REVIEW

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Dyslipidemia in HIV patients

ABSTRACT

Thanks to antiretroviral therapy, people with human immunodeficiency virus (HIV) infection are living longer, but as they do, non-HIV medical problems become more relevant. In particular, dyslipidemia, an important reversible risk factor for cardiovascular disease, has been linked to HIV infection and its treatment. Although controversy remains as to whether people with HIV infections will develop premature coronary heart disease, it seems prudent to manage dyslipidemia in these patients just as we do in our HIV-negative patients. Interactions between lipid-lowering drugs and antiretroviral drugs require special attention.

KEY POINTS

Symptoms that suggest cardiovascular events that we might initially dismiss as noncardiac in younger patients without traditional cardiac risk factors may in fact be significant in HIV-infected patients with dyslipidemia.

The severity of the dyslipidemia and the typical pattern of the lipid profile differ among and within the classes of antiretroviral agents. Also, dyslipidemia does not develop in everyone who takes these drugs, suggesting that host factors play a major role in its development.

Lipid effects are only one factor to consider when choosing antiretroviral drugs, and because dyslipidemia in HIV patients is often multifactorial, switching antiretroviral drugs may not resolve the dyslipidemia.

Giving statins to patients receiving antiretroviral therapy can cause problems, since many statins and some antiretroviral drugs are metabolized by the same cytochrome P450 isoenzyme, CYP3A4, and inhibition of the isoenzymes may result in excessively high levels of statins.

HUMAN IMMUNODEFIENCY VIRUS (HIV) seems to raise people's lipid levels, as do the antiretroviral drugs used to treat it.

Although we do not yet know that people with HIV will develop premature coronary heart disease, we have no reason to expect that they would be immune to the cardiovascular effects of dyslipidemia, especially given their longer life-span due to the effectiveness of antiretroviral therapy. Therefore, it is prudent to treat their dyslipidemia as aggressively as we do in those without HIV, with the added caveat that many lipid-lowering drugs have interactions with antiretroviral drugs.

In this article we examine the data linking HIV and antiretroviral therapy with dyslipidemia and discuss the role of lipid-lowering drugs in HIV patients.

SURVIVAL IS INCREASING

Antiretroviral therapy has reduced the rates of sickness and death and has increased survival in patients with HIV infection,[1] at least in countries where people have access to it. For example, the adjusted death rate from HIV and acquired immunodeficiency syndrome (AIDS) in the United States declined nearly 4% from 2000 to 2001,[2] a larger decline than in the previous year, and continuing a trend that began in 1995. Indeed, HIV-related deaths decreased by nearly 70% over this 6-year period.[2,3]

As people with HIV infection live longer, non-HIV medical conditions become more important and relevant, particularly coronary heart disease, the leading cause of death in the United States.[4]

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TABLE 1

Current antiretroviral drugs

Nucleoside/nucleotide reverse transcriptase inhibitors
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zalcitabine
- Zidovudine

Non-nucleoside reverse transcriptase inhibitors
- Delavirdine
- Efavirenz
- Nevirapine

Protease inhibitors
- Amprenavir/fosamprenavir
- Atazanavir
- Indinavir
- Lopinavir/ritonavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Fusion inhibitor
- Enfuvirtide

HIV itself has been associated with dyslipidemia

The risk factors for cardiovascular disease have cumulative and interacting effects. While some risk factors such as male sex and family history are not modifiable, others are, including unhealthy diet, smoking, hypertension, dyslipidemia, diabetes, and physical inactivity. Aggressive treatment of dyslipidemia is key to managing and preventing cardiovascular disease in patients with or without HIV infection.

ANTIRETROVIRAL DRUGS AND REGIMENS

Current antiretroviral drugs comprise four classes (TABLE 1):

- Nucleoside/nucleotide reverse transcriptase inhibitors: zidovudine, lamivudine, emtricitabine, stavudine, didanosine, zalcitabine, abacavir, tenofovir
- Non-nucleoside reverse transcriptase inhibitors: efavirenz, nevirapine, delavirdine
- Protease inhibitors: amprenavir/fosamprenavir, atazanavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, tipranavir, ritonavir (not commonly used as the sole protease inhibitor in an antiretroviral regimen, but often used in low doses to "boost" the levels of other protease inhibitors).
- Fusion inhibitors, of which only enfuvirtide is approved by the US Food and Drug Administration (FDA).

