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Authors
Waters, David D
Hsue, Priscilla Y

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Review

Lipid Abnormalities in Persons Living With HIV Infection

David D. Waters, MD, and Priscilla Y. Hsue, MD

Division of Cardiology, Zuckerberg San Francisco General Hospital, and Department of Medicine, University of California, San Francisco, California, USA

ABSTRACT

Lipid abnormalities are prevalent among persons living with HIV infection and contribute to increasing the risk of cardiovascular events. Antiretroviral therapy (ART) is associated with lipid abnormalities, most commonly hypertriglyceridemia, but also increases in low-density lipoprotein cholesterol and total cholesterol. Different classes of ART, and different drugs within classes, have differing effects on lipid levels, but in general newer drugs have more favourable effects compared with older ones. Low-level inflammation and chronic immune activation act on lipids through a variety of mechanisms to make them more atherogenic. As a consequence, risk is higher than would be expected for any given cholesterol level. Clinical outcome trials of cholesterol-lowering therapies have not yet been completed in people living with HIV, so that treatment decisions depend on extrapolation from studies in uninfected populations. Traditional risk assessment tools underestimate cardiovascular risk in individuals with HIV. Statins are the mainstay of lipid-lowering drug treatment; however, drug–drug interactions with ART must be considered. Simvastatin and lovastatin

RÉSUMÉ

Les anomalies lipidiques sont répandues chez les personnes qui vivent avec le VIH et contribuent à l'augmentation du risque d'événements cardiovasculaires. Le traitement antirétroviral (TARV) est associé aux anomalies lipidiques, plus fréquemment à l'hypertriglycéridémie, mais aussi à l'augmentation du cholestérol à lipoprotéines de basse densité et du cholestérol total. Les différentes classes de TARV et les différents médicaments parmi ces classes ont des effets distincts sur les taux de lipides, mais en général les nouveaux médicaments ont des effets plus favorables que les anciens médicaments. L'inflammation de faible degré et l'activation chronique du système immunitaire agissent sur les lipides par divers mécanismes pour les rendre plus athérogènes. Par conséquent, le risque est supérieur à ce que l'on s'attendrait pour tout taux de cholestérol donné. Les études sur les résultats cliniques des traitements hypocholestérolémiants chez les personnes atteintes du VIH n'étant pas encore achevées, les décisions en matière de traitement dépendent donc de l'extrapolation des résultats des études auprès des populations non infectées. Les outils traditionnels

Lipid abnormalities are prevalent among persons living with HIV infection and are important for several reasons. From a clinical perspective, HIV increases the risk of cardiovascular (CV) events to the same extent as traditional risk factors such as diabetes or hypertension.[1,2] Lipid abnormalities are a clear therapeutic target to decrease this risk. Second, antiretroviral therapy (ART) has reduced mortality and has turned HIV infection into a chronic disease; however, ART, particularly older drugs such as the early protease inhibitors (PIs), are associated with lipid abnormalities and lipodystrophy.[3] ART also complicates treatment of lipids because of drug–drug interactions. Lipids interact with inflammatory markers, and inflammatory markers induce changes in lipoproteins to make them more atherogenic.[4] Heightened inflammation, highly atherogenic lipoproteins, and residual HIV infection contribute to a specific type of atherosclerosis in HIV, characterized by a higher prevalence of rupture-prone coronary plaques compared with "ordinary" atherosclerosis.[5]

The primary goals of this review are: (1) to describe the lipid abnormalities associated with HIV; (2) to summarize how lipoproteins might be influenced by HIV-associated inflammation; (3) to discuss treatment of lipid abnormalities in individuals with HIV; and (4) to summarize important features of other CV risk factors in people living with HIV.

Lipid Abnormalities

The onset of HIV infection was associated in one study with a decrease in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), by a mean of 0.78, 0.57, and 0.31 mmol/L, respectively.[6] In a study that compared HIV-infected with uninfected controls matched for age, sex, and body mass index, the HIV patients had lower HDL-C and LDL-C levels, and higher triglyceride, C-reactive protein (CRP), and interleukin (IL)-6 levels.[7] Initiation of ART is recommended nowadays at the time of HIV diagnosis,[8] so that the lipid abnormalities of untreated HIV patients are now limited to individuals in resource-limited countries for whom treatment is unavailable.

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Corresponding author: Dr David D. Waters, Division of Cardiology, Room 5G1, Zuckerberg San Francisco General Hospital, 1001 Potrero Ave, San Francisco, California 94110, USA. Tel.: +1-415-420-6646.

E-mail: David.Waters@ucsf.edu

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are contraindicated in patients taking protease inhibitors, and the dose of atorvastatin and rosuvastatin should be limited to 40 mg and 10 mg/d with some ART combinations. Switching from older forms of ART to lipid-friendly newer ones is a useful strategy as long as virologic suppression is maintained, but adding a statin lowers low-density lipoprotein cholesterol more effectively. Studies indicate that lipid abnormalities are not treated as aggressively in individuals living with HIV as they are in uninfected people, making this an opportunity to improve care.

d'évaluation des risques sous-estiment les risques cardiovasculaires chez les individus infectés par le VIH. Les statines constituent le pilier du traitement par hypolipidémiants. Toutefois, les interactions médicamenteuses avec le TARV doivent être considérées. La simvastatine et la lovastatine sont contre-indiquées chez les patients qui prennent des inhibiteurs de protéase, et la dose respective d'atorvastatine et de rosuvastatine devrait être limitée à 40 mg et à 10 mg/j avec certaines combinaisons de TARV. Le passage des anciens TARV vers les nouveaux TARV dont les effets sur le profil lipidique sont favorables est une stratégie utile pourvu que la suppression virologique soit maintenue, mais l'utilisation supplémentaire d'une statine abaisse plus efficacement le cholestérol à lipoprotéines de faible densité. Les études montrent que les anomalies des lipides ne sont pas traitées aussi énergiquement chez les individus qui vivent avec le VIH qu'elles le sont chez les personnes non infectées et offrent une occasion d'amélioration des soins.

