 24 months to assess the utility of statins on coronary artery disease (CAD) and circulating biomarkers associated with CAD [63].

The introduction of PIs heralded the improved survival from HIV infection and ushered in the concerns about dyslipidemia and cardiovascular disease. Protease inhibitors undergo extensive oxidative metabolism through cytochrome p450 3A isozymes. One of the initially developed PIs, ritonavir, is now exclusively used because of its inherent properties as an inhibitor of cytochrome p450 3A metabolism to boost concentrations of other PIs [64]. Because of these known drug metabolism pathways, initial studies of lipid lowering therapy in PWH had to demonstrate the safety of using statins with PIs. Indeed, it took a number of years before sponsors were willing to support the use of more potent statins in PWH in clinical trials. Thus, pravastatin was initially recommended for use in PWH because of fewer drug interactions though it is not as potent as other statins [65].

3.2 Statin Effects on Lipids

Table 2 describes major trials to date of different statins in PWH. In general, lipid-lowering from statins has been consistent with that observed in the general population. In the moderate potency statin group pravastatin and pitavastatin generally result in lower cholesterol levels 15–20% compared to higher potency statins like atorvastatin and rosuvastatin that lower cholesterol levels on average, 20–40%. However, there may be differences observed in those with or without HIV infection. In a meta-analysis of statin effects, the authors estimated that for each statin evaluated, there were 3–16% less reduction of total cholesterol in PWH compared to benefits seen in the general population [5]. Similarly, LDL-C benefits were reduced by an average of 5–18% in PWH compared to the general population [5]. These blunted effects of statins may be mediated through drug interactions that diminish the lipid-lowering effectiveness of statins. However, it is important to note that direct head-to-head comparisons with statins between those with and without HIV infection have not been done.

3.3 Statin effects on atherosclerosis and Inflammation

Atherosclerosis and circulating markers of inflammation, immune activation, endothelial function, and coagulation often correlate with clinical outcomes. HIV infection has

independent effects on these factors and thus it would be valuable to know whether the benefits observed with statins is present in PWH. Several studies suggest that statins reduce the progression of atherosclerosis and alter plaque morphology to become less unstable. Calza reported an 18.7% reduction in the right carotid artery intimal thickness (cIMT) at the bifurcation and similar reductions on the left side (21.4%) and within the internal carotids in 36 individuals taking rosuvastatin for 24 months [66]. Longenecker reported a 0.019 mm reduction in cIMT progression with rosuvastatin compared to placebo over 96 weeks [56]. Two studies of pravastatin 40 mg daily showed conflicting results following short-term changes in flow-mediated dilatation, a marker of endothelial function [67-68]. Lo reported reduction in non-calcified plaque volume and the number of high-risk plaques with the use of atorvastatin 40 mg daily compared to placebo [55].

A number of studies have evaluated circulating biomarkers associated with atherosclerosis progression in HIV. Multiple statins have been associated with a reduction in many of these biomarkers. However, there is no consistent pattern of reduction in specific biomarkers with statin use. For example, Toribio demonstrated that Pitavastatin and pravastatin reduced oxidized LDL, lipoprotein-associated phospholipase 2 and soluble CD14 (Pitavastatin group only) [60]. Atorvastatin 20 mg daily also reduced oxidized LDL by 33%, lipoprotein-associated phospholipase 2 by 31% but had no effect on soluble CD14, soluble CD163, high-sensitivity C-reactive protein, P-selectin, CD40L or markers of T-cell and monocyte activation [54]. Rosuvastatin 10 mg daily also resulted in declines in Lp-PLA2 levels but did not affect high-sensitivity C-reactive protein, IL-6 levels and a number of other biomarkers after 24 weeks [48]. Interestingly, high-dose atorvastatin (80 mg daily) decreased markers of immune activation in PWH not taking antiretroviral therapy [69]. This included reductions in HLA-DR+ CD4 and CD8 cells as well as CD38+ T cells. In conclusion, it may be that while statins clearly lower circulating biomarkers in the general population that ongoing inflammation and immune activation in chronic HIV infection along with drug interactions may obscure some of these changes in PWH.

3.4 Statins and Drug Interactions with Antiretrovirals

Drug interactions emerged as an important issue because potent antiretroviral therapy to treat HIV infection often involves the use of medications that undergo metabolism by oxidative and non-oxidative mechanisms. HIV protease inhibitors, the first class of medications that demonstrated the ability to improve mortality from HIV infection, typically require pharmacologic boosting with ritonavir or cobicistat. Both of these drugs are potent inhibitors of cytochrome P450 enzymes [64, 70]. Early drug interaction studies demonstrated a 30-fold increase in simvastatin concentrations with the use of saquinavir and ritonavir [71]. In that same trial, the use of saquinavir 400 mg and ritonavir 400 mg daily increased the effective concentration of atorvastatin by 75% while pravastatin concentrations decreased by 50%. These early studies demonstrated that simvastatin and lovastatin should be avoided when using HIV PIs that inhibit the Cytochrome P450 3A metabolism.

Several classes of antiretrovirals appear to have limited clinically significant drug interactions with lipid-lowering agents. Integrase inhibitors and nucleoside/tide reverse transcriptase inhibitors do not appreciably affect metabolism of lipid-lowering agents. Entry

inhibitors like enfuvirtide do not affect lipid-lowering drugs. Although the CCR5 inhibitor, maraviroc is metabolized by CYP3A4/5 it is not an inhibitor or inducer and thus limited drug interactions occur with statins. Non-nucleoside reverse transcriptase inhibitors induce CYP3A4/5 metabolism and may lower the concentrations of some statins. In ACTG 5108, Gerber and colleagues noted that efavirenz, an NNRTI, reduced simvastatin concentrations by 58%, active atorvastatin concentrations by 34% and pravastatin concentrations by 40% [72]. In the group receiving simvastatin, HMG-CoA reductase inhibition was decreased by 60%. Thus, use of inducers of CYP3A 4/5 isozymes like efavirenz may reduce the effectiveness of some statins.

Subsequently a number of studies have shown more complex drug interactions with antiretroviral agents. In addition to the effects on oxidative metabolism, there are other effects on P glycoprotein and drug transporters. For example, rosuvastatin concentrations are increased in the extracellular compartment but the lipid-lowering effect is diminished in the presence of darunavir-ritonavir co-administration [73]. A similar effect was observed with the co-administration of lopinavir-ritonavir and rosuvastatin resulting in a 2.1 fold higher exposure to the latter drug [74]. Protease inhibitors like lopinavir-ritonavir and darunavir-ritonavir may affect human organic anion transporting polypeptide 1B1 transporter or the breast cancer resistance protein efflux mediator [75-76]. This is important because co-administration of fostamatinib, a specific inhibitor of BCRP and OATP1B1 resulted in higher 1.96 fold and 1.88 fold increase in rosuvastatin area under the plasma concentration-time curve and maximum concentration, respectively [75]. In addition, P glycoprotein has been shown to mediate the efflux of darunavir in intestinal cells [76]. Thus, there may be a number of complex drug interactions that affect the co-administration of statins and some antiretroviral agents.

Drug-drug interactions should be consistently monitored with the co-administration of ARTs and statins. In situations where concentrations of statins are known to be increased it is generally recommended to start at a lower dosage and titrate up while monitoring tolerability [5]. In other circumstances where statin concentrations may be decreased, higher doses may be required to achieve suitable reduction in LDL-C. Table 3 summaries the some of the most important drug interactions between HIV medications and lipid-lowering agents [77].

3.5 Statin Adverse Effects

There are a number of class effects that occur with statins. The most common adverse events with statins reported include elevated liver transaminases and muscle aches. In addition, insulin resistance and diabetes mellitus have been linked to statins. In a meta-analysis of statins in PWH, 3% of individuals (N=736) interrupted statins due to adverse events with a calculated event rate of 0.12 per 100 person-years [5]. This compares favorably to discontinuation rates (5.6%) reported in pooled analysis of randomized controlled trials in persons without HIV [78]. In a systematic analysis of statins of 71,344 persons in 19 randomized controlled trials by the United States Preventive Services Task force, statins were not associated with increased risk of serious adverse events (RR, 0.99 [95% CI, 0.94 to 1.04]), myalgias (RR, 0.96 [95% CI, 0.79 to 1.16]), or liver-related harms (RR, 1.10 [95% CI, 0.90 to 1.35]) [79]. In addition, in pooled analysis, statins were not associated with

increased risk of diabetes (RR, 1.05 [95% CI, 0.91 to 1.20]) [78]. In contrast, statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1·09; 95% CI 1·02–1·17) [80]. Thus, there remains controversy about the relationship between reported adverse events and statins. Regardless of the reported adverse events, it does not appear that adverse events are reported in any higher rates in PWH.

4.0 Miscellaneous Lipid-Lowering treatments

Statins are generally considered the first-line therapy for lipid-lowering. However, some individuals are intolerant of statins and others do not have sufficient lipid-lowering sometimes requiring the use of other agents. All of these medications have generally not been shown to reduce clinical events with the exception of the PCSK-9 inhibitors. There are a number of clinical studies utilizing fish oil, fibrates, niacin, cholesterol absorption inhibitors and PCSK-9 inhibitors in PWH.

4.1 Omega 3 Fatty Acids (Fish Oil)

Fish consumption and fish oil have been inversely associated with the development of ASCVD leading some to speculate that the active components Omega-3 polyunsaturated fatty acids (PUFAs) are cardioprotective [81]. PUFAs are thought to both increase very-low density lipoproteins (VLDL) clearance and reduce hepatic VLDL-TG production [82]. The REDUCE-IT trial analyzed the effects of high dose icosapent ethyl in persons without HIV infection [83]. The study focused on patients who had elevated TG levels despite receiving statin treatment. The study demonstrated that patients receiving two doses of 2 g icosapent ethyl daily had significantly lower ischemic events compared to those receiving placebo. In PWH, HIV infection and some antiretrovirals, namely PIs, induce higher production of VLDL-TG. Several studies have evaluated the use of fish oil in PWH. In a clinical effectiveness study, fish oil consumption lead to an average decline of 40 mg/dL in TG (P=0.02) but only 9% of individuals (n=76 total) had TG < 150 mg/dL [84]. In a randomized, diet and exercise-controlled study analyzed the efficacy of PUFAs (2.9 grams) for the treatment of TG>200 mg/dL in PWH. After 16 weeks the mean TG decreased non-significantly to 304 mg/dL from a baseline mean value of 461 mg/dL (P=0.12) [85]. In another study of 122 PWH, PUFAs 1 gram thrice daily was shown to decrease triglyceride levels to <200 mg/dL for 22.4% compared to only 6.4% in the placebo arm (P=0.013) after 8 weeks [86]. Finally, in a randomized trial of PWH with TG>400 mg/dL, PUFAs 3 grams twice daily resulted in a median decline in TG of 283 mg/dL (46%) after 8 weeks [87]. However, there was a 30 mg increase (P<0.001), on average, in LDL-C levels in the group receiving PUFAs. Thus, while several studies demonstrate that fish oil can reduce TG levels in PWH and reduce clinical events in persons without HIV, there are no data on the effectiveness of reducing MACE in PWH.

4.2 Fibrates

One of the hallmarks of untreated HIV infection is hypertriglyceridemia. Initial potent antiretroviral therapy options were associated with very elevated levels of triglycerides. Hypertriglyceridemia may be associated with an atherogenic phenotype and thus, treatment has been tried to reduce ASCVD risk and MACE endpoints. Fibrates work by activating

peroxisome proliferator-activated receptor alpha (PPARα) lowering cholesterol by limiting substrate availability in the liver for TG synthesis, inhibiting their release and stimulating lipoprotein lipase thereby increasing TG clearance [88]. Gemfibrozil was effective in lowering hypertriglyceridemia induced by PIs in a randomized controlled trial of 37 participants with a 1.22 mmol/L decrease in triglycerides and few adverse effects or drug interactions [89]. In a retrospective study of clinical effectiveness in PWH gemfibrozil lowered TG 80 mg/dL, on average, whereas fenofibrate lowered TG 49 mg/dL [84]. Fenofibrate decreased TG by a median 118 mg/dL in 87 PWH after 12 weeks [46]. Combination therapy with Pravastatin and fenofibrate for 36 weeks lowered TG by a median 93 mg/dL [46]. In general, fibrates have been safe in PWH with few adverse events. Clinical trials of fibrates in the general population demonstrate reduction in ASCVD risk and mortality in one trial but most studies did not confirm this benefit [88]. Recent guidelines recommend that if TG>500 mg/dL initial management should begin with statins and if those fail, fibrates can be added largely to avoid pancreatitis [39].

One potentially newer approach is the discovery of selective peroxisome proliferator-activated receptor alpha modulators (SPPARM α) to lower ASCVD risk [90]. Pemafibrate was compared to fenofibrate in patients with high TG and low HDL-C levels and found to have more favorable safety profile with less kidney and liver toxicity [91]. However, no trials of this class of agents have been reported in PWH to date.

4.3 Niacin

Niacin is known to inhibit the hepatic production of TG resulting in accelerated hepatic apolipoprotein B degradation and thus decreased levels of VLDL-cholesterol (VLDL-C) and LDL-C. Niacin also decreases the catabolism of HDL-apolipoprotein A-1, resulting in higher blood HDL levels. Despite known effects on lipid levels, evidence is lacking that niacin is useful in preventing ASCVD events [92]. Common adverse side effects like flushing, itching and insulin resistance also limit its use [92]. Dube and colleagues evaluated 1000–2000 mg of sustained release niacin in ACTG A5148 in PWH with fasting non-HDL-C ≥4.66 mmol/L and TG≥2.26 mmol/L [93]. They found significant declines in TC, non-HDL-C, and TG and an increase in HDL in 33 participants. Four participants (12%) discontinued treatment prematurely due to adverse events with transient changes in glycemia and insulin resistance. Balasubramanyam et al reported increased HDL-C from baseline 39.7 mg/dL to 43.3 mg/dL with niacin 2 grams daily sustained release preparation (P=0.03) but no other significant changes in lipid profiles [94]. Flushing was noted in 35–40% of those receiving niacin. In another study evaluating endothelial reactivity and circulating biomarkers associated with inflammation there was no improvement with the use of niacin for 24 weeks [95]. Thus, these small studies of niacin in PWH suggest limited benefits and that caution should be exercised when treating patients predisposed to diabetes or insulin resistance.

4.4 Absorption Inhibitors (Ezetimibe)

Ezetimibe lowers serum cholesterol levels by inhibiting the absorption of dietary cholesterol in the small intestine. The IMPROVE-IT was a large randomized trial in persons with prior ASCVD of ezetimibe added to a simvastatin resulting in significantly lowered on-treatment

LDL-C from 70 to 54 mg/dl, with a concomitant statistically significant reduction in MACE endpoints at 7 years (32.7% vs 34.7%, P=0.016) compared to the simvastatin alone [96]. Several smaller studies in PWH show improvement in lipid values with the use of ezetimibe [92-95]. In a placebo-controlled, crossover study of 48 PWH who received ezetimibe 10 mg daily, LDL-C decreased by 5.3% (11 mg/dL) compared to an increase of 5.5% in the placebo arm [97]. In another placebo-controlled trial ezetimibe significantly lowered LDL-C by 14.1% and TC by 18.6% after 12 weeks within 44 PWH who were on stable statin therapy with either pravastatin or atorvastatin [98]. In a small trial comparing ezetimibe plus fenofibrate to pravastatin, the combination resulted in significant declines in TC, LDL-C, non-HDL-C, TG and increases in HDL-C [99]. In a study comparing the lipid-lowering effects of ezetimibe 10 mg daily plus rosuvastatin 10 mg daily versus an increased dose of rosuvastatin (from 10 mg to 20 mg daily) there were declines in TC (−1.1 mmol/L vs. −0.5 mmol/L, P=0.03), LDL-C (−0.68 mmol/L vs. 0.48 mmol/L, P=0.37) and TG (−0.62 mmol/L vs. −0.17 mmol/L, P=0.03) in the combination group [100]. Currently, there have been no adverse drug interactions and few side effects using ezetimibe alone or in combination with statins.

4.5 Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors (PCSK-9 Inhibitors)

PCSK-9 inhibitors are an emerging therapy to lower ASCVD risk and MACE endpoints. PCSK-9 are hepatic proteins that regulate blood cholesterol levels via the inhibition of LDL receptors, thereby reducing LDL-C clearance and increasing circulation LDL-C [101]. PCSK9 inhibitors, a monoclonal antibody, prevent this interaction and lower the amount of blood LDL-C. The FOURIER and SPIRE trials demonstrate that PCSK-9 inhibitors, evolocumab and bococizumab, respectively, lower ASCVD events [42-43]. These agents demonstrate significant lowering of LDL-C by 45–70% in multiple studies [102-103]. There is currently very limited information about the utility of PCSK-9 inhibitors in PWH. Kohli reported on clinical experience with alirocumab or evolocumab in the United Kingdom and 1 individual had HIV infection with a reduction in LDL-C of 66% [104]. Evolocumab is being compared to placebo in HIV infected persons to lower LDL-C [105]. The study is fully accrued and expected to be completed in 2020.

5.0 Conclusion

Dyslipidemia is a significant problem in PWH, linked ASCVD and cardiovascular endpoints. There are numerous small studies of the efficacy of statins, omega-3 fatty acids, fibrates, niacin, and ezetimibe, but the clinical relevance is limited by the absence of clinical endpoint data. The current recommendations for screening, risk assessment, and treatment of dyslipidemia are based upon the unified updated guidelines [39]. The goals of treatment of dyslipidemia are increasingly heading toward lowering LDL-C levels below 70 mg/dL which appears to be safe and prevents clinical events [103]. Preliminary studies of statins indicate relatively similar efficacy in PWH compared to HIV-uninfected persons however, clinical endpoint data are lacking. Drug interactions between lipid-lowering agents and antiretrovirals are clinically important and guide choices and doses of statins, in particular. The REPRIEVE clinical trial is an on-going study evaluating the efficacy of pitavastatin in reducing the risk of ASCVD in PWH [62]. Cardiovascular risk reduction remains an

important issue with treatment of dyslipidemia as a high priority for persons with HIV infection.

6.0 Expert Opinion

The issue of dyslipidemia in the PWH has been a recognized problem since the advent of potent antiretroviral therapy. In the past two decades, convincing evidence demonstrates a higher risk of ASCVD and cardiovascular events in PWH, making it one the leading causes of morbidity and mortality in PWH. While there is some controversy over the optimal assessment of cardiovascular risk and screening, there is little disagreement that it should be done in PWH. Newly diagnosed persons with HIV infection should undergo cardiovascular risk assessment with fasting lipids. Lifestyle changes and tobacco cessation should be strongly encouraged. Reassessment of ASCVD risk should be done with changes in antiretroviral regimens and every 2–3 years. If there are clinically important changes like significant weight gain or new diagnosis of hypertension, ASCVD risk should be reassessed. Beyond lifestyle changes and tobacco cessation, treatment of dyslipidemia should be considered in those at higher risk of ASCVD events. Because HIV is an inflammatory process and likely elevates the risk of ASCVD, discussions about treatment of dyslipidemia should begin in any person over the age of 40 years with an ASCVD pooled risk score of 5.0% or greater.

A major limitation for treating dyslipidemia in this population is the uncertainty of when to initiate therapy for primary ASCVD prevention and the lack of a risk assessment scale unique for PWH. Nearly all the risk assessment scales were created with the seronegative population in mind. The Study of Adverse Drug Events (D:A:D) and CNICS groups have attempted to improve upon existing tools to assess ASCVD risk. However, none are better than the current ASCVD 2013 pooled risk equation tool which underestimates the number of clinical events by 40–60% in PWH. Until we have clinical endpoint data in PWH, it makes sense to discuss ASCVD risk and limitations in our understanding when there are significant risks present in persons over 40 years of age with HIV (e.g., hypertension, smoking, family history of premature cardiovascular disease, elevated LDL-C greater than 100 mg/dL or other significant risks). Secondary ASCVD prevention after MACE endpoints should follow standard guidelines regardless of HIV infection.

Primary and secondary prevention first line therapy should be done with statins. The choice of which statin should be based upon the goals of therapy and consideration for drug interactions. In general, it is safe to use rosuvastatin or atorvastatin in most individuals with HIV infection. Pitavastatin is a reasonable alternative if a moderate potency statin is desirable. Simvastatin should only be used in those not on HIV protease inhibitors or cobicistat because of the risk for rhabdomyolysis. The use of less potent statins like fluvastatin or pravastatin should be limited. Patients should be instructed about possible side effects like muscle aches. Safety screening should include monitoring for insulin resistance and diabetes; drug interactions and transaminase levels annually. In most PWH, the need to use alternative therapies like fibrates, niacin, ezetimibe, fish oil, or PCSK-9 inhibitors should be reserved to those at very high risk or proven ASCVD. Consultation with experts in the

management of dyslipidemia should be sought if these alternatives agents are being considered for use.

The major research gaps are proof that statins decrease clinical events and reduce mortality in PWH. The REPRIEVE trial is a very important randomized, placebo-controlled study of pitavastatin for the reduction of cardiovascular endpoints in persons with well-controlled HIV infection (Table 4). Pitavastatin was an ideal candidate to study because of the limited drug interactions and relatively lower risk population with HIV that is being evaluated in this trial. The mechanistic sub-study is likely to reveal whether statins improve coronary plaque in PWH and shed further light on the role of inflammation in CAD progression.

Pro-protein convertase subtilisin-kexin 9 (PCSK-9) inhibitors are a new class of drugs that have been shown to be both clinically and statistically significant in reducing LDL levels and cardiovascular events. PCSK-9 inhibitors are monoclonal antibodies with promising results in persons without HIV infection. There is an ongoing phase three clinical trial studying the effects of 24 weeks of evolocumab on persons with HIV intolerant of statins or with an LDL-C > 70 mg/dL with prior ASCVD or > 100 mg/dL at higher ASCVD risk on moderate to high dose statins (Table 4) [105]. Alirocumab is being studied in 140 PWH in a trial entitled EPIC-HIV with a primary objective to determine PCSK9 inhibitors reduce arterial inflammation and non-calcified plaque by FDG-PET (Table 4) [106]. PCSK-9 inhibitors are likely to have an important role in preventing ASCVD events in PWH provided that the cost of therapy decreases over time.

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Article Highlights:

- Dyslipidemia is associated with HIV infection and many of the antiretroviral agents used to HIV.
- Dyslipidemia is an important risk factor associated with the development of cardiovascular disease that is 1.5–2.0 fold higher in persons with HIV compared to uninfected persons.
- HMG-CoA reductase inhibitors or Statins are effective in lowering cholesterol and low-density lipoprotein-cholesterol but have not been demonstrated to reduce cardiovascular events in randomized controlled trials of persons with HIV infection.
- Statins have a number of significant drug-drug interactions with antiretroviral agents.
- PCSK-9 inhibitors are a newer class of lipid-lowering agents that may have some value in treating dyslipidemia in persons with HIV infection though there is little published information to date.

Table 1

Lipid Alterations with Selected Antiretroviral Regimens

Name	Sample	Duration	TC	LDL-C	HDL-C	TG
ABC/3TC/Dolutegravir[17]	N=953	48 wks	+9.9 mg/dL	+4.8 mg/dL	+3.6 mg/dL	+8.7 mg/dL
TAF/FTC/Bictegravir[20]	N=320	48 wks	+12 mg/dL	+9 mg/dL	+5 mg/dL	+3 mg/dL
TAF/FTC+Dolutegravir[20]	N=325	48 wks	+15 mg/dL	+12 mg/dL	+5 mg/dL	+7 mg/dL
TAF/FTC/Elvitegravir/Cobi[21]	N=866	48 wks	+14 mg/dL	+5 mg/dL	+4 mg/dL	+8 mg/dL
TDF/FTC+Raltegravir[19]	N=600	96 wks	+5.1 mg/dL	+0.4 mg/dL	+5.9 mg/dL	−7.1 mg/dL
TDF/FTC/Efavirenz[17]	N=355	48 wks	+24.1 mg/dL	+13.1 mg/dL	+8.0 mg/dL	+18.6 mg/dL
TDF/FTC/Rilpivirine[22]	N=550	96 wks	−0.8 mg/dL	+3.1 mg/dL	−1.2 mg/dL	−9.0 mg/dL
TDF/FTC/Doravirine[23]	N=364	48 wks	−2.0 mg/dL	−12.4 mg/dL	+1.9 mg/dL	−1.6 mg/dL
TDF/FTC+Atazanavir/ritonavir[19]	N=602	96 wks	+15.6 mg/dL	+5.7 mg/dL	+6.4 mg/dL	+17.1 mg/dL
TAF/FTC/Darunavir/ritonavir[19]	N=595	96 wks	+15.4 mg/dL	+6.9 mg/dL	+5.2 mg/dL	+16.8 mg/dL
TDF/FTC+Lopinavir/ritonavir[24]	N=443	48 wks	+38 mg/dL	+17 mg/dL	+11 mg/dL	+58 mg/dL

ABC=Abacavir; 3TC=Lamivudine; FTC=Emitricitabine; Cobi=Cobicistat; TDF=Tenofovir disprovoxil fumurate; TAF=Tenofovir alafenamide; TC=Total Cholesterol; LDL-C=Low density lipoprotein cholesterol; HDL=High density lipoprotein cholesterol; TG=Triglyceride

Table 2

Selected Studies of Statin Therapy in Persons with HIV

	Sample Size	Dose	Duration	TC	TG	HDL	LDL
Pravastatin[47] **Atorvastatin**[47] **Rosuvastatin**[47]	N=280 † N=303 † N=95 †	40 mg * 10 mg * 20 mg *	52 wks	−25 mg/dL −39 mg/dL −43 mg/dL	−24 mg/dL −60 mg/dL −83 mg/dL	−1.1 mg/dL −0.6 mg/dL +0.6 mg/dL	−12 mg/dL −26 mg/dL −23 mg/dL
Atorvastatin[55]	N=63	20 mg	20 wks	−35.5 mg/dL	Not available	Not available	−36 mg/dL
Pravastatin[45]	N=83	40 mg	12 wks	−16%	−13%	No change	−20%
Pravastatin[52]	N=36	40 mg	48 wks	−46%	−41%	+10%	−40%
Atorvastatin[53]	N=20	10 mg	24 wks	−81 mg/dL (−27%)	−130 mg/dL (−41%)	+1.3 mg/dL (+4%)	−76 mg/dL (−37%)
Rosuvastatin[51]	N=16	10 mg	24 wks	−22%	−30%	+29%	−22%
Rosuvastatin[49] **Placebo**[49]	N=72 N=75	10 mg	48 wks	Not available Not available	+5.5% +4.2%	+0.7% +3.7%	−23.4% +7.5%
Pravastatin[68]	N=29	40 mg	8 wks	−34.8 mg/dL	−62 mg/dL	+3.9 mg/dL	−34.8 mg/dL
Pravastatin[50] **Pitavastatin**[50]	N=126 N=126	40 mg 4 mg	52 wks	−13.7% −19.1%	−8.3% −2.0%	+7.2% +8.9%	−20.5% −29.7%

† Initial statin prescribed with analysis providing average changes adjusted for baseline lipid values, age, race, sex, baseline antiretroviral therapy and CD4+ cell count nadir. Comparative effectiveness retrospective study.

* Average doses

Table 3

Major Drug-Drug Interactions between Statins and Selected Antiretrovirals

Name	Atorvastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Protease Inhibitors	Start 10-20 mg; titrate carefully	No dose adjustment	Start 40 mg; titrate as needed	Start at 10 mg; titrate carefully	Contraindicated
Atazanavir/R or Cobi	No data	↑ AUC 31%	No data	↑ AUC 3-Fold	No data
Darunavir/R or Cobi	↑ AUC 4-Fold	↓ AUC 9%	↑ AUC 23%	↑ AUC 48%	No data
Lopinavir/R	↑AUC 488%	↓ AUC 20%	↑ AUC 33%	↑ AUC 108%	No data
Saquinavir/R	↑ AUC 79%	No data	↓ AUC 49%	No data	↑ AUC 3059%
NNRTIs	Start 20 mg; titrate up	No dose adjustment	No dose adjustment	No dose adjustment	20-40 mg; May need to increase dose
Efavirenz	↓ AUC 14%	↓ AUC 11%	↓ AUC 32%	No data	↓ AUC 72%
Etravirine	↓ AUC 37%	No data	No interaction expected	No interaction expected	No data
Nevirapine	No data	No data	No interaction expected	No interaction expected	No data
Rilpivirine	No change	No data	No data		No data

R=Ritonavir; Cobi=Cobicistat; AUC=Area Under the Curve Drug Concentration; Data represents alterations in statin concentrations.

Note: Use of cobicistat as a pharmacokinetic booster is analogous to that of ritonavir with similar recommendations.

Table 4

Ongoing Lipid-lowering Therapy Trials in Persons with HIV

Trial	Major Entry Criteria	Design	Endpoint	Timeline
REPRIEVE[62-63]	Age 40-75 years CD4>100 cell/mm^3 Fasting triglycerides <500 md/dL No prior ASCVD **ASCVD Risk Score:** <7.5% plus LDL<190 mg/dL 7.5%-10% plus LDL<160 mg/dL 10-15% plus LDL<130 mg/dL >15% plus LDL<70 mg/dL	Placebo-controlled RCT N=7500 Pitavastatin Embedded Mechanistic Substudy with CTA N=800	Clinical Events – Major Adverse Cardiovascular Events *	Opened: March 2015 Completion: March 2023
AMGEN[105]	Age >18 years CD4>250 cell/mm^3 Fasting triglycerides ≤ 600 md/dL LDL-C ≥ 100mg/dL AND High CVD Risk OR LDL-C ≥ 70mg/dL AND ASCVD On maximal statin OR Statin intolerant	Placebo-controlled RCT 24 weeks – Blinded 24 weeks – Open label N=467 Evolocumab	Reduction in LDL-C	Opened: May 2017 Completion: June 2020
EPIC-HIV[106]	Age ≥40 years CD4 T Cells ≥200 cells/mm^3 LDL≥ 70 mg/dL Fasting triglycerides ≤ 600 md/dL Moderate or High CVD risk †	Placebo-controlled RCT 52 weeks N=140 Alirocumab	Arterial Inflammation by FDG-PET-CT	Opened: April 2018 Completion: November 2021

LDL= Low-density lipoproteins, RCT= Randomized controlled trial, FDG- PET- CT= Fluorodeoxyglucose positron emission tomography, CTA= Computed tomography angiography, ASCVD= Atherosclerotic cardiovascular disease

† Moderate or High CDV risk- At least 1 of three criteria: Coronary artery disease, cerebrovascular disease, peripheral arterial disease; OR Diabetes, Family history of premature coronary artery disease, Hypertension, Smoking or Elevated CRP.

* Major Adverse Cardiovascular Events- Myocardial infarction, new onset heart failure, percutaneous coronary revascularization intervention, coronary artery bypass grafting, malignant cardiac dysrhythmia, and sudden death.