Highly active antiretroviral therapy

"Highly active" antiretroviral therapy (HAART) is a term used to distinguish aggressive multidrug regimens from earlier, less potent ones. Currently, antiretroviral therapy (ART) and HAART both refer to any potent combination of agents that can reduce the plasma HIV level to less than can be detected by polymerase chain reaction or b-DNA assay. These regimens most often consist of a protease inhibitor or non-nucleoside reverse transcriptase inhibitor in addition to a "backbone" of two nucleoside reverse transcriptase inhibitors.

LIPID EFFECTS OF HIV AND ANTIRETROVIRAL DRUGS

HIV has been associated with dyslipidemia independent of antiretroviral therapy.[5] Grunfeld et al[6] found that HIV infection was associated with elevated triglyceride levels that worsened with progression of HIV-related disease.

Antiretroviral therapy can also contribute to dyslipidemia. Dyslipidemia has been described as being more common and more severe in HIV patients receiving antiretroviral therapy than in patients not on therapy.[7–9]

The severity of the dyslipidemia and the typical pattern of the lipid profile differ among and within the classes of antiretroviral agents.[10] Also, dyslipidemia does not develop in everyone who takes these medications, suggesting that host factors play a major role in its development.

Reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors have been associated with elevated levels of high-density lipoprotein cholesterol (HDL-C)

and total cholesterol.[11]

Nucleoside reverse transcriptase inhibitors, on the other hand, are heterogeneous in their lipid effects, which may depend somewhat on interactions with other antiretroviral drugs in the regimen.[12,13] For example, stavudine is often associated with elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels.

In comparison, tenofovir appears to be more "lipid-friendly" than other nucleoside reverse transcriptase inhibitors.[12,14] Cheng et al[14,15] found that, after 24 weeks of therapy, total cholesterol levels decreased by 17.5 mg/dL in patients receiving tenofovir, compared with a decrease of 3.8 mg/dL in patients receiving placebo. Triglyceride levels decreased by 24 mg/dL in the tenofovir group and by 3.4 mg/dL in the placebo group. When the placebo group crossed over to receive tenofovir from weeks 24 to 48, their total cholesterol levels decreased by 12.1 mg/dL and triglyceride levels by 22.0 mg/dL.

Protease inhibitors

Protease inhibitors are generally associated with elevated levels of total cholesterol and triglycerides. Triglyceride levels of greater than 1,000 mg/dL have been reported in association with protease inhibitors.[7] Carr et al[8] reported elevated total cholesterol levels, defined as greater than 5.5 mmol/L, in 58% of patients receiving protease inhibitors vs 11% of those not receiving them; elevated triglycerides, defined as greater than 2.0 mmol/L, were seen in 50% of patients receiving these drugs vs 22% of those not receiving them. Segerer et al,[9] in another study, reported a 15% increase in total cholesterol and a 25% increase in triglycerides after 3 to 6 months of protease inhibitor therapy.

All protease inhibitors are not the same in regard to dyslipidemia, however, and lipid abnormalities may vary. Ritonavir has been most associated with triglyceride elevations, whereas indinavir is more associated with elevations of LDL-C. Atazanavir is an exception in that it appears to have very little or no effect on cholesterol and triglycerides. In a trial comparing atazanavir with nelfinavir, both with a backbone of stavudine and lamivudine, nelfinavir was associated with an approximately 50% increase in triglyceride levels vs a 7% increase with atazanavir.[16]

Sex and ethnicity may influence lipid effects

Kumar et al,[13] in a trial comparing three antiretroviral regimens (zidovudine-lamivudine-abacavir, zidovudine-lamivudine-nelfinavir, and stavudine-lamivudine-nelfinavir), found that among patients taking nelfinavir, women were more likely than men to develop increased LDL-C, and the association between female sex and LDL-C elevations was even stronger in those taking stavudine-lamivudine-nelfinavir than with the two other regimens. Also, black patients were more likely than white or Hispanic patients to develop increased LDL-C levels, whereas Hispanic patients had more significant elevations of triglycerides.[17]

Unfortunately, this study was underpowered to evaluate these apparent effects more specifically. Also, the people studied may not be representative of all members classified within a group.