The effect of ART on lipid levels varies a great deal among the classes of ART drugs, and even among drugs within the same class. The effects of specific ART drugs are often difficult to ascertain because HIV treatment requires multidrug therapy to limit replication of the virus through multiple mechanisms, as depicted in Figure 1.[9] HIV drugs approved by the US Food and Drug Administration according to class are listed in Table 1, and combinations in Table 2. In general, PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitor analogues (NRTIs) all increase triglyceride levels and might adversely affect LDL-C levels.

With initiation of older PIs, LDL-C and triglyceride levels increase, as do glucose and insulin levels.[10] The increase in cholesterol levels with PIs is thought to be caused by increased cholesterol absorption rather than increased synthesis.[11] Increases in LDL-C and triglyceride levels are higher with dual than with single PI therapy. Important differences have been described among PIs; in a report from the **D**ata Collection on **A**dverse Events of Anti-HIV **D**rugs (D:A:D) study, ritonavir and ritonavir-containing regimens increased triglyceride and LDL-C levels more, whereas saquinavir caused less abnormally low HDL-C levels, and nelfinavir was associated with fewer patients with high total cholesterol:HDL-C ratio.[12] Interestingly, even after adjustment for lipid levels, cumulative exposure to lopinavir-ritonavir, indinavir, and didanosine were associated with increased risk of myocardial infarction (MI).[13]

In another study, the mean increase in LDL-C with initiation of a PI was 2.0 mmol/L with ritonavir, 0.8 mmol/L with indinavir, and 1.2 mmol/L with nelfinavir.[14] Ritonavir, but not indinavir or nelfinavir, was associated with markedly elevated plasma triglyceride levels.[14] Compared with older PIs, atazanavir and darunavir have more favourable lipid profiles.[15]

In clinical practice ritonavir might sometimes cause extreme hypertriglyceridemia with levels greater than 10 mmol/L and the risk of pancreatitis.[16] Nowadays lower doses of ritonavir are usually used, with correspondingly less hypertriglyceridemia; however, increased triglyceride levels are also seen with combinations of ritonavir-saquinavir and ritonavir-lopinavir.[16]

NNRTIs also increase LDL-C levels, but do not depress HDL-C levels.[12] Among NNRTIs, efavirenz was associated with slightly more patients developing hypercholesterolemia and hypertriglyceridemia compared with nevirapine.[12] Efavirenz has been associated with greater increases in total and LDL-C but not total:HDL-C ratio compared with atazanavir-ritonavir.[17] Compared with rilpivirine (another NNRTI), efavirenz is associated with higher total, HDL-C, LDL-C, and triglyceride levels.[18] The NRTI tenofovir alafenamide, a newer formulation of tenofovir disoproxil fumarate (TDF), is associated with higher levels of LDL-C and HDL-C, but similar total cholesterol:HDL-C ratios compared with tenofovir disoproxil fumarate.[19]

Overall, the prevalence of hyperlipidemia among people living with HIV across various studies ranges from 28% to 80%, with hypertriglyceridemia being the most common abnormality.[16] This wide range is understandable, because of intrinsic differences in study populations and the evolution of HIV drug treatments. Hypertriglyceridemia in HIV patients has been related to their higher intake of total fat, saturated fat, trans fat, and cholesterol compared with HIV-negative controls.[20] Saturated fat intake was strongly correlated with triglyceride levels, suggesting that increased saturated fat intake could be targeted for dietary modification in HIV patients.

Second-generation PIs such as atazanavir, the integrase inhibitors, and the C-C chemokine receptor type 5 coreceptor antagonist maraviroc have favourable effects on lipids, particularly compared with older forms of ART, as shown in Table 3.[21] Lipid changes with 2 different integrase inhibitors, dolutegravir and raltegravir, appear to be similar.[22] Most of the studies documenting these effects compared the newer agents with standard ART, or against placebo on a background of standard ART. In practice, suppression of HIV requires combination therapy, usually with 3-4 drugs. The effects of several of the most commonly used combinations on total cholesterol, LDL-C, HDL-C, triglycerides, and total:HDL-C ratio are illustrated in Figure 2.[3]

Improvements in surrogate markers of atherosclerosis such as flow-mediated vasodilatation and carotid intima-media thickness have been reported with newer ART drugs.[21] Interestingly, in one study carotid intima-media thickness progression was less among participants who initiated atazanavir treatment.[23] This benefit was attributed to atazanavir-related increases in bilirubin levels. Higher bilirubin levels, even within the normal range, appear to protect against

