
LIPID DISORDERS IN PEOPLE WITH HIV

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ABSTRACT

Dyslipidemia is highly prevalent in people with HIV (PWH) and contributes to the increased risk of cardiovascular disease seen in this patient population. Factors that contribute to dyslipidemia include HIV infection itself and certain types of antiretroviral therapy (ART). Moreover, the effects of ART on lipids have changed over time as newer therapies have become available. Because some ART medications interact with lipid-lowering therapies, the type of lipid-lowering therapy initiated needs to be considered in this context. Of note, current cardiovascular disease (CVD) risk calculators underestimate CVD risk in PWH because HIV-specific factors also contribute to CVD. HIV-specific variables should be taken into account when calculating atherosclerotic CVD risk in PWH. In addition to statins, other lipid lowering agents, including PCSK9 inhibitors, have been studied in PWH and can be considered in the treatment of dyslipidemia, particularly for low-density lipoprotein (LDL-C) lowering. The ongoing REPRIEVE study will contribute to a better understanding of the use of statins in primary prevention of CV disease in PWH with low CVD risk. Aggressive lipid management in PWH is essential for primary and secondary CVD prevention and optimization of health span and lifespan in this high-risk population.

CARDIOVASCULAR DISEASE IN PEOPLE WITH HIV

People with HIV (PWH) are at increased risk of developing cardiovascular (CV) disease, including acute myocardial infarction (MI), even after adjusting for traditional CVD risk factors. Multiple factors, including HIV itself, antiretroviral therapy (ART), inflammation, and dyslipidemia, account for this finding (1). In the SMART study, PWH were randomized to either drug conservation, in which ART was administered or held based on pre-specified CD4 cell counts, or viral suppression, in which ART was continued uninterrupted. Published in 2006, the SMART study showed that drug conservation was associated with a greater rate of death from any cause compared to continuous viral suppression. PWH in the drug conservation experienced a greater number of CV events, compared to those participants in the continuous viral suppression group (hazard ratio 1.6, 95% confidence interval (1.0 to 2.5), $p = 0.05$) (2). This finding was the opposite of the investigators' hypothesis that increased exposure to ART might be associated with greater CV events in the continuous viral suppression group (2), based on data from that time period, including an association between longer duration of combination ART (including a protease

inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) and incident MI (Table 1) (3). This study unequivocally showed the importance of

uncontrolled HIV, even with relatively preserved immune function, in the pathogenesis of CVD.

Table 1. Classes of ART and Some Individual Drugs within the Classes	
Class of ART	Drugs
NRTIs	Emtricitabine Tenofovir alafenamide Tenofovir disoproxil fumarate Abacavir Lamivudine
NNRTIs	Efavirenz Rilpivirine Doravirine Rilipvirine Nevirapine
PIs	Atazanavir Darunavir Ritonavir
INSTIs	Bictegravir Dolutegravir Raltegravir Elvitegravir
Medications used for boosting or increasing another ART medication's effect	Ritonavir Cobicistat

NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = non-nucleoside reverse transcriptase inhibitor; PIs = protease inhibitors; INSTIs = integrase inhibitors

Another landmark study on the risk of CV disease in PWH, conducted within the Veterans' Administration from 2003 to 2009, found that HIV serostatus was associated with a 50% increased risk of acute MI in a predominantly male cohort of veterans, despite controlling for traditional CV disease risk factors including hypertension, dyslipidemia, and smoking (1). Other major studies found similar findings. In the Multicenter AIDS Cohort Study of men with and without HIV, Post et al showed that men with HIV had greater coronary artery plaque prevalence than men without HIV, as measured by coronary CT angiography, and among men with coronary artery

plaque, men with HIV had a greater extent of non-calcified plaque, which is more prone to rupture (4). Similarly, in a cohort study within the Partners HealthCare system, investigators demonstrated that the rate of acute MI was greater in PWH compared to individuals without HIV, particularly in women with HIV (unadjusted acute MI rate of 12.71 in women with HIV versus 4.88 in women without HIV) (5). Thus, studies from several different cohorts of PWH and individuals without HIV exhibit the association of HIV serostatus with CV disease and subclinical coronary atherosclerosis.

One question that has been raised is the effect of ART on CV disease risk, a topic that is addressed further below in this chapter. In the multicenter, international Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, the predicted risk of MI in those PWH without prior MI was highest in those patients who were taking 3 different classes of ART (nucleoside reverse transcriptase inhibitor (NRTI), NNRTI, and PI) (6). Certain types of ART, including the NRTI abacavir, and the PIs darunavir (with ritonavir boosting), indinavir, and lopinavir (with ritonavir boosting), have been associated with a higher risk of adverse cardiovascular events (7,8). (Pharmacokinetic boosting or enhancing of ART is achieved via medications including ritonavir and cobicistat). Most recently, in a large multicenter cohort study of PWH from Europe and Australia, recent integrase strand transfer inhibitor (InSTI) exposure (<6 months) was associated with an increase risk of MI, compared to a lack of InSTI exposure, after accounting for CVD risk factors. After 6 months exposure, however, this elevated risk decreased and was no longer observed after 24 months. This finding requires replication in other cohorts and the potential underlying mechanisms need to be further explored.

Also, up to 30% of PWH have hepatitis C co-infection (9). Individuals with HIV and hepatitis C co-infection are at greater risk of CV disease than individuals with HIV infection alone (10). One reason for this may include higher levels of inflammatory markers seen in PWH with hepatitis C co-infection, including sICAM-1 and IL-6, that have been associated with CV disease in PWH (11).

In summary, multiple factors, including dyslipidemia, inflammation, diabetes, smoking, hypertension, and central obesity, as well as ART-specific effects, contribute to increased CV disease risk in PWH.

HISTORY OF LIPID DISORDERS IN PEOPLE WITH HIV (PWH)

HIV infection is associated with dyslipidemia. In the absence of antiretroviral therapy (ART), HIV infection results in lower total cholesterol (TC), high-density lipoprotein (HDL-C), and low-density lipoprotein (LDL-C) levels (Table 2) (12). The decreases in HDL-C and LDL-C can also be seen in other states of infection and/or inflammation (13).

Table 2. The Effect on Lipid Levels in Different Clinical Situations of PWH (12,14,15)

Class of ART	Effect on TC	Effect on LDL-C	Effect on HDL-C	Effect on TG
HIV not on ART	Decrease (v. pre-seroconversion)	Decrease (v. pre-seroconversion)	Decrease (v. pre-seroconversion)	No change (v. individuals without HIV)
HIV on ART	Increase (v. before ART initiation)	Increase (v. before ART initiation)	No change (v. before ART initiation)	Effect can depend on ART type
HIV with AIDS	Decrease (v. individuals without HIV)	Decrease (v. individuals without HIV)	Decrease (v. individuals without HIV)	Increase (v. PWH without AIDS and individuals without HIV)

Early studies of lipids in PWH described differences in levels of triglycerides (TG), HDL-C, and LDL-C between individuals with AIDS, individuals with HIV but without AIDS, and control participants. Grunfeld et al found that participants with AIDS had the highest levels of TG compared to participants with HIV and controls. TC and HDL-C were lower in individuals with AIDS and in those with HIV compared to controls, and LDL-C was significantly lower in individuals with AIDS compared to control participants. The high levels of TG in participants with AIDS is secondary to increased hepatic output of VLDL and slower TG clearance (14,16).

In a study of lipid level changes pre- and post-HIV seroconversion and pre- and post-ART initiation in 50 men from the Multicenter Cohort AIDS Study, investigators observed mean increases in TC and LDL-C three years after ART initiation, compared to before ART initiation, with a minimal change in HDL. In addition, they found that TC, HDL-C, and LDL-C decreased from pre-seroconversion to the time before initiating ART (12). These findings demonstrated that ART is associated with an increase in TC and LDL-C in PWH. It is unclear however whether these changes with ART initiation were due to return to health with reduction of systemic inflammation with virologic suppression or metabolic toxicity of ART. Of note, the majority of men in this study, which was published in 2003, received older generation protease inhibitor (PI) based regimens so the findings may not be as applicable to PWH treated with current ART regimens.

In addition, changes in non-traditional lipid markers have been studied in HIV infection. A higher proportion of men with AIDS have been shown to have small, dense LDL, compared to control patients without AIDS (17). In the Swiss National HIV Cohort, greater pro-atherogenic small dense LDL was directly associated with coronary heart disease events (18). In addition to

small dense LDL, lipoprotein(a) (Lp(a)) has also been studied in PWH. In the general population, lipoprotein (Lp(a)) is associated with increased CVD risk (19,20). However, the association between HIV and Lp(a) levels has been equivocal (21,22). Nonetheless, poorly controlled HIV infection is thought to increase the atherogenic effect of allele-specific apolipoprotein(a), which is carried by Lp(a) (23). Moreover, Lp(a) and pro-atherogenic smaller apo(a) have been associated with greater carotid intima media thickness in women with HIV (24).

As alluded to above, the study and management of lipids in PWH have evolved over the course of the history of HIV infection and can be divided into the following time periods: before ART, early ART, and present-day ART.

MONITORING LIPIDS IN PATIENTS WITH HIV

CDC, NIH, and HIV Medicine Association of the IDSA guidelines recommend that a fasting or random lipid profile be obtained in PWH at the following time points: at introduction to care, at ART initiation or at the time of change in ART, and then every year, if the previous lipid test results were normal, or every 6 months, if the previous lipid test results were abnormal. If a random lipid panel is outside of the reference range, then the guidelines recommend obtaining a fasting lipid panel (25). Specialized tests, including Lp(a) or small dense LDL, are not specifically mentioned in the IDSA guidelines.

ART EFFECTS ON LIPIDS BY MEDICATION CLASS

Background

Current IDSA guidelines recommend the following ART regimens: 2 NRTIs plus a 3rd agent from the following categories, integrase inhibitors (INSTIs), NNRTIs, or PIs with either cobicistat or ritonavir added as pharmacokinetic boosters. An alternative regimen can consist of the INSTI dolutegravir and the NRTI lamivudine. Specific considerations are outlined in detail and accessible on the website aidsinfo.nih.gov (26).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Tenofovir is an NRTI, and tenofovir-based regimens are among the initial treatments recommended for most PWH by current CDC, NIH, and HIV Medicine Association of the IDSA guidelines (27). Tenofovir disoproxil fumarate (TDF)-based regimens result in elevated plasma levels of tenofovir, which can cause adverse renal and bone effects. On the other hand, tenofovir alafenamide (TAF)-based regimens result in lower plasma levels of tenofovir, but greater intracellular levels of tenofovir-diphosphate than TDF and fewer adverse renal and bone effects.

Moreover, TAF results in a more atherogenic lipid profile than TDF (Table 3), and a “statin-like” effect of TDF has been reported. In one study of PWH switching to a TAF-based regimen, investigators observed significant increases in TC, HDL-C, LDL-C, and TG post switch; the mean increase in LDL-C was 9.8 mg/dL (28). In a safety and efficacy study of 1733 treatment-naïve PWH randomized to either a TDF-based regimen or TAF-based regimen over a 144 week duration, TAF-based regimens increased median levels of TC, HDL-C, LDL-C, and TG, compared to the TDF treatment group (at 144 weeks, median increase in LDL-C of 19 mg/dL in TAF-based treatment group versus 6 mg/dL in TDF-based treatment group, $p < 0.001$). However, no significant differences in either CV or cerebrovascular events between the treatment groups (2.8% of participants in the TAF group, 3.8% of participants in the TDF group, $p = 0.28$) was noted (29). The investigators also found that atherosclerotic CV disease (ASCVD) risk when estimated at week 96 and as calculated using the ACC/AHA 2013 Pooled Cohort equations was similar between the two treatment groups, and no difference was detected in the proportion of participants in each treatment group eligible for high-intensity statin use based on 2013 ACC/AHA guidelines (30). Thus, despite the more negative effect of TAF-based regimens on lipids compared to TDF-based regimens, studies to date have not shown that there is a difference between the two treatment regimens in cardiovascular outcomes.

Table 3. Some Effects of Different Classes of ART on Lipid Levels*				
Class of ART	Effect on TC	Effect on LDL-C	Effect on HDL-C	Effect on TG
NRTIs	Increase, no change with lamivudine	Increase, no change with lamivudine	Increase, no change with lamivudine	Increase, no change with lamivudine
NNRTIs	Increase, except no change with etravirine	Increase, except no change with etravirine	Increase, except no change with etravirine	Increase, except no change with etravirine
PIs	Increase	Increase by most PIs	Decrease by low dose ritonavir	Increase
INSTIs	No change	No change	No change	No change

*This table was adapted from Myerson *et al.* "Management of lipid disorders in patients living with HIV." *Journal of Clinical Pharmacology* 2015, 55(9) 957-974 and Lagathu *et al.* "Metabolic complications affecting adipose tissue, lipid, and glucose metabolism associated with HIV antiretroviral treatment." *Expert Opin Drug Saf.* 2019 Sep;18(9):829-840.

Another point of difference between TAF- and TDF-based regimens is the effect of each on weight. In one study of PWH with a mean history of HIV infection of 18 years who switched from a TDF-based regimen to a TAF-based regimen, participants had a significant increase in weight, from 73.8 ± 14.3 kg (mean ± standard deviation) at 12 months before switch to 77.7 ± 42.3 kg at 3 months after switch and 75.5 ± 14.5 kg at 6 months after switch ($p < 0.0001$ for trend) (31). Similar findings have been seen in PWH who were ART naïve (32). The different effects of TAF- and TDF-based regimens on weight should be taken into consideration in the treatment of PWH, as these weight changes may alter CVD risk.

As noted previously, the NRTI abacavir has been linked to adverse cardiovascular events. However, studies comparing CVD risk with abacavir to other NRTIs have had equivocal results, and a clear mechanism that would explain such an association has not been presented (33). Of note, switching to an abacavir-based regimen from a TDF-based regimen has not been associated with a significant change in lipid levels (34).

Another point of interest with regards to NRTIs is the legacy effect of older generation NRTIs on metabolic health, as defined by having ≤ 2 of the National Cholesterol Education Program Adult Treatment Panel criteria, including TG > 150 mg/dL and HDL-C < 40 mg/dL. In a study focused on the prevalence of metabolic health in men with HIV in the MACS, both zidovudine and stavudine use were associated with a lower probability of being metabolically healthy, even though very few participants were receiving these medications at the time of assessment (35). Of note, stavudine, an older generation NRTI, is no longer recommended (25).

Protease Inhibitors (PIs)

PIs can be divided into older and newer-generation categories. Older-generation PIs include indinavir, saquinavir, and full dose ritonavir, and newer-generation PIs include atazanavir and darunavir (36). Current guidelines do not recommend indinavir (25). Newer generation PIs that are part of first-line ART

have fewer adverse effects on lipids than older generation PIs (37).

Hypertriglyceridemia is associated with specific PIs (38,39), and in particular, the PI ritonavir has been associated with hyperlipidemia (40). In a study that compared cholesterol levels among PI-naïve participants and PI-treated participants started on ritonavir, indinavir, or nelfinavir, either alone or in addition to saquinavir, the greatest increases in TC and TG were seen in the ritonavir based treatment group (77.3 ± 11.6 mg/dL (mean \pm standard error of mean), $p \leq 0.001$ versus change in the PI-naïve group, and 70.8 ± 17.8 mg/dL, $p \leq 0.001$ versus change in the PI-naïve group, respectively) (41). In another study of 415 PWH on a boosted PI regimen and at high risk of CV disease, a switch from taking a boosted PI to the integrase inhibitor (INSTI) dolutegravir (N = 205 participants) resulted in significant decreases in TC (mean change from baseline -8.7% versus 0.7%) and LDL-C (mean change from baseline -7.7% versus 2%) compared to those seen in participants who did not switch (N = 210 participants) (42).

In a 24-week study focusing on the effects of newer generation PIs, including atazanavir and darunavir on lipids, PWH were randomized to the NRTIs TDF/emtricitabine and either ritonavir-boosted atazanavir or ritonavir-boosted darunavir. No significant differences in TC, LDL-C, or HDL-C were observed between the two treatment groups. TG increased in both treatment groups, but there was no significant difference in TG change between the two groups (43). Similarly, in another study of PWH, the effects of ritonavir-boosted darunavir and ritonavir-boosted atazanavir on TG over 12 weeks were similar (44). Of note, ritonavir-boosted lopinavir increases in TG more than ritonavir-boosted darunavir (45) or ritonavir-boosted atazanavir (46).

In summary, newer PIs have less metabolic side effects, but their effects on lipids should be considered in the care of PWH with dyslipidemia.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The effects of NNRTIs on lipids varies depending on the individual drug. Etravirine has a neutral effect on TC, LDL-C, and TG. Efavirenz increases LDL-C more than rilpivirine and increases TG more than both rilpivirine and nevirapine (15). However, nevirapine is not a first-line recommended ART in part because of its side effect profile. Switching from nevirapine-based ART to rilpivirine-based ART was shown to result in a mean (95% confidence interval) decrease in TC of -25.9 mg/dL (-19.3 to -32.1 mg/dL) and LDL-C of -13.9 (-8.1 to -19.7 mg/dL) at 24 weeks (47). The NNRTI, doravirine, has been associated with decreases in LDL-C and non-HDL-C in those switching from a PI-based regimen. With ART initiation, doravirine was associated with fewer lipid changes compared to efavirenz.

Integrase Inhibitors (INSTIs)

Integrase inhibitors (INSTIs), in particular, bictegravir, dolutegravir and raltegravir, are among the initial ART recommended in ART-naïve PWH, based on their efficacy in lowering viral load and favorable adverse effect profiles (15). With respect to the effects of individual INSTIs on lipid profiles, in a phase 3 study of PWH randomized to 2 NRTIs and either the INSTI dolutegravir or the INSTI raltegravir, no significant differences in fasting lipid panels were observed between the two groups over the study duration of 48 weeks (48).

The effects of INSTIs on lipids in comparison to other classes of ART has also been studied. In the Surveillance Cohort Long-Term Toxicity Antiretrovirals (SCOLTA), an observational cohort study, 490 PWH on either 2 NRTIs and the NNRTI efavirenz or a ritonavir-boosted PI switched either from efavirenz or a ritonavir-boosted PI to dolutegravir, elvitegravir, or the NNRTI rilpivirine. Among those who switched to an INSTI, a decrease in TC was seen in all groups except in the efavirenz to elvitegravir group, and a decrease in LDL-C was noted in those patients who switched from a ritonavir-boosted PI to elvitegravir (-12 ± 5.6 mg/dL for LDL-C (mean \pm standard error). No significant change in TG was noted in any of the participants who switched to an INSTI-based regimen. In summary, the investigators found that switching off of a ritonavir-boosted PI-based regimen to either dolutegravir, elvitegravir, or rilpivirine improved TC, whereas switching off of a ritonavir-boosted PI-based regimen to rilpivirine improved TG and LDL-C also. Moreover, the switch from efavirenz to rilpivirine improved LDL and TG, compared to switching to an INSTI, although inter-group differences were not significant (49).

With regards to those ART naïve PWH, in the FLAMINGO study of PWH who were ART naïve and randomized to either dolutegravir-based or ritonavir-boosted darunavir-based ART, LDL-C was significantly greater at 96 weeks in the ritonavir-based darunavir-based ART arm compared to the dolutegravir-based ART arm (adjusted mean difference -12.8 mg/dL, 95% CI -17.4 to -8.1 mg/dL). Similarly, TG increased more in the ritonavir-boosted darunavir-based ART group than in the dolutegravir-based ART group (50). In summary, in ART naïve PWH started on either an INSTI-based or ritonavir-boosted PI based ART, those who received an INSTI-based treatment regimen had lower TG and TC at 96 weeks.

Another aspect of metabolic health to consider in patients on integrase inhibitors, in particular, dolutegravir and bictegravir, is their effects on weight. Data from observational and retrospective studies suggests that weight gain is seen in PWH who start or switch to an INSTI (51). In addition, data from randomized trials also supports this. For example, in the open-label ADVANCE study conducted in South Africa, ART naïve PWH were randomized to either TDF-emtricitabine (or lamivudine)-efavirenz or one of the following: TAF-emtricitabine-dolutegravir or TDF-emtricitabine-dolutegravir. After 48 weeks, absolute weight gain and incident obesity (body mass index ≥ 30 kg/m²) was greater in the dolutegravir-based arms (6 kg in the TAF-emtricitabine-dolutegravir group and 3 kg in the TDF-emtricitabine-dolutegravir group compared to 1 kg in the TDF-emtricitabine (or lamivudine)-efavirenz group) (52).

INSTI use has also been associated with incident diabetes mellitus. In an administrative database from the US examining PWH who initiated ART, INSTI use was associated with a 31% increase in incident diabetes compared to non-INSTI use. In the NA_ACCORD study, INSTI initiation was associated with an increased risk of diabetes compared to ART initiation with either a PI or NNRTI-based regimen, an effect which was mediated in part by weight gain. In the treatment of overall metabolic health of PWH, the effect of INSTIs on weight gain should be kept in mind.

Additional Considerations Regarding ART and Dyslipidemia

The question of whether one type of ART should be changed to another to avoid negative effects on lipids must take into consideration multiple factors, including compliance with medications, resistance to ART, and additional co-morbidities (37,53). The effects on CVD outcomes of switching from a PI-based ART regimen to an NNRTI- or INSTI-based treatment in PWH with

dyslipidemia have not been studied in controlled trials (54). However, in patients who are receiving PIs and have significant dyslipidemia, a switch to an INSTI or a lipid neutral NNRTI (rilpivirine, etravirine, doravirine) should be considered if equally as efficacious from an HIV control standpoint. In general, older generation PIs should be avoided.

MANAGEMENT OF DYSLIPIDEMIA IN PATIENTS WITH HIV

CV Risk Calculators in Patients With HIV and Goal LDL-C

Because of non-traditional risk factors that place PWH at heightened risk of CV disease, the question of whether risk calculators including the Pooled Cohort equations (PCE) are accurate in PWH has been raised. A 2018 *Circulation* study compared CV risk calculators, including the Framingham equation for coronary heart disease, the Framingham equation for ASCVD, and the PCE and found that all of these equations underestimated CV outcomes in men with HIV, with suboptimal discrimination (*c* statistics 0.68, 0.67, and 0.65, respectively). In other words, these equations may not be able to detect those patients with HIV at high risk of CVD who would benefit from treatment of modifiable risk factors (55).

Risk models specific to PWH were created using the D:A:D Study. In addition to including traditional CV risk

factors, the D:A:D models included exposure to specific ART agents, including abacavir, ritonavir-boosted lopinavir, and indinavir (56). However, in a study that compared 4 CV risk algorithms, including the D:A:D and the PCE, within the ATHENA cohort of PWH in the Netherlands, both the D:A:D and PCE algorithms underestimated CV disease risk in PWH with low baseline CV disease risk, with mean observed:expected ratios of 1.34 and 1.4 (57).

Questions that providers may have include which CV risk equation(s) should be used in PWH. A 2019 Scientific Statement from the American Heart Association (AHA) on CV disease in PWH notes that no optimal CV risk calculator exists, although HIV-specific risk factors, including hepatitis C co-infection, a current or nadir CD4 T cell count of < 350 cells/mm³, and lipodystrophy, contribute to increased ASCVD risk (Figure 1) (37). However, the statement does not specify what the goal LDL-C level should be in PWH. For the general population, the 2019 American College of Cardiology/AHA (ACC/AHA) Primary Prevention of Cardiovascular Disease recommend that LDL-C should be lowered by $\geq 50\%$ in those patients at high risk of CV disease (ASCVD risk score $\geq 20\%$). In those patients with intermediate risk of CV disease (ASCVD risk score of ≥ 7.5 to $< 20\%$), risk enhancers, of which HIV is considered one, should be considered in the decision to start a moderate intensity statin with the goal of lowering LDL by 30-49% (58).

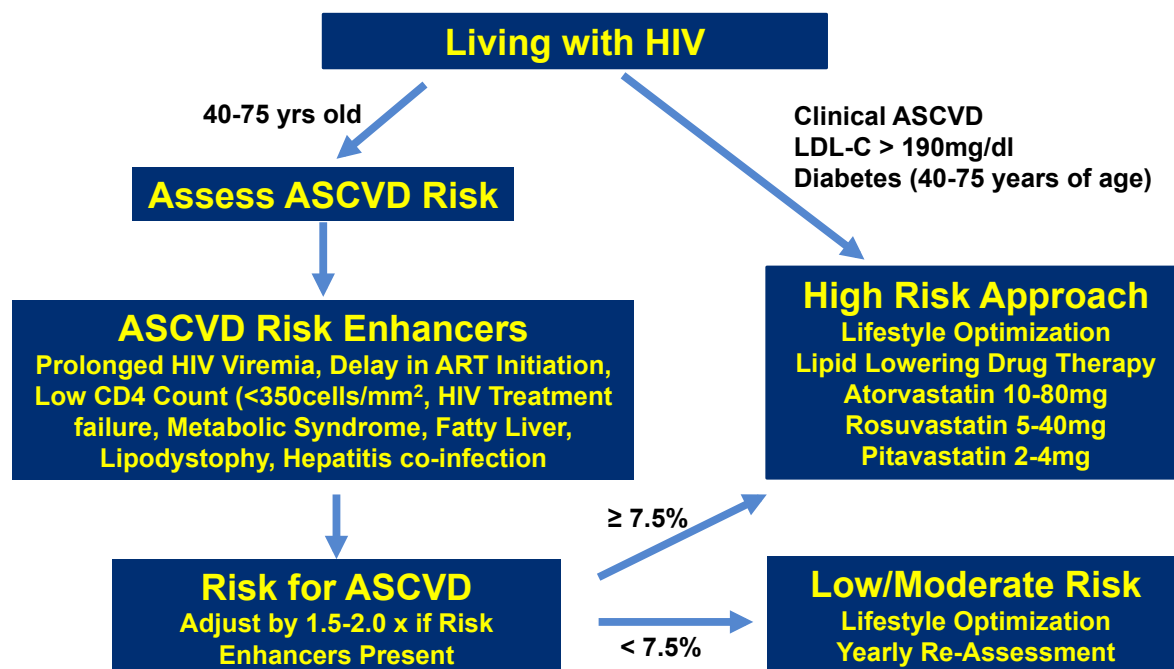


Figure 1: Estimating and Treating Atherosclerotic Cardiovascular Disease (ASCVD) Risk in People with HIV. *In patients on atazanavir/cobicistat, atorvastatin is contraindicated. In patients on darunavir/ritonavir, darunavir/cobicistat, or elvitegravir/cobicistat, the maximum recommended dose of atorvastatin is 20 mg daily. Similarly, atazanavir/ritonavir and lopinavir/cobicistat, the maximum recommended dose of rosuvastatin is 10 mg daily.

Statin Initiation Decision Making: When to Start a Statin in Patients With HIV?

As noted above, the 2019 ACC/AHA Primary Prevention of Cardiovascular Disease guidelines recognize HIV infection as a risk-enhancing factor for CV disease. As such, for those PWH who are at either borderline or intermediate risk of CV disease, HIV infection should be considered in the patient-provider discussion on statin initiation (58). The 2019 AHA Scientific Statement on CV disease in PWH also recommends that treatment decisions, such as statin initiation, should be based on an individualized assessment of CV disease risk, taking into account factors including prolonged viremia (Figure 1) (37). Coronary artery calcium (CAC) may also be useful in

determining whether a patient with HIV is at high risk for ASCVD. If CAC > 0, then healthy lifestyle changes and statin treatment are indicated (37).

However, evidence has shown a disconnect between guidelines regarding CV disease and the practice of these guidelines, specifically in the care of PWH. Agents used in the primary and secondary prevention of CV disease, including statins, aspirin, and antihypertensives, are often under-prescribed in PWH compared to people without HIV (59).

An ongoing study to date that will better inform the patient-provider discussion on statin initiation for primary prevention of CV disease in PWH is the Randomized Trial to Prevent Vascular Events in HIV

(REPRIEVE). REPRIEVE is a multisite, international study of PWH on ART, aged 40-75 years at low CVD risk. Participants were randomized to either placebo or pitavastatin 4 mg daily, and the primary outcome is time to major adverse cardiac event. Between March 2015 and March 2019, more than 7000 participants were enrolled, with a median follow-up time planned for 6 years (60).

Considerations to make in the decision to start a statin include the type of ART the patient is taking (Table 4). Several types of ART increase levels of atorvastatin, including ritonavir-boosted lopinavir, darunavir, and

atazanavir, atazanavir alone, and cobicistat-boosted atazanavir and darunavir. As such, atorvastatin doses should be adjusted accordingly, and patients should be monitored for any adverse drug effects. Similarly, ritonavir-boosted lopinavir, darunavir, and atazanavir and cobicistat-boosted atazanavir and darunavir increase rosuvastatin levels. Although atazanavir and ritonavir-boosted lopinavir and darunavir affect pitavastatin levels, no dose adjustment of pitavastatin is recommended. A comprehensive list of statin-ART interactions is shown in Table 5 and detailed on the website <https://aidsinfo.nih.gov/guidelines/> (under Drug-Drug Interactions) (26,61).

Table 4. Some Statin-ART Interactions*				
Statin	PIs	NRTIs	NNRTIs	INSTIs
Atorvastatin	Contraindicated with cobicistat-boosted atazanavir		Decrease levels with etravirine	No change in levels
Rosuvastatin	With some PIs, levels increase		No change in levels	Increase levels with cobicistat-boosted elvitegravir
Pitavastatin	No interactions with PIs		No change in levels	No change in levels; no data however with elvitegravir

*Reference: <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/>

** PIs=protease inhibitors; NRTIs=nucleoside reverse transcriptase inhibitors; NNRTIs=non-nucleoside reverse transcriptase inhibitors; INSTIs=integrase inhibitors

Table 5. Interaction of Antiretroviral Therapy and Statins		
Statin	Antiretroviral Drug	Recommendations
<i>Protease Inhibitors</i>		
Atorvastatin	Atazanavir	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities.
	Atazanavir/ritonavir	Do not co-administer.
	Atazanavir/cobicistat	Do not co-administer.
	Darunavir/cobicistat Darunavir/ritonavir	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	Lopinavir/ritonavir	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	Tipranavir/ritonavir	Do not co-administer.
Lovastatin	All protease inhibitors	Contraindicated
Pitavastatin	All protease inhibitors	No dose adjustment needed.
Pravastatin	Atazanavir/ritonavir Atazanavir/cobicistat	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	Darunavir/cobicistat Darunavir/ritonavir	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	Lopinavir/ritonavir	No dose adjustment needed.
Rosuvastatin	Atazanavir/ritonavir	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events.
	Atazanavir/cobicistat	Do not exceed rosuvastatin 10 mg daily.
	Darunavir/cobicistat	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events. Do not exceed rosuvastatin 20 mg daily.
	Darunavir/ritonavir	Titrate rosuvastatin dose carefully and administer the lowest effective dose while monitoring for rosuvastatin-related adverse events.
	Lopinavir/ritonavir	Titrate rosuvastatin dose carefully and administer the lowest effective dose. Do not exceed rosuvastatin 10 mg daily.
	Tipranavir/ritonavir	No dose adjustment needed.
Simvastatin	All protease inhibitors	Contraindicated.
<i>Non-Nucleoside Reverse Transcriptase Inhibitors</i>		
Atorvastatin	Doravirine	No dose adjustment needed.
	Rilpivirine	

	Efavirenz Etravirine	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	Nevirapine	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Fluvastatin	Doravirine Rilpivirine Nevirapine	No dose adjustment needed.
	Efavirenz Etravirine	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.
Lovastatin Simvastatin	Doravirine Rilpivirine	No dose adjustment needed.
	Efavirenz	Adjust simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	Etravirine Nevirapine	Adjust lovastatin or simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Pitavastatin	All NNRTIs	No dose adjustment needed.
Pravastatin	Doravirine Rilpivirine Nevirapine	No dose adjustment needed.
	Efavirenz Etravirine	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.
Rosuvastatin	All NNRTIs	No dose adjustment needed.
<i>Nucleoside Reverse Transcriptase Inhibitors</i>		
All Statins	All NRTIs	No dose adjustment needed.
<i>Integrase Strand Transfer Inhibitors</i>		
Atorvastatin	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Titrate statin dose carefully and administer the lowest effective dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.
Lovastatin	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Contraindicated.
Pitavastatin Pravastatin	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.

	Elvitegravir/cobicistat	No data available for dose recommendation.
Rosuvastatin	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Titrate statin dose carefully and use the lowest effective dose while monitoring for adverse events.
Simvastatin	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Contraindicated.

We generally prefer the high potency statins, atorvastatin and rosuvastatin, but will limit the dose if needed depending on the specific antiretroviral medications the patient is receiving and the potential for drug-drug interactions. In patients receiving concomitant PIs, the maximum dose of atorvastatin is 20 mg daily and the maximum dose of rosuvastatin is 10-20 mg daily (<https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/drug-interactions-between-protease-inhibitors-and-other-drugs?view=full>). If drug-drug interactions are a major concern, pitavastatin, which does not have drug-drug interactions with PIs, is a good alternative.

Lifestyle Interventions

Lifestyle interventions to improve lipids and CV risk include change in diet, weight loss, and/or exercise.

The 2019 ACC/AHA Primary Prevention of Cardiovascular Disease guidelines recommend either ≥ 150 minutes of moderate intensity exercise per week or ≥ 75 minutes of vigorous intensity exercise per week (58). However, factors associated with decreased activity in PWH include older age, lower CD4 T cell count, and having lipodystrophy (62). These factors and any other barriers to exercise should be considered when counseling PWH about exercise.

The Primary Prevention guidelines also recommend greater intake of fruits, vegetables, whole grains, legumes, nuts and fish and less intake of trans fats, sugar sweetened beverages, processed meats, and refined carbohydrates (58). Studies on diet quality in PWH, however, have demonstrated lower diet quality, as measured by the Healthy Eating Index, in PWH compared to individuals without HIV (63-65). Diet is an important modifiable risk factor in primary prevention ASCVD and should be addressed in the care of PWH.

In a study of PWH with a Framingham score $> 10\%$ randomized to either intensive lifestyle intervention, which included diet and exercise counseling, or routine care, TC in the participants in the intensive lifestyle arm decreased by -27.1 mg/dL ($p = 0.021$) at 36 months, compared to baseline, whereas the change in TC in the routine care arm was not significant. Similarly, at 24 months, LDL-C decreased significantly ($p = 0.011$) in the treatment arm, compared to the routine care arm (66). However, a meta-analysis of dietary interventions in PWH demonstrated that dietary intervention did not result in a significant change in TC or LDL-C compared to control, but did result in a significantly lower TG level, with a weighted mean difference (95% confidence interval) of -41 mg/dL (-75 to -6) (67). Thus, the above data on the effect of lifestyle interventions on specific lipid parameters in PWH are somewhat equivocal,

although in general, anti-atherogenic lipid changes were noted with lifestyle interventions.

Weight loss improves ASCVD risk factors in patients who are overweight or obese (58). Especially because the median BMI of ART-naïve PWH has increased over time (68), weight loss is an important point to address in PWH when discussing ASCVD risk reduction. However, studies in PWH to date have not necessarily demonstrated an improvement in lipids with weight loss. In women with obesity with and without HIV who lost 6-8% weight, no significant changes from baseline in either LDL-C or triglycerides was observed in either group of women (69). Similar findings were observed in another study (70). However, other CV benefits were seen, including improved insulin sensitivity (69).

When to Start Non-Statin Agents in Patients With HIV for LDL-C Lowering?

EZETIMIBE

Ezetimibe has been studied as monotherapy for treatment of dyslipidemia in PWH. In PWH with LDL \geq 130 mg/dL on low-dose pravastatin, the addition of ezetimibe resulted in LDL levels $<$ 130 mg/dL in 62.5% of the participants (71). In PWH with LDL-C \geq 130 mg/dL already on statin therapy (stable doses of either fluvastatin, pravastatin, or atorvastatin), ezetimibe has been shown to significantly lower LDL-C (median (interquartile range) percent change -20.8% (-25.4, -10.7), compared to placebo (72). In a separate study of 43 PWH on either rosuvastatin 10 mg daily and ezetimibe 10 mg daily or rosuvastatin 20 mg daily alone for 12 weeks, Saeedi et al noted that participants in the two treatment groups had similar levels of LDL-C lowering (-26.3 ± 20.9 mg/dL in the combined treatment group and -18.6 ± 21.3 mg/dL in the rosuvastatin only group). No significant change in

HDL-C was noted in either arm, but a significant decrease in TG (mean \pm standard deviation -54.9 mg/dL \pm 51.4) from baseline was noted in the ezetimibe add-on arm. In terms of adverse drug effects, both treatments were tolerated well (73). Ezetimibe should be considered in a PWH at higher CVD risk if a statin is not tolerated or as an adjunctive treatment to maximum tolerated doses of statins if the treatment goal has not been achieved (either by % LDL-c reduction or LDL-c $>$ 70 mg/dL).

PCSK9 INHIBITORS

PCSK9 inhibitors have not been well studied in PWH. However, given the interactions of statins with some ART, PCSK9 inhibitors do appear to be an attractive alternative LDL lowering medication class.

In a meta-analysis not restricted to PWH, PCSK9 levels were found to be independently associated with incident CV disease (74). PCSK9 levels have been studied in PWH, with some studies finding elevated levels in PWH compared to people without HIV (75,76). A cross-sectional study within the Swiss HIV Cohort Study that included PWH \geq 40 years of age not on statin treatment found that in a multivariate analysis with traditional CV risk factors, low CD4 count (\leq 200 cells/ μ L) was positively associated with plasma PCSK9 levels (77). In another study, in individuals with HIV and hepatitis C co-infection, PCSK9 levels were found to be higher and TC, HDL-C, and LDL-C lower, than in uninfected controls or individuals with HIV infection alone, thought to be in part secondary to a greater level of IL-6 negatively impacting hepatic production of lipoproteins.

As LDL lowering medications, PCSK9 inhibitors' use in PWH is beginning to be studied. In one study, "Evolocumab in HIV-Infected Patients With Dyslipidemia: Primary Results of the Randomized,

Double-Blind BEIJERINCK Study,” participants were randomized to either placebo or evolocumab for 24 weeks. The primary outcome of this study was change in LDL-C from baseline. Compared to placebo, the treatment decreased LDL-C by 56.9% (95% confidence interval: -61.6% to -52.3%). In addition, evolocumab was found to be safe and was well-tolerated (78).

In an ongoing study, the Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection (EPIC-HIV Study), PWH on ART with either established ASCVD or moderate or high risk for ASCVD will be randomized to either alirocumab or placebo for 52 weeks. Two of the primary outcomes of this study are change in arterial inflammation as measured by FDG PET/CT and change in lipids and lipoproteins (79). PCSK9 inhibitors should be considered in high-risk CVD patients, especially in those with a previous CVD event, who have not reached LDL-c goals on a statin +/- ezetimibe.

To date, no studies have been published on the effects of bempedoic acid or bile acid sequestrants on lipids in PWH.

When to Start Non-Statins in Patients With HIV for TG Lowering?

BACKGROUND

In the general population, the 2018 ACC/AHA Cholesterol Clinical Practice Guidelines note that TG levels from 500 to 999 mg/dL are a risk factor for acute pancreatitis (80). General population studies have shown a direct association between triglyceride levels and atherosclerotic CVD (ASCVD) (81,82), with some suggesting that certain gene alleles associated with elevated TG may be causal factors in the development

of ASCVD (83,84). However, this link is not completely certain (85).

The 2019 AHA Scientific Statement on CV disease in PWH does not note a specific TG goal for PWH. However, studies of PWH treated with non-statin agents have addressed their effects on TG.

NIACIN

As seen in the general population AIM-HIGH study, the use of niacin in patients on statins with ASCVD and LDL-C < 70 mg/dL did not reduce ASCVD events, despite significant TG lowering (86). Niacin has been studied in PWH. In one study of PWH on ART with TG levels between 150 to 800 mg/dL, extended-strength niacin was compared to fenofibrate on the primary outcome of endothelial function as measured by brachial artery flow-mediated dilation. Over the 24-week study duration, the decreases in TG and increases in HDL-C were similar between the two treatment groups (for TG, -65 mg/dL (interquartile range -163 to 8 mg/dL) in the niacin group and -54 mg/dL (interquartile range -113 to -1 mg/dL) in the fenofibrate group). Flushing was the most common adverse effect among participants on niacin. No change in endothelial function was observed in either treatment group (87). Given that the results of AIM-HIGH did not demonstrate a benefit in ASCVD event reduction, we would not recommend the first-line use of niacin for TG lowering.

EZETIMIBE

In a study by Saeedi et al cited earlier of PWH on either rosuvastatin 10 mg daily and ezetimibe 10 mg daily or rosuvastatin 20 mg daily for 12 weeks, participants in the combined statin-ezetimibe group experienced a significant drop in TG, compared to the other treatment group (-55 mg/dL versus -15 mg/dL, p

= 0.03) (73). Similarly, in the IMPROVE-IT study in which participants from the general population with a history of an acute coronary syndrome were randomized to either simvastatin/ezetimibe or simvastatin/placebo, simvastatin/ezetimibe resulted in a greater reduction in triglycerides (least squares estimate difference in means at 1 year, -14.04 mg/dL (-15.71, -12.37) (88). However, the American Heart Association guidelines focus on ezetimibe as an LDL-C lowering adjunct to statins, not as a triglyceride lowering agent (80).

FIBRATES

The Heart Positive study of 191 PWH on ART participants randomized to one of five treatment groups: usual care, low saturated fat diet and exercise, diet exercise plus fenofibrate, diet and exercise plus niacin, or diet and exercise plus fenofibrate and niacin. Compared to usual care, a combination of fenofibrate, niacin, and diet and exercise significantly decreased TG by 52% over 24 weeks (89).

OMEGA-3-FATTY ACIDS

In a meta-analysis of PWH treated with omega-3-fatty acids, Oliveira et al found that omega-3-fatty acids reduced TG by about 80 mg/dL. However, limitations of the meta-analysis were that the included studies varied with respect to dose of omega-3-fatty acids studied and study duration (90). Omega-3-fatty acids do not interact with available ART formulations. The current literature does not have any studies on the effect of icosapent ethyl in PWH, although the

REDUCE-IT trial, which was conducted in a general population group of participants with either ASCVD or diabetes and a fasting TG of 135 to 499 mg/dL and on statin therapy, showed a benefit from icosapent ethyl in reducing ASCVD events (91).

SUMMARY

Our general approach is to focus on triglyceride lowering if the TG>500 mg/dL to prevent possible pancreatitis. In addition to controlling secondary factors (e.g., hyperglycemia, excess adiposity, heavy alcohol use, estrogen use, other drugs that increase triglycerides, etc.), pharmacologic treatment with fibrates or omega-3 fatty acids is indicated in this population. For patients with TG between 150 and 500 mg/dL, pharmacologic interventions (fibrates or omega-3 fatty acids) can be considered after the LDL-C goal has been reached, especially in those at higher CVD risk (>20% 10-year risk). Note that in these patients non-HDL-C levels will likely be above goal.

CONCLUSIONS

Dyslipidemia is common in PWH and is a modifiable risk factor for CV disease. PWH are at increased risk for developing interactions of specific ART with lipid lowering agents and this should be kept in mind in the treatment of dyslipidemia in PWH. Non-statin agents have been studied in the treatment of dyslipidemia in PWH and can be considered in cases of statin intolerance or contraindication. Ongoing research will provide more information on the use of statins in primary prevention of CV disease in PWH.

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