HIV, antiretroviral therapy, and the metabolic syndrome

The metabolic syndrome in HIV resembles that in non-HIV patients

Exactly how HIV and antiretroviral therapy cause dyslipidemia has not been determined. The dyslipidemia can occur with or without the metabolic syndrome (insulin resistance, central fat accumulation, peripheral fat loss, and inflammatory states), which in the general population is associated with an increased risk of cardiovascular events and which the National Cholesterol Education Program (NCEP) has identified as a secondary target for prevention of cardiovascular events.[18] In patients with HIV, the metabolic syndrome has many of the same features as in HIV-negative patients.

DOES HIV THERAPY INCREASE CARDIAC RISK?

Although HIV and its treatment have been associated with dyslipidemia in some studies, no one has definitively established that this association translates to an increased risk of cardiovascular events. The relatively long natural history of cardiovascular disease and

risk interventions makes it difficult to establish this relationship.

For example, investigators for the Kaiser Permanente HIV Cohort[19] reported that in a study of more than 5,000 HIV-infected patients, both cardiovascular disease and myocardial infarction rates were significantly higher among the HIV-infected patients. During the 3-year study period from 2001 to 2004, 22% of patients started lipid-lowering therapy, and 27% started a regimen containing atazanavir. Stavudine use had declined from 48% to 17%.

There is no evidence to suggest that HIV patients would be not be vulnerable to the increased cardiovascular risk associated with dyslipidemia in HIV-negative patients.

Risk of myocardial infarction

The most compelling evidence that dyslipidemia in HIV patients may increase the risk of myocardial infarction comes from the Data Collection of Adverse Events of Anti-HIV Drugs study.[20] In this prospective, observational study, the relative risk of myocardial infarction attributed to antiretroviral therapy increased by 26% per year. Despite such limitations as short follow-up, this finding suggests that we should not disregard dyslipidemia in HIV patients.

Consequently, patients with HIV, especially those receiving antiretroviral therapy, should be regularly screened for dyslipidemia. Furthermore, in patients with preexisting cardiovascular risk factors, the most lipid-friendly antiretroviral drugs should be chosen as initial therapy. Obviously, HIV itself should be treated first with considerations for underlying comorbidities.

Tenofovir appears to be more 'lipid-friendly' than other nucleoside reverse transcriptase inhibitors

Moreover, we need to take seriously any symptoms that suggest cardiovascular events in HIV-infected patients with dyslipidemia, even though we might consider the same symptoms noncardiac in younger patients without traditional cardiac risk factors or HIV.

TREATMENT

Targeting LDL cholesterol

Recommendations for managing dyslipidemia in HIV patients are based on the NCEP's third Adult Treatment Panel guidelines for the general population.[21]

The first step is to assess the patient's cardiovascular risk, which affects the decision whether to start treatment and the goals of treatment. The main factor is the LDL-C concentration, but the assessment also takes into account other risk factors such as confirmed cardiovascular disease, age older than 45 years in men and 55 in women, cigarette smoking, hypertension, low HDL-C (< 40 mg/dL), and diabetes.[18]

The level of cardiovascular risk is traditionally classified as low, intermediate, or high, and each category entails a different LDL-C treatment goal:

- Lowest risk means no risk factors or one risk factor; the goal LDL-C concentration is less than 160 mg/dL.
- Intermediate risk means one or two risk factors; the goal LDL-C is less than 130 mg/dL.
- High risk means confirmed coronary heart disease or coronary heart disease equivalents, or two or more cardiovascular risk factors and a Framingham 10-year risk score of 20%; the goal LDL-C is less than 100 mg/dL.[18]

In view of several recent studies,[22–26] the NCEP recently modified these guidelines to include an LDL-C goal of less than 70 mg/dL as an option in patients at very high risk, ie, those with established cardiovascular disease and multiple major risk factors (especially diabetes), severe and poorly controlled risk factors, multiple risk factors of the metabolic syndrome, and acute coronary syndromes.[27]

Targeting triglycerides, other lipids

Although lower LDL-C levels are the primary goal of lipid-lowering therapy, the triglyceride level and the "non-HDL" cholesterol level (ie, total cholesterol minus HDL-C) are often significant factors in patients with antiretroviral therapy-related dyslipidemia, who commonly have triglyceride elevations.

When triglyceride levels are borderline-high (150–199 mg/dL), dietary and exercise interventions are emphasized. When triglyceride levels are high (200–499 mg/dL), non-HDL cholesterol becomes a secondary target of therapy. When triglyceride levels are 500 mg/dL or higher, triglycerides are the primary target of therapy. The NCEP guidelines recommend non-HDL cholesterol as a secondary

TABLE 2

Drug interactions of antiretroviral drugs and lipid-lowering drugs

	PROTEASE INHIBITORS		NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
	REGULAR DOSE	'BOOSTER' DOSE	EFAVIRENZ	NEVIRAPINE
Statins				
Simvastatin	Increase "area under the curve" (AUC) of simvastatin by 505% to 3,059% Do not coadminister[29,38,39]	May increase blood levels of simvastatin Do not coadminister[40]	Decreases AUC of simvastatin by 58% May need to increase simvastatin dose[32]	No data
Atorvastatin	Increase AUC of atorvastatin by 71%–130% Use lowest starting dose of atorvastatin[38,39,41]	Increase AUC of atorvastatin by 130%–488% Use lowest starting dose of atorvastatin[41,42]	Decreases AUC of atorvastatin by 43% Higher dose of atorvastatin may be needed[32]	No data
Pravastatin	Minimal change in pravastatin level No dose adjustment[29,32]	Minimal change in pravastatin level No dose adjustment[40,44]	No data	No data
Fibrates[21]	Possible reduced effect No dose adjustment	Possible reduced effect No dose adjustment	Probably no change No dose adjustment	Probably no change No dose adjustment
Niacin[21]	Probably no change No dose adjustment	Probably no change No dose adjustment	Probably no change No dose adjustment	Probably no change No dose adjustment
Bile acid sequestrants[21]	May interfere with antiretroviral therapy absorption Do not coadminister	May interfere with antiretroviral therapy absorption Do not coadminister	May interfere with antiretroviral therapy absorption Do not coadminister	May interfere with antiretroviral therapy absorption Do not coadminister

target of therapy in people with high triglyceride levels (200 mg/dL). The goals for non-HDL cholesterol are defined as 30 mg/dL higher than those for LDL-C.[18]

Starting treatment

Starting treatment of dyslipidemia in HIV patients is similar to starting it in any other patients. Some situations call for drug therapy to be started in combination with lifestyle changes. However, a trial of nondrug interventions such as diet and exercise is generally recommended first. Other reversible risk factors such as smoking, diabetes, and hypertension should also be addressed at this time.[16]

Adapting the antiretroviral regimen

Because antiretroviral therapy has been implicated as a cause of dyslipidemia, altering the antiretroviral regimen has been evaluated as a way to minimize or reverse this dyslipidemia. However, lipid effects are only one factor to consider when choosing antiretroviral drugs, and because dyslipidemia in HIV patients is often multifactorial, switching antiretroviral drugs may not resolve the dyslipidemia. Therefore, switching antiretroviral drugs should be considered but may not always be a viable option.

Lipid-lowering drugs

The lipid-lowering agents commonly used to treat lipid disorders in the general population are HMG-CoA reductase inhibitors (statins), fibric acid derivatives (fibrates), bile acid binding resins, niacin, and inhibitors of intestinal absorption such as ezetimibe. Of these, statins are the first-line treatment if the primary problem is elevated LDL-C or non-HDL cholesterol levels and with triglyceride

levels below 500 mg/dL, as they have been shown to reduce the progression of coronary artery stenosis and to reduce the risk of subsequent myocardial events.[28]

Statins should also be the first-line treatment in HIV patients with increased LDL-C or non-HDL cholesterol levels and with triglyceride levels below 500 mg/dL. The HIV Medical Association of the Infectious Disease Society of America and the AIDS Clinical Trials Group advocate using statins for initial therapy if the primary problem is elevated LDL-C and non-HDL cholesterol. When the primary risk factor is elevated triglycerides, they recommend starting with a fibrate.[21]

TABLE 2 lists interactions between antiretrovirals and lipid-lowering drugs.

Statin drug interactions with antiretroviral therapy

Giving statins to patients receiving antiretroviral therapy can cause problems, since many statins and some antiretroviral drugs are metabolized by the same cytochrome P450 isoenzyme CYP3A4, and inhibition of the isoenzymes may result in excessively high levels of statins.

Statins are the first-line treatment in HIV patients with high LDL-C or non-HDL cholesterol

Simvastatin and protease inhibitors. A 30-fold increase in the area under the curve of simvastatin has been seen when it is given with ritonavir-boosted saquinavir,[29] greatly increasing the risk of rhabdomyolysis.[30] These findings suggest that simvastatin should be avoided in patients taking protease inhibitors.

Lovastatin would be expected to behave in the same way.

Atorvastatin levels may also increase when it is given with protease inhibitors; however, as these increases are not to the point of toxicity, atorvastatin can be used, but at lower doses than in the general population.[21]

Pravastatin metabolism is complex, utilizing both oxidative and conjugative enzymes for elimination, but CYP3A4 is not a significant enzyme in its metabolism. Therefore, it appears a safe option in patients taking protease inhibitors. However, pravastatin may be less effective at lowering lipid levels in these patients due to the induction of enzymes responsible for the metabolism of pravastatin.

Rosuvastatin. The guidelines of the HIV Medical Association of the Infectious Disease Society of America and the AIDS Clinical Trials Group do not mention rosuvastatin, which was not yet approved at the time the guidelines were published. Rosuvastatin has the potential to be an effective option in dyslipidemia related to antiretroviral therapy because of its potency. Rosuvastatin is metabolized similarly to pravastatin but may have slightly more CYP3A4 activity.[31] However, in the absence of data, no formal recommendations can be made.

Statins and non-nucleoside reverse transcriptase inhibitors. Efavirenz has been shown to decrease the area under the curve of atorvastatin by 43%[32] and of simvastatin by 58%, suggesting that higher doses of atorvastatin and simvastatin may be needed to effectively reduce LDL-C in patients taking efavirenz.

Statins do not appear to have any effect on HIV drugs.

Other lipid-lowering drugs

Fibrates have been described as safe for people with HIV.[33] However, their main use would be in patients with hypertriglyceridemia. Another advantage of fibrates is that they increase HDL-C.

Niacin is another option for patients with high triglycerides. A small pilot study suggested that it may be safe in HIV patients on antiretroviral therapy.[34] However, the HIV Medical Association of the Infectious Disease Society of America and the AIDS Clinical Trials Group guidelines do not advocate using it as first-line therapy in patients receiving protease inhibitors or with lipodystrophy because of the potential for insulin resistance. Additional studies evaluating the safety of niacin among HIV patients are ongoing.

Fish oil. A pilot study evaluated the efficacy of fish oil for hypertriglyceridemia. After 8 weeks of therapy, patients randomized to receive 2 g of fish oil had a 26% reduction in triglyceride levels compared with a 1% increase in the placebo group ($P = .003$).[35,36]

Bile sequestrants are not recommended because they can interfere with the absorption of antiretroviral drugs.

Other treatments need to be tested, since lipid-lowering goals are not always achieved with current treatments. A trial comparing fenofibrate and pravastatin for the treatment of antiretroviral-therapy-related elevations of LDL-C and triglycerides showed that only 3%

of patients achieved their NCEP lipid-lowering goals with a single agent, as did only 16% of patients who received fenofibrate and then added pravastatin.[37] This study showed that patients on combination fenofibrate and pravastatin therapy received substantial lipid-lowering benefits similar to those in the general population, but this combination is unlikely to achieve all clinical goals recommended by the NCEP.

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