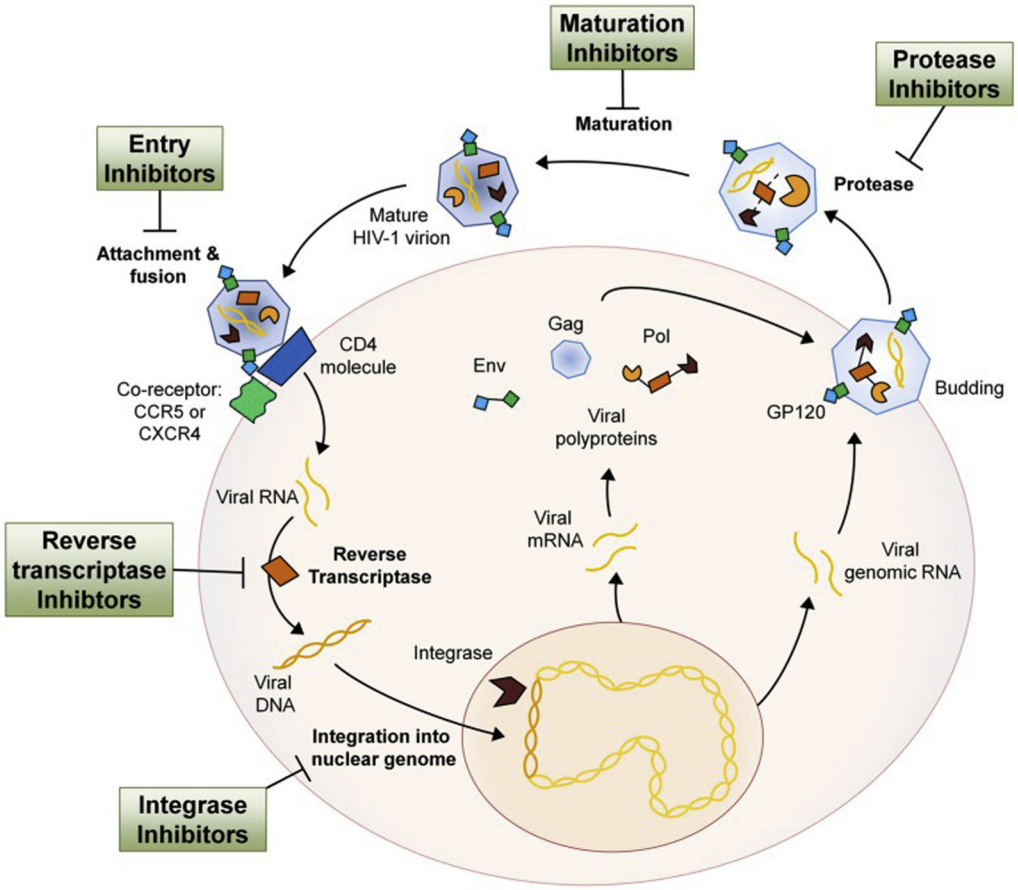

Figure 1. Targets for antiretroviral therapy during the lifecycle of the HIV virus. Multiple drugs with different mechanisms of action are used for effective treatment. See Table 1 for specific names of antiretroviral therapy drugs. CCR, C-C chemokine receptor; CXCR, chemokine receptor type 4; Env, envelope protein; Gag, group specific antigen; GP120, envelope glycoprotein 120; Pol, reverse transcriptase. Reproduced from Smith et al.[9] with permission under Creative Commons License (CC BY 3.0). © 2013 Smith, de Boer, Brul, Budovskaya and van der Spek.

atherosclerosis in Gilbert syndrome,[24] and were associated with a lower risk of incident cardiovascular disease in individuals with and without HIV in the Veterans Aging Cohort Study.[25] However, incident events in this study did not appear to be related to atazanavir use, and the mechanism by which atazanavir yields benefit, or even whether it does, remains controversial.

Most of the studies described in this section were of relatively short duration and were usually carried out in North American or European populations. However, ART is now begun most often in people living in sub-Saharan Africa, where fewer data are available on the metabolic effects of treatment. In a recent meta-analysis of 14 trials of 21,023 individuals assessed between 2003 and 2014 from this region, ART was associated with an increased risk of hypertriglyceridemia (relative risk, 2.05; 95% confidence interval [CI], 1.51-2.77).[26] The associations between ART and raised blood pressure, glucose, hemoglobin A1c, and other lipids were inconsistent across studies.

The use of newer drugs with fewer adverse metabolic consequences might lead to a reduction in CV events among patients living with HIV. Initiation of ART in the earliest stages of HIV infection, as is now recommended,[8] reduces inflammation, preserves immunologic function, and might be expected to reduce the potential of HIV infection to induce atherosclerosis.

Interaction Between Inflammation and Lipoproteins in HIV

In individuals without HIV infection, increased levels of LDL-C promote cholesterol accumulation and inflammation in the arterial wall. LDL-C within the vessel wall becomes oxidized and triggers proinflammatory pathways. Modified LDL-C is engulfed by macrophages, which increases toll-like receptor activity and leads to increased production of cytokines and chemokines.[27] Counter-regulatory mechanisms oppose these changes. Cellular cholesterol accumulation activates adenosine triphosphate (ATP)-binding cassette transporters, which promote the efflux of cholesterol onto HDL-C or apolipoprotein A1, so that cholesterol is transported back to the liver for excretion.

Acute infections, or lipopolysaccharide administration in animals, interfere with reverse cholesterol transport at multiple points.[27] HDL-C, which usually is an anti-inflammatory lipoprotein that suppresses monocyte adhesion to the endothelium, becomes proinflammatory and loses its protective effect against monocyte adhesion. The antioxidative properties of HDL-C are also impaired because of a loss of antioxidant proteins and accumulation of oxidized phospholipids.[26] Macrophage myeloperoxidase, which is induced by inflammatory stimuli in atherosclerotic plaques, also mediates reductions in HDL-C function via oxidation.

Table 1. Antiretroviral therapy

Class	Generic name	Abbreviation	Brand name	FDA approval
PI	Atazanavir	ATV	Reyataz	2003
PI	Darunavir	DRV	Prezista	2006
PI	Fosamprenavir	FOS-APV, FPV	Lexiva	2003
PI*	Ritonavir	RTV	Norvir	1996
PI	Saquinavir	SQV	Invirase	1995
PI	Tipranavir	TPV	Aptivus	2005
NRTI	Abacavir	ABC	Ziagen	1998
NRTI	Emtricitabine	FTC	Emtriva	2003
NRTI	Lamivudine	3TC	Epivir	1995
NRTI	Tenofovir fumarate disoproxil	TDF	Viread	2001
NRTI	Zidovudine	AZT	Retrovir	1987
NNRTI	Doravirine	DOR	Pifeltro	2018
NNRTI	Efavirenz	EFV	Sustiva	1998
NNRTI	Etravirine	ETR	Intelence	2008
NNRTI	Nevirapine	NVP	Viramune	1996
NNRTI	Rilpivirine	RPV	Edurant	2011
CCR5 antag	Maraviroc	MVC	Selzentry	2007
II	Dolutegravir	DTG	Tivicay	2013
II	Raltegravir	RAL	Isentress	2007
FI	Enfuvirtide	T-20	Fuzeon	2003
PE	Cobicistat	COBI	Tybost	2014
PAI	Ibalizumab	IBA	Trogarzo	2018

antag, antagonist; CCR5, C-C chemokine receptor type 5; FDA, US Food and Drug Administration; FI, fusion inhibitor; II, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PAI, postattachment inhibitor; PE, pharmacokinetic enhancer; PI, protease inhibitor.

*Although ritonavir is a PI it is generally used as a pharmacokinetic enhancer.

Data from the US Department of Health and Human Services.[95]

Many of these mechanisms might be further enhanced because of their involvement in the pathogenesis of HIV infection. The gut is the portal of entry for HIV and macrophages. Because of microbial translocation, plasma levels of lipopolysaccharide and other microbial products, are increased in HIV-infected people.[28] Lipopolysaccharide reduces ATP-binding cassette transporter activity, HDL-C function, and reverse cholesterol transport.[29] Monocytes exposed to serum from HIV-infected patients are more likely to transform into foam cells than monocytes exposed to serum from uninfected persons.[30] Thus, monocyte and HDL-C dysfunction probably contribute to reduced reverse cholesterol transport in HIV infection, likely driven by chronic immune activation.[4] Circulating markers of monocyte activation (sCD14) predict mortality in HIV[31] and sCD163, a marker of macrophage activation, is associated with plaque in coronary lesions in HIV patients.[32] Compared with uninfected controls, participants infected with HIV in one study had heightened inflammation assessed using 18fluorine-2-deoxy-D-glucose positron emission tomography (FDG-PET), which was associated with a circulating marker of monocyte and macrophage activation.[33] Taken collectively, these data suggest that monocytes play a unique and important role in HIV-related atherosclerosis.

One aspect of HDL-C function can be assessed by cholesterol efflux capacity, a measurement that has been shown to predict future CV events in the general population.[34] Among persons living with HIV, receiving ART, and with relatively benign lipid profiles, cholesterol efflux capacity was shown to be impaired.[35] LDL-C particle number was increased and particle size decreased, and there was a decrease in large protective HDL-C particles. Thus, persons living with HIV have an underlying atherogenic lipid profile even when standard lipid measurements do not appear alarming.

Oxidized LDL-C and HDL-C levels are elevated in HIV-infected individuals, and might drive monocyte and endothelial cell activation.[36] Oxidized lipoproteins are associated with inflammatory biomarkers (IL-6, CRP, and D-dimer) and multiple markers of immune activation.[37] In one study, oxidized LDL-C levels were independently associated with carotid intima-media thickness in HIV.[38] It remains unclear as to whether targeting oxidized LDL-C will translate into clinical benefit because in clinical trials of uninfected individuals, antioxidant vitamins did not reduce CV events.

To summarize, the low-grade inflammation of chronic HIV infection impairs reverse cholesterol transport, and induces proinflammatory changes in lipids, leading to atherogenesis. In turn, these abnormal lipids stimulate inflammatory pathways and immune activation, factors that independently contribute to atherosclerosis in HIV. Markers of chronic inflammation and immune activation remain elevated in the setting of effectively treated HIV infection[39] and are strongly predictive of mortality and CV events.[40] Thus, aggressive treatment of lipids and HIV infection, and likely chronic inflammation as well, appear to be a reasonable approach to reduce the risk of CV events in this population.

Treating Lipids in HIV Patients

Diet and lifestyle optimization should form the foundation for treatment of lipids in persons living with HIV.[41] As with all overweight individuals, caloric restriction and exercise should be used to attain ideal body weight. Reducing carbohydrate intake can have a favourable effect on triglyceride levels. In one report, fasting triglyceride levels and adipose tissue mass decreased, and muscle mass increased in HIV-infected men with hypertriglyceridemia after 16 weeks of resistance training.[42] Nevertheless, diet and exercise are by themselves rarely sufficient treatment.[43]

A large number of controlled clinical trials have documented that LDL−C-lowering, usually with statins, reduces the risk of CV events across a broad spectrum of patients without HIV infection. Similar data are not available for people living with HIV; however, the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), launched in 2015, will address this issue.[44] In this trial 6500 HIV-infected participants without known CV disease will be randomized to pitavastatin 4 mg/d or to placebo with a planned average follow-up of 4 years. The primary end point of REPRIEVE will be a composite of CV mortality, MI, stroke or transient ischemic attack, unstable angina, peripheral artery disease, and arterial revascularization.

As previously noted, coronary lesions in persons living with HIV are more likely to be noncalcified, and thus prone to rupture compared with lesions in uninfected individuals. Even after adjustment for coronary risk factors, coronary artery plaque, especially noncalcified plaque, is more prevalent and extensive in HIV-infected men compared with controls.[45] In a meta-analysis of 9 studies with 1229 persons with HIV and 1029 controls, noncalcified coronary plaques were much more

Table 2. Combination HIV drugs

Combination drugs (abbreviations)	Brand name	FDA approval
Abacavir, lamivudine (ABC/3TC)	Epzicom	2004
Abacavir, dolutegravir, lamivudine (ABC/DTG/3TC)	Triumeq	2014
Abacavir, lamivudine, zidovudine (ABC/3TC/ZDV)	Trizivir	2000
Atazanavir, cobicistat (ATV/COBI)	Evotaz	2015
Bictegravir, emtricitabine, tenofovir alafenamide (BIC/FTC/TAF)	Biktarvy	2018
Darunavir, cobicistat (DRV/COBI)	Prezcobix	2015
Darunavir, cobicistat, emtricitabine, tenofovir alafenamide (DRV/COBI/FTC/TAF)	Symtuza	2018
Dolutegravir, rilpivirine (DTG/RPV)	Juluca	2017
Doravirine, lamivudine, tenofovir disoproxil fumarate (DOR/3TC/TDF)	Delstrigo	2018
Efavirenz, lamivudine, tenofovir disoproxil fumarate (EFV/3TC/TDF)	Symfi	2018
Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF)	Genvoya	2015
Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF)	Stribild	2012
Emtricitabine, rilpivirine, tenofovir alafenamide (FTC/RPV/TAF)	Odefsey	2016
Emtricitabine, rilpivirine, tenofovir disoproxil fumarate (FTC/RPF/TDF)	Complera	2011
Emtricitabine, tenofovir alafenamide (FTC/TAF)	Descovy	2016
Emtricitabine, tenofovir disoproxil fumarate (FTC/TDF)	Truvada	2004
Lamivudine, tenofovir disoproxil fumarate (3TC/TDF)	Cimduo	2018
Lamivudine, zidovudine (3TC/ZDF)	Combivir	1997
Lopinavir, ritonavir (LPV/RTV)	Kaletra	2000

FDA, US Food and Drug Administration.
Data from the US Department of Health and Human Services.[95]

common in HIV patients: 58% vs 17%, respectively (odds ratio, 3.26; 95% CI, 1.30-8.18).[5]

Evidence from a small, randomized, placebo-controlled trial indicates that these lesions respond favourably to statins.[46] Forty individuals with HIV, evidence of arterial inflammation in the aorta using FDG-PET, and LDL-C levels < 3.37 mmol/L were randomized to 1 year of treatment with atorvastatin or placebo. Atorvastatin reduced noncalcified coronary plaque volume relative to placebo with a median reduction of 19.4% compared with an increase of 20.4% in the placebo group ($P = 0.009$). No difference between the groups was shown for aortic FDG-PET uptake, but this could only be evaluated in 21 of the 40 subjects.

Several lines of argument suggest that individuals living with HIV should use statins to reduce the risk of CV events. The risk of CV events in HIV-infected individuals is approximately double the risk in uninfected individuals,[1] an increase in risk similar to what is seen with diabetes or hypertension.[2] Statins have anti-inflammatory and LDL−C-lowering properties, a combination that might be particularly effective in breaking the cycle of inflammation and atherogenic lipoproteins described in the previous section. The effect of atorvastatin on noncalcified plaques in HIV patients in the just-described trial is impressive, although the sample size of the trial was small. In a recent review and meta-analysis, statin treatment was reported to effectively reduce total, LDL-C, and non−HDL-C, with a small increase in HDL-C and no significant change in triglycerides among individuals with HIV.[47] Despite the LDL−C-lowering effect of statins, their effect in lowering inflammatory marker levels such as CRP and IL-6 are less pronounced than the response seen in uninfected persons.[48] In the absence of outcomes data from large clinical trials, it might be worth noting that a meta-analysis of more than 35,000 individuals living with HIV showed that statin use was associated with a 33% reduction in all-cause mortality.[49] Finally, it has been suggested on the basis of observational data that statins, presumably because of their anti-inflammatory effect, might reduce the incidence of malignancies in people with HIV.[50]

With the exception of the 2016 European Society of Cardiology/European Atherosclerosis Society guidelines,[51] cholesterol guidelines do not address management of persons living with HIV. The European Society of Cardiology/European Atherosclerosis Society guidelines recommend dietary changes and exercise, as well as switching, when feasible, to more lipid-friendly ART. The guidelines also state that statins should be considered to achieve the target LDL-C level for high-risk patients, namely 2.8 mmol/L. As in subjects without HIV infection, underlying causes of dyslipidemia such as hypothyroidism should be ruled out.

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend consideration of cholesterol-lowering treatment for individuals 40-79 years old with an LDL-C level of 1.8-5.0 mmol/L and a 10-year risk for a CV event of 7.5% or higher. Unfortunately,

Table 3. Effects of selected new ART drugs on lipid and related parameters

	Maraviroc	Raltegravir	Atazanavir
Type of drug	Entry inhibitor	Integrase inhibitor	Protease inhibitor
Effect on lipids	Improved TC and LDL-C	Improved TC, LDL-C, TGs vs most regimens	Improved TC, LDL-C, TGs
Metabolic effects	Increased BMI, more new-onset diabetes	Increased BMI, truncal fat, less lipoatrophy	Increased truncal fat vs some regimens
Flow-mediated dilatation	Improved	No change	No change; decreased cIMT

The findings listed in the table are usually from studies comparing these drugs with other commonly used ART drugs, or with placebo against a background of ART.

ART, antiretroviral therapy; BMI, body mass index; cIMT, carotid intima-media thickness; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

Data from Worm et al.[13]

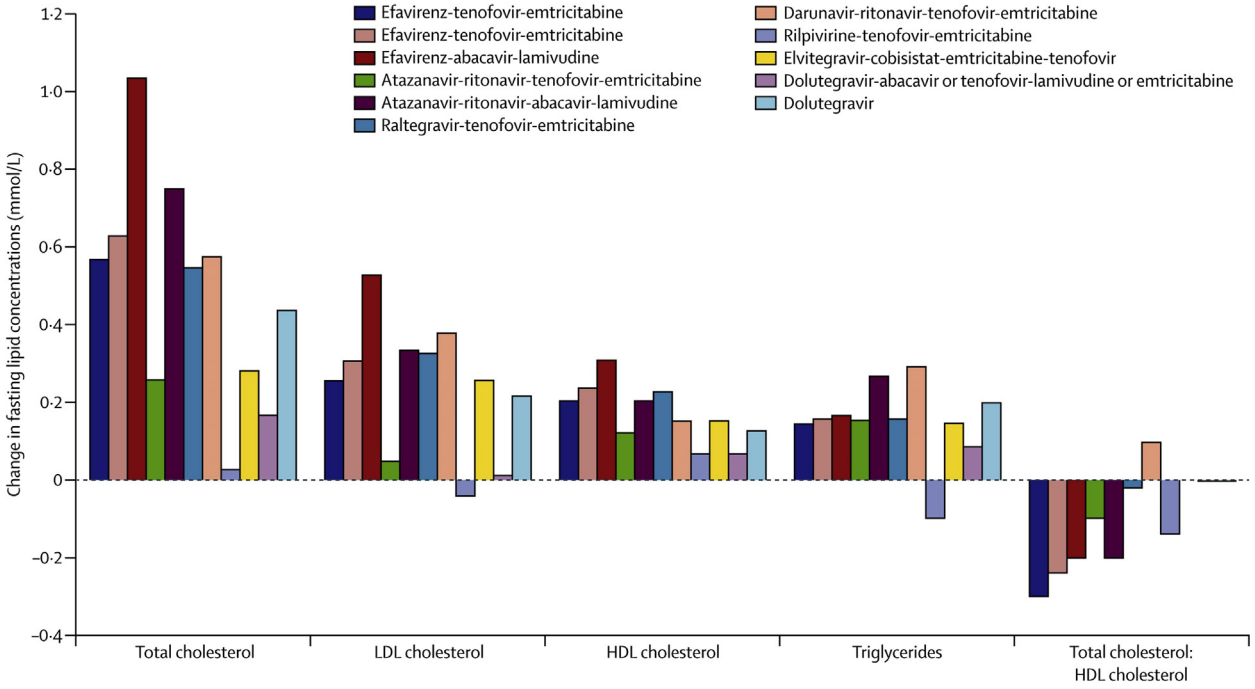

Figure 2. Effects of common combinations of antiretroviral therapy on lipid levels. HDL, high-density lipoprotein; LDL, low-density lipoprotein. Reproduced from Lake and Currier[3] from *The Lancet* with permission from Elsevier.

the usual risk assessment tools are inaccurate in the setting of HIV. For example, in one recent study, high-risk coronary plaque morphology was seen on computed tomography angiography in 36% of 108 HIV patients, but the 2013 ACC/AHA guidelines would recommend statins for only 19% of them.[52] Similarly, in another study the guidelines fail to recommend statin therapy for two-thirds of individuals with HIV who had carotid plaque on ultrasound imaging.[53]

CV risk prediction using either Framingham or the 2013 ACC/AHA risk calculators systematically underestimates risk in HIV. Risk assessment tools have been designed specifically for HIV populations. One of them is on the basis of 1010 CV events that occurred in 32,663 HIV-positive persons from 20 countries in Europe, and Australia.[54] The detailed model includes age, sex, systolic blood pressure, smoking status, family history of CV disease, diabetes, total cholesterol, HDL-C, CD4 lymphocyte count, cumulative exposure to PIs and NRTIs, and current use of abacavir. A reduced model excluded ART and current use of abacavir. The model performed better than the Framingham Risk Score even after the Framingham Risk Score had been recalibrated to the HIV population.

The 2018 AHA/ACC guidelines have recently been published.[55] They mention HIV as a "risk enhancer" and make 3 recommendations for adults with chronic inflammatory disorders or HIV: (1) that these risk enhancers favour opting for moderate or high-intensity statin therapy in a discussion of risk; (2) that a risk assessment, including fasting lipid profile, be done before and 4-12 weeks after starting ART; and (3) for adults with rheumatoid arthritis, that risk assessment be repeated 2-4 months after the inflammatory disease has been controlled.[55]

Drug—drug interactions must be considered when initiating lipid-lowering drugs in persons living with HIV. Table 4 summarizes the hepatic metabolic pathways and ART interactions for each of the 7 statins. A systemic review of 18 clinical trials in HIV-infected patients receiving ART confirmed that statin administration is safe when drug—drug interactions are accounted for.[56] Simvastatin and lovastatin are contraindicated with PIs because of the risk of rhabdomyolysis from high statin blood levels.[16] Similarly, no more than 40 mg/d of atorvastatin should be used for individuals taking ritonavir-boosted PIs. Rosuvastatin blood levels are increased when used with atazanavir/ritonavir and lopinavir/ritonavir, so limiting the rosuvastatin dose to 10 mg is advised with these drugs.[57] Pravastatin and fluvastatin are safe but do not lower LDL-C as much as atorvastatin or rosuvastatin. These weaker statins were widely used after the introduction of ART, but are less popular now because of the growing realization, reflected in contemporary guidelines, that greater degrees of LDL—C-lowering produce greater CV event reduction.[58]

Although not available in Canada, pitavastatin is theoretically a good choice for individuals living with HIV, because at higher doses its LDL—C-lowering effect is moderate, and because its metabolism is via glucuronidation, drug—drug interactions are avoided.[59] In a randomized, double-blind comparison study in 252 subjects with HIV, pitavastatin 4 mg/d reduced LDL-C by 31% and pravastatin 40 mg/d reduced LDL-C by 21%, with similar low rates of adverse events in the 2 treatment groups.[60] Levels of soluble CD14, oxidized LDL-C, and lipoprotein-associated phospholipase 2 were significantly lower in the pitavastatin group compared with the pravastatin group.[61]

As with other patients, statins should be the mainstay of lipid-lowering drug therapy for persons living with HIV.[16,51] Several studies indicate that statins are underused in the setting of HIV.[59,62,63]

Table 4. Metabolic pathways of statins and interactions with ART

Drug	Metabolism	Lipophilic	ART interactions	Comment
Lovastatin	CYP3A4	Yes	PI, NNRTI	Limited efficacy
Simvastatin	CYP3A4	Yes	PI, NNRTI	Contraindicated
Pravastatin	Partial hepatic	No	PI	Limited efficacy
Fluvastatin	CYP2C9, CYP3A4	Yes		Limited efficacy
Atorvastatin	CYP3A4	Yes	PI	More potent
Rosuvastatin	CYP2C9 (< 10%)	No	PI	More potent
Pitavastatin	Glucuronidation	Yes		Least D-D interaction

ART, antiretroviral therapy; D-D, drug–drug; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

In individuals living with HIV who do not tolerate statins, ezetimibe is a safe option, albeit with limited LDL–C-lowering efficacy.[64] Ezetimibe could be considered as add-on therapy for very high-risk individuals with HIV who do not achieve satisfactory LDL-C lowering with statins. Bile acid sequestrants are not recommended in HIV-infected individuals because they increase triglyceride levels and their effects on the absorption of antiretroviral drugs have not been studied.[50] Add-on therapy can be problematic for individuals with HIV because they often already suffer from a high pill burden because of ART and other medications.

We have reported high proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in the setting of HIV,[65] and are currently investigating PCSK9 inhibitors in a randomized, placebo-controlled trial as a potential treatment to reduce CV risk using multimodality assessment of coronary plaque, arterial inflammation, and endothelial function for individuals with HIV.[66] PCSK9 inhibitors have inherent advantages in this circumstance, including profound LDL–C-lowering, a reduction in pill burden, avoidance of the drug–drug interactions of statins, and ease of use in patients with chronic liver disease, a common problem in this population.

Switching ART to drugs that do not adversely affect lipid levels is a worthwhile strategy as long as viral suppression is maintained. Switching from older PIs to integrase inhibitors has been shown to improve lipid levels, but at the cost of an increased risk of virologic failure,[67] and thus is not recommended for individuals with this history. In another study of 415 subjects with HIV and high CV risk, half were randomized to continue a ritonavir-boosted PI regimen and half were switched to dolutegravir, an integrase inhibitor.[68] After 48 weeks, no difference between the treatment groups was seen for virologic failure, but total cholesterol, LDL-C, and triglyceride levels all improved ($P < 0.0001$) in the dolutegravir group. Additional use of a statin might be preferable to switching for those not already taking a statin; in one study the additional use of rosuvastatin 10 mg/d yielded better lipid results and was better tolerated compared with switching.[69]

Hypertriglyceridemia is a common finding in individuals with HIV and might be related to ART or HIV itself. Reducing alcohol and carbohydrate intake has a favourable effect in persons with or without HIV infection. Consideration should be given to a change in ART to drugs that induce less hypertriglyceridemia. Fibrates reduce triglycerides, often at low doses, but have a drug–drug interaction with statins and some types of ART; for example, the lopinavir-ritonavir PI combination greatly reduces gemfibrozil absorption.[70] Monitoring of hepatic enzymes and creatine phosphokinase levels is advised for patients taking ART, a statin, and a fibrate. Fish oil has been shown to reduce triglyceride levels in persons with HIV and hypertriglyceridemia, and has the advantage of no important drug–drug interactions; however, fish oil does increase LDL-C levels modestly.[71,72] When triglycerides exceed 10 mmol/L, pancreatitis is a serious risk; lower levels of hypertriglyceridemia probably increase CV risk. If pancreatitis does develop, the offending drug must be withdrawn and supportive care instituted.[73]

The recently published **Reduc**tion of **C**ardiovascular **E**vents with Icosapent Ethyl-**I**ntervention **T**rial (REDUCE-IT) tested the effect of icosapent ethyl, a stable eicosapentaenoic acid ethyl ester, as add-on therapy with statins in 8179 patients with CV disease or diabetes and other CV risk factors, and a fasting triglyceride level of 1.69-5.63 mmol/L (150-499 mg/dL).[74] The dose of icosapent ethyl was 2 g twice daily and the median follow-up was 4.9 years. The primary end point, a composite of CV death, MI, stroke, coronary revascularization, or unstable angina, occurred in 17.2% of the icosapent ethyl patients compared with 22.0% of the placebo patients (hazard ratio, 0.75; 95% CI, 0.68-0.83; $P < 0.001$).[74] Although outcome data such as this are not available for hypertriglyceridemic individuals living with HIV, icosapent ethyl should now be considered as treatment for such persons.

Inflammation is a potential therapeutic target for a reduction of CV events, in persons with and without HIV infection. Canakinumab, a monoclonal antibody targeting IL-1β, was recently evaluated in a randomized, placebo-controlled trial of 10,061 patients with previous MI and a CRP level of $\geq$ 2 mg/L.[75] The 3 doses of canakinumab that were tested all reduced CRP, from 26% to 41%, but did not affect LDL-C levels. At the intermediate and higher doses, canakinumab reduced the primary composite end point of CV death, MI, and stroke. Patients who had a CRP reduction to < 2 mg/L experienced significant reductions in CV events, coronary heart disease death, and all-cause mortality, whereas those without a CRP reduction to this level did not.[76]

Would canakinumab reduce CV risk in HIV-infected subjects? Our group has shown that canakinumab significantly reduced IL-6 and CRP levels with no effect on CD4, CD8, RNA viral levels, or lipids in a small study of subjects with HIV infection.[77] Another anti-inflammatory drug, methotrexate, has been associated with reductions in CV events among individuals with rheumatoid arthritis,[78] an inflammatory condition with elevated markers of inflammation and elevated CV risk. The effect of low-dose methotrexate on CV events was studied in the recently published **C**ardiovascular **I**nflammation **R**eduction **T**rial (CIRT), in 4786 individuals with known CV disease or diabetes.[79] The trial was

stopped after a median follow-up of 2.3 years. Compared with placebo, methotrexate did not lower levels of IL-1β, IL-6, or CRP, and had no effect on CV events.

Similarly, in a multicentre study, our group reported no effect of low-dose methotrexate on inflammatory markers or endothelial function[80] but methotrexate did favourably affect coronary artery echogenicity, a surrogate marker of plaque composition.[81] These preliminary studies with inflammatory biomarkers as surrogate end points will hopefully lead to larger trials of anti-inflammatory treatments with CV events as end points among individuals living with HIV.

Unique Features of Other CV Risk Factors in HIV Patients

Whether HIV infection is associated with an increased risk of diabetes has been controversial. PIs and thymidine analogues, specifically stavudine, can cause insulin resistance[82]; however, these drugs are rarely used nowadays because of their toxicity. In a large cohort study from Denmark, the risk of diabetes among HIV-infected individuals was nearly 3 times higher than in the general population from 1996 to 1999, but this excess was no longer present from 1999 to 2010.[83] However, in a recent cross-sectional study from sub-Saharan Africa, the prevalence of diabetes was higher in people living with HIV compared with uninfected controls, as was the prevalence of a glycated hemoglobin level of at least 6%.[84]

Lipodystrophy is a syndrome that results in central adiposity from accumulation of fat in the dorsocervical region, with increased or preserved visceral fat and peripheral fat loss.[3,41] Lipodystrophy develops in 20%-35% of patients taking PIs or the NRTIs didanosine or stavudine. Newer PIs such as atazanavir do not appear to cause lipodystrophy. Lipodystrophy in HIV is commonly associated with components of the metabolic syndrome: insulin resistance, impaired glucose tolerance, hypertriglyceridemia, low HDL-C levels, and hypertension. The insulin resistance associated with lipodystrophy can be severe, and might even precipitate diabetes. Reported rates of the metabolic syndrome in persons living with HIV range from 8.5% to 52%, with rates at the higher end of this range found in Latin American countries and rates at the lower end in multicentre studies in which patients had less exposure to ART.[82] Metabolic syndrome commonly develops during the first 3 years after initiation of an ART regimen that includes lopinavir/ritonavir or stavudine. The metabolic syndrome is a predictor of CV events and death in HIV-infected individuals according to most studies.[82]

Hypertension and prehypertension have been shown to be risk factors for CV events in HIV-infected persons, just as they are for uninfected individuals.[85] Similarly, chronic kidney disease), expressed as either albuminuria or a decreased glomerular filtration rate, is associated with an increased risk of CV events in HIV-infected patients.[86] In a cohort of 35,357 persons with HIV, lower glomerular filtration rate was strongly associated with higher CV risk.[87] The prevalence of hypertension and chronic kidney disease appears to be higher than normal in HIV-infected persons among individuals exposed to some forms of ART.[88]

Smoking is highly prevalent among those infected with HIV. In a large cohort study from Denmark, nearly half of HIV patients were smokers compared with one-fifth of uninfected people.[89] All-cause mortality rates were much higher among smokers compared with nonsmokers with HIV. For example, a 35-year-old person living with HIV had a median life expectancy of 62.6 years (95% CI, 59.9-64.6) if a smoker and 78.4 years (95% CI, 70.8-84.0) if a nonsmoker. Smoking caused more lost life-years than HIV, 12.3 vs 5.1. The population-attributable risk of death due to smoking was 61.5% in individuals with HIV and 34.2% among uninfected people.

Smoking cessation programs appear to have the same modest success rates in people with HIV as in noninfected individuals. In a meta-analysis of 8 trials including 1822 HIV-infected smokers, behavioural interventions increased abstinence rates by approximately half (relative risk, 1.51; 95% CI, 1.17-1.95).[90] Training physicians who care for individuals living with HIV to provide smoking cessation counselling and treatment increased smoking cessation rates and decreased relapse rates in one study.[91] Potential drug−drug interactions between ART and drugs for smoking cessation have not been well studied. Studies of varenicline, bupropion, and nicotine replacement therapy in persons with HIