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REVIEW

HIV: how to manage dyslipidaemia in HIV

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Abstract

Background: Dyslipidaemia is a common metabolic condition occurring in people with HIV (PWH), whether treated or untreated with antiretroviral therapy (ART). As people live longer with HIV, ongoing lipid abnormalities may contribute to increased cardiovascular disease risk. This article aims to provide a narrative updated review on the clinical evaluation and management of dyslipidaemia in PWH.

Methods: A PubMed search was performed with Clinical Queries using the key term "HIV dyslipidemia". The search strategy included clinical trials, randomized controlled trials, observational studies and reviews. The search was restricted to the English literature and the population of PWH.

Results: HIV infection causes dysregulation of metabolic processes, including lipid metabolism, thus leading to dyslipidaemia. The main lipid changes seen in untreated HIV infection are elevated triglyceride levels but lower total, LDL and HDL-cholesterol levels. Treatment of HIV infection with ART often leads to a 'return to health' increase in total cholesterol and LDL-cholesterol back towards pre-HIV infection levels. However, specific ART may cause a further increase in triglyceride and cholesterol levels. The treatment of dyslipidaemia is similar in both HIV and non-HIV populations and includes both non-pharmacological and pharmacological options, with a few caveats.

Conclusions: The management of dyslipidaemia is aimed at reducing cardiovascular risk via the utilization of non-pharmacological and pharmacological interventions. Whilst treatment options are similar, awareness of the impact of polypharmacy and drug interactions between ART and lipid-lowering medications in addition to close monitoring for adverse events is key to being successful in managing dyslipidaemia in PWH.

Keywords: dyslipidaemia, hyperlipidaemia, lipids, fibrates, statins, HIV.

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Introduction

Human immunodeficiency virus (HIV) infection, whether treated or untreated, has always been associated with a variety of metabolic complications such as dyslipidaemia, insulin resistance and lipodystrophy.[1–4] This review focuses specifically on dyslipidaemia. Prior to the initiation of antiretroviral therapy (ART), HIV infection results in lower total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).[5] However, triglyceride (TG) levels were often elevated, especially those with advanced acquired immunodeficiency syndrome (AIDS), which was related to increased hepatic release of very-low-density lipoprotein and reduced TG clearance.[6–8] After initiation of ART, increases in TC and LDL-C back towards baseline levels often occurred and were considered to be a 'return to health'.[2,9] Due to the ongoing presence of these lipid abnormalities over time as people with HIV (PWH) are living longer, there is continued concern for long-term cardiovascular risk.[10]

Methods

This article provides a narrative updated review on the evaluation, diagnosis and management of dyslipidaemia in HIV. A PubMed search was performed in August 2021 with Clinical Queries using the key term "HIV dyslipidemia". The search strategy included clinical trials, randomized controlled trials, observational studies and reviews published within the past 30 years, as much of the key literature and basic science research in this area was performed early in the HIV epidemic. The search was restricted to the English literature and the HIV population. The information retrieved from the abovementioned search was used in the compilation of this article.

Review

Aetiology

The aetiology of HIV dyslipidaemia is multifactorial and has been postulated to include a combination of elevations in circulating cytokines that modulate lipid metabolism (such as IFNα and TNF), impaired TG clearance and increased *de novo* lipogenesis in addition to the effects of individual ART.[6–8,11,12] Early in the HIV epidemic, the use of older protease inhibitors (PI), such as indinavir, saquinavir and ritonavir, were commonly associated with dyslipidaemia.[1,2] Newer PI therapies, such as atazanavir/ritonavir and darunavir/ritonavir, can still cause some early lipid changes, though less dramatic than older PIs.[13] Older nucleoside reverse transcriptase inhibitors (NRTI), such as stavudine and zidovudine, tended to also lead to dyslipidaemia, in combination with PIs.[14] Other older NRTIs, such as lamivudine and abacavir, do not have significant effects on lipids.[15] Tenofovir disoproxil fumarate (TDF) actually has a lipid-lowering effect, whilst the newer formulation of tenofovir called tenofovir alafenamide (TAF), though safer from a renal and bone perspective, does not have a lipid-lowering effect.[16,17] Efavirenz is the only non-NRTI (NNRTI) that has an adverse effect in slightly raising LDL-C in comparison to other NNRTIs such as nevirapine and rilpivirine.[18] Integrase strand transfer inhibitors (INSTI), including raltegravir, dolutegravir and bictegravir, are now part of the first-line recommended initial ART, in part due to the absence of significant effects on lipids.[19] Other factors to consider with dyslipidaemia are non-HIV factors, such as dietary choices, level of physical activity, concomitant medications and other comorbidities such as obesity, hypothyroidism, hypogonadism and diabetes mellitus.[4]

Clinical evaluation

History

Whilst the diagnosis of a person with HIV dyslipidaemia is primarily made through laboratory examination, there is still value in taking a thorough medical history. Review of comorbid medical conditions and medications that may contribute to dyslipidaemia should be performed as this offers an opportunity for intervention. The history should also focus on the timing of the onset of dyslipidaemia in relationship to the initiation of ART. With the start of any ART, weight increase can be expected as part of the 'return to health' phenomenon, which may adversely affect lipids and increase the risk of insulin resistance.[5] Whilst the current ART recommended regimens are fairly lipid neutral, recent research suggests that the use of INSTIs and TAF may lead to more significant increases in weight.[20] A review of dietary intake and physical activity is also useful, especially if improvements can be made or a referral to a registered dietician is indicated.

Physical examination

The physical examination for someone with HIV dyslipidaemia is often unremarkable. Typical findings of hypercholesterolemia, such as xanthoma, xanthelasma and arcus senilis, are rarely seen in HIV dyslipidaemia, though must be kept in mind.[18] However, monitoring of weight and waist circumference are useful markers of weight gain, obesity and metabolic syndrome, which is often associated with dyslipidaemia in HIV.[18]

Laboratory examination

The standard measurement of lipids ideally is performed in the fasting state in HIV dyslipidaemia.[18] Additional laboratory studies that may be useful to evaluate include screening for thyroid abnormalities and diabetes mellitus, as these conditions may affect lipid levels.[18] One may also consider checking other lipoprotein levels or inflammatory markers; however, there is no clear indication and this is not routinely recommended.[18]

Clinical management

The actual management of dyslipidaemia in HIV is not that different than in people without HIV and is outlined in Table 1. However, there are several differences as noted in different guidelines.[3,4,22] Experts recommend screening for dyslipidaemia at baseline, prior to initiating highly active ART, within 1–3 months after starting a new regimen and every 6–12 months thereafter.[4,22] Determination of the causes of dyslipidaemia, evaluation of cardiovascular disease risk factors and standard risk reduction measures, such as smoking cessation, improving diet and increasing exercise, should be implemented.[4] If the current ART is determined to be contributing to dyslipidaemia, it is often best to try to switch out the offending agent, if possible, as long as it can be performed safely to maintain virological control.[4] The indications for treatment of dyslipidaemia are essentially the same in PWH as in people without HIV.[4]

The need for lipid management depends on whether or not an individual is achieving their lipid targets. Most guidelines focus on the treatment of LDL-C. The European AIDS Clinical Society specifically recommends a target of <155 mg/dL for TC and <80 mg/dL for LDL-C.[21] On the other hand, the HIV Medical Association of the Infectious Diseases Society of America recommends following lipid targets based on the National Lipid Association Part 2 and 2018 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, which is dependent on the calculation of the 10-year atherosclerotic cardiovascular disease (CVD) risk score to determine if a high- or moderate-intensity statin is indicated.[22–24] Most recently, a 2019 Scientific Statement from the American Heart Association on CVD in PWH recognized that HIV had been missing as a potential risk factor in prior guidelines and, thus, included HIV infection as a risk-enhancing factor for CVD, though it did not specify the goal LDL-C for PWH.[25] In addition, the European Society of Cardiology and European Atherosclerosis Society issued similar 2019 guidelines including treatment for HIV infection as a CVD risk modifier.[26] For hypertriglyceridaemia in HIV, the National Lipid Association guidelines recommend treatment with either a fibrate or

Table 1. Treatment options for managing dyslipidaemia in HIV.

Intervention	Recommendations and comments (including drug–drug interactions)
Behaviour modification	Goal is the reduction of cholesterol, triglycerides and weight; recommended for everyone
Diet	Eat more vegetables, fruits, whole grains, legumes, healthy protein sources, non-tropical vegetable oils; limit intake of sweets and red meats
Exercise	150 min/week of moderate activity or 75 min/week of vigorous intensity aerobic physical activity
Modification/substitution of ART	Consider only if the aetiology of dyslipidaemia is related to an offending ART based on clinical judgment; consider adherence, tolerability, prior resistance and comorbidities
Current regimen includes ritonavir or cobicistat	Consider switching to an unboosted regimen
Current regimen includes PI	Consider switching to a newer generation PI (atazanavir or darunavir) or other lipid-neutral regimen
Current regimen includes non-NRTI	Consider switching to lipid-neutral non-NRTI, including rilpivirine, doravirine and etravirine or other lipid-neutral regimen
Current regimen includes NRTI	Lamivudine and emtricitabine have negligible effects on lipids; may consider switching to tenofovir disoproxil fumarate as it has lipid-lowering properties but must consider potential for renal and bone toxicity
Current regimen includes INSTI	Consider switching to lipid-neutral INSTI, including raltegravir, dolutegravir, and bictegravir or other lipid-neutral regimen; however, must be aware of potential for weight gain with INSTI
Pharmacological therapies	Treatment options are similar for those living with and without HIV
Statins	Used to lower LDL-C and TG, may raise HDL-C; many statins are metabolized by hepatic cytochrome P450 CYP3A4; many ARTs are also metabolized by CYP3A4 and, thus, may have interactions with statins; simvastatin and lovastatin are contraindicated with PI; atorvastatin has less of a CYP3A4 interaction; pravastatin, fluvastatin, pitavastatin and rosuvastatin are not or minimally metabolized through CYP3A4
Fibrates	Used to lower TG; fenofibrate preferred due to daily dosing and less drug interactions with statins; gemfibrozil with statins may result in muscle and liver toxicity
Ezetimibe	Used to lower LDL-C; well-tolerated, synergistic with statins and has no drug interactions with ART nor does it interact with CYP3A4
Niacin	Used to raise HDL-C and lower TG and LDL-C; known for its side effect of flushing but may also cause hyperglycaemia and exacerbate peptic ulcer disease; no interactions with ART
Omega-3 fatty acids	Used to lower TG; active ingredients are eicosapentaenoic acid and docosahexaenoic acid; recommended dose is ~2–4 g/day; advantage is lack of drug interactions with ART but increased pill burden may be an issue
PCSK9 inhibitors	Used to lower LDL-C with high effectiveness; requires subcutaneous administration every 2 or 4 weeks, cost may be an issue; may be ideal for statin-intolerant individuals; no known interactions with ART
Bempedoic acid	Used to lower LDL-C; not yet studied in PWH but may be ideal for statin-intolerant individuals; no known drug interactions with ART

ART, antiretroviral therapy; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; LDL-C, low-density lipoprotein cholesterol; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV; TG, triglyceride.

omega-3 fatty acids for elevated TG (>500 mg/dL) that is refractory to lifestyle modification or changes in ART.[23]

The treatment options for dyslipidaemia in individuals with HIV include behaviour modification, modification/substitution of ART and/or initiation of pharmacological therapies.

Behaviour modification strategies

Behaviour modification strategies include the reduction of dietary cholesterol and triglycerides as outlined by the 2018 guidelines on the management of blood cholesterol from the American College of Cardiology/American Heart Association.[24]

General recommendations include eating more vegetables, fruits, whole grains, legumes, healthy protein sources and non-tropical vegetable oils, whilst limiting intake of sweets, sugar-sweetened beverages and red meats.[24] Caloric intake should also be adjusted to avoid weight gain.[24] In regards to exercise, the American Heart Association recommends 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity aerobic physical activity.[27] Alcohol cessation is recommended to reduce triglycerides, and smoking cessation is recommended to reduce cardiovascular risk.[24]

Modification/substitution of ART

Considering the modification or substitution of ART is a viable strategy if the aetiology of dyslipidaemia is deemed to be related to an offending ART.[4] The advantages of switching ART for dyslipidaemia include avoiding increasing pill burden with the addition of a lipid-lowering agent and avoiding potential new drug–drug interactions. Factors to consider prior to switching include adherence and tolerability to medications, resistance to ART, and other comorbidities.[25,28,29] However, due to the multifactorial nature of HIV dyslipidaemia, lipid elevations may still persist even after switching.[4] One can choose to modify a highly active ART regimen by switching from a boosted regimen containing ritonavir or cobicistat to a non-boosted regimen. This is based on many clinical studies showing a slight elevation in lipids with boosted *versus* unboosted regimens.[30] Amongst PIs, the newer generation PIs such as atazanavir and darunavir have fewer adverse effects on lipids than older generation PIs, though these are still often used boosted with either ritonavir or cobicistat.[25] Lipid-neutral NNRTIs include rilpivirine, doravirine and etravirine.[18,29] Amongst NRTIs, TDF has some lipid-lowering properties, whilst TAF does not.[16,17] Lamivudine and emtricitabine are thought to have negligible effects on lipids. Lipid-neutral INSTIs include raltegravir, dolutegravir and bictegravir.[31,32]

Pharmacological therapies

Pharmacological therapy for dyslipidaemia is also similar for those living with and without HIV infection.[4,22] Treatment of HIV dyslipidaemia may include the use of HMG-coenzyme A inhibitors (known as statins), fibric acid derivatives (known as fibrates), ezetimibe, niacin, omega-3 fatty acids (known as fish oil), proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (known as PCSK9 inhibitors) and bempedoic acid.

Statins

Statins are the most widely used medication for the treatment of dyslipidaemia. They are first-line treatment to lower LDL-C but may also raise HDL-C whilst lowering TG.[8,18,24] Using statins in the HIV population requires caution as many statins are metabolized by the hepatic cytochrome P450 CYP3A4 isoenzyme pathway just as many ARTs are.[8,18] Thus, there is the potential for adverse drug interactions with many ritonavir-boosted or cobicistat-boosted regimens (including PI and INSTI) and some NNRTI regimens. For instance, simvastatin and lovastatin are contraindicated with a PI as levels of the statin are greatly increased potentially leading to toxicity.[8,18] Atorvastatin has less of a CYP3A4 interaction, and doses up to 40 mg are considered safe.[18] Thus, the safest statins to use in combination with ART are those that are not or minimally metabolized through CYP3A4, are metabolized through a different CYP isoenzyme or are glucuronidated. These include pravastatin, fluvastatin, pitavastatin and rosuvastatin.[8,18,29,33,34] The choice of statin used may depend on safety, efficacy, potency and availability of the desired statin. Whilst rosuvastatin is the most potent statin, it is mainly metabolized by CYP2C9, with lesser contributions from CYP2C19 and CYP3A4.[18] A randomized controlled trial of rosuvastatin *versus* pravastatin in PWH receiving PIs showed that rosuvastatin was more efficacious than pravastatin in lowering LDL-C and TG and there were no renal, hepatic or muscle events attributable to rosuvastatin.[35] However, caution must still be taken to monitor for statin toxicity, namely muscle and liver toxicity. Of note, statin drugs do not seem to affect concentrations of ART.[8,36,37]

Fibrates

For the treatment of hypertriglyceridaemia in HIV, fibrates are the mainstay of therapy.[38] These drugs are peroxisome proliferator activator receptor-α agonists. Fenofibrate is generally preferred over gemfibrozil in the treatment in PWH on ART. This is mainly due to reduced pill burden with daily dosing of fenofibrate (*versus* twice daily with gemfibrozil) and less drug interactions with statins compared to gemfibrozil (resulting in exacerbation of statin adverse events of myositis and hepatitis).[18,38–40] The FDA-approved product labelling recommends that the combined use of gemfibrozil with lovastatin, fluvastatin, pravastatin, pitavastatin, atorvastatin and rosuvastatin should be avoided whilst the FDA-approved product labelling for simvastatin indicates that gemfibrozil is contraindicated with simvastatin.[41] In general, the tolerability of both of these fibrates is favourable with only minimal gastrointestinal side effects.

Ezetimibe

One of several non-statin options is ezetimibe. Ezetimibe is an inhibitor of intestinal cholesterol absorption and has been used as a second-line therapy for those who are unable to tolerate high-dose statins or are not able to reach their target levels.[42] In HIV dyslipidaemia, it has been studied for use in combination with statin therapy (both high dose and low dose) and in those with poor response to statins.[42–46] Ezetimibe as an add-on to statin combination therapy was found to be an effective treatment option that led to additional LDL-C lowering and atherosclerotic CVD risk reduction, without raising significant safety concerns.[47] In people with chronic kidney disease, the use of ezetimibe was

found to be safe and may provide some renal protection and may suppress the complications of CVD in this population.[48] The benefits of ezetimibe is its high tolerability, known synergy with statins, and lack of drug interactions with cytochrome P450 CYP3A4, including ART.[46]

Niacin

Niacin favourably raises HDL-C and lowers TG and LDL-C levels.[49] It has been studied extensively for the treatment of lipids but its limitation is the well-known side effect of flushing, seen commonly with the use of regular, immediate-release niacin.[49] Other side effects of niacin include hyperglycaemia and peptic ulcer disease.[49] Extended-release niacin has been studied for use in increasing HDL-C levels in PWH.[50] Low HDL-C is very common in HIV infection and is associated with disease progression, greater immunosuppression and immune activation.[51] Whilst the use of ART can increase HDL-C, it is rare that HDL-C levels return back to normal. Thus, extended-release niacin was studied in PWH on ART with elevated TG and low HDL. Over the 24-week study duration, favourable decreases in TG and increases in HDL-C were seen.[50] Flushing was still the most common adverse event at 26% in participants receiving extended-release niacin. Thus, whilst effective, extended-release niacin remains less tolerable than other alternatives.

Omega-3 fatty acids

Omega-3 fatty acids, otherwise known as fish oil, is another option for the treatment of hypertriglyceridaemia in HIV.[52–54] The active ingredients of omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid, which are responsible for lowering TG.[55] The mechanism of action of fish oil is not exactly known but involves the inhibition of enzymes involved in TG biosynthesis and increased TG clearance through an enhancement in endogenous lipoprotein lipase activity.[52] In a meta-analysis of PWH treated with omega-3 fatty acids, there was a reduction of TG by about 80 mg/dL.[52] However, a limitation of this study was that different dosages were used, ranging from 900 to 3360 mg. The recommended dose of EPA and docosahexaenoic acid for TG lowering is approximately 2–4 g/day,[55] but there is a dose–response effect that has been reported in healthy volunteers.[56] Icosapent ethyl, which contains purified EPA, has been shown to reduce CVD risk in those with elevated TG in the general population.[57] It may be considered for use especially in PWH, who may have a higher CVD risk than the standard population. The advantages of using fish oil include the absence of reported drug interactions with ART and the greater acceptability in the eyes of some people due to the perception that fish oil is more natural than a pharmaceutically produced agent. The disadvantage of using fish oil includes an increased pill burden as the treatment of hypertriglyceridaemia often requires several capsules. In addition, an increase in LDL-C of ~15–36% can be seen with treatment with omega-3 fatty acids in those with very high TG >500 mg/dL.[58]

PCSK9 inhibitors

PCSK9 inhibitors have only recently been studied for use in the HIV population. Due to the potential drug interaction of statins with some ARTs, thereby potentiating muscle and liver toxicities, PCSK9 inhibitors appear to be another option for LDL-C lowering. In ART-naive patients, PCSK9 levels were found to be elevated and positively associated with both HIV progression and plasma triglycerides.[59] After boosting PI initiation, PCSK9 levels remained elevated and were only associated with standard metabolic variables such as LDL-C, TG and glucose/insulin resistance.[59] Serum PCSK9 levels have been found to be elevated in treated PWH and are associated with coronary endothelial dysfunction.[60] The BEIJERINCK study was the first study to evaluate a PCSK9 inhibitor in PWH and it demonstrated that evolocumab was effective in lowering LDL-C by 56.9%.[61] Evolocumab was safe and well tolerated with few study drug discontinuations (~2%) and the incidence of treatment-emergent and serious adverse events was similar between the placebo and evolocumab groups.[61] Other studies are currently ongoing to look at the use of another PCSK9 inhibitor, alirocumab, in PWH. The challenges of using PCSK9 inhibitors include the potential cost of the medication[62] and perhaps the acceptability of a subcutaneous mode of administration for those with needle phobias. However, several advantages of using PCSK9 inhibitors include that administration can be given every 2 or 4 weeks and that these may be ideal agents to use in statin-intolerant individuals who require LDL-C lowering.[62]

Bempedoic acid

Bempedoic acid is a recently approved oral medication to lower LDL-C.[62] Bempedoic acid acts by inhibiting ATP-citrate lyase, an enzyme upstream in the same cholesterol biosynthetic pathway as statins, leading to an upregulation in LDL-receptor density and thus increasing clearance of LDL particles and lowering LDL-C levels.[62,63] It has been shown to reduce LDL-C by about 20% and has a low incidence of myalgias in the non-HIV population.[62–64] It has not yet been studied in PWH. However, bempedoic acid may be an attractive candidate for use in PWH who need lipid lowering and who may be intolerant to statins.

Conclusion

The clinical management of dyslipidaemia in PWH is similar to the management of those without HIV. However, there are several unique considerations to keep in mind when treating dyslipidaemia in PWH. First of all, HIV infection itself may contribute to dyslipidaemia, whether treated or not. In addition, dyslipidaemia may also be caused by the ART that is being used to treat HIV infection and, sometimes, there may not be options to switch to other lipid-neutral ART due to drug resistance and/or intolerability to other medications. As a result, response to non-pharmacological and pharmacological interventions may be less than that seen in people without HIV infection. The consequence of this may be the need to use higher doses of lipid-lowering medications.

However, combined with the potential cytochrome P450 drug interactions with ART and statin therapies, for instance, increased toxicities may be seen as a result of polypharmacy. Lastly, it is important to realize that as PWH live longer, changes in lipid, glucose and fat metabolism may continue to evolve, which can lead to dyslipidaemia. Continued regular monitoring of fasting lipids and ongoing evaluation for adverse events in those people receiving lipid-lowering therapies are key in diagnosing and managing dyslipidaemia to reduce cardiovascular risk in PWH.

Key practice points

- Dyslipidaemia is a common condition occurring in people with HIV (PWH), whether treated or untreated with antiretroviral therapy.
- The management of dyslipidaemia is aimed at reducing cardiovascular risk as PWH are living longer.
- The treatment of dyslipidaemia in HIV includes both non-pharmacological and pharmacological options.
- Special attention to the impact of polypharmacy, drug interactions between antiretroviral therapy and lipid-lowering medications, in addition to close monitoring for adverse events is key to being successful in managing dyslipidaemia in PWH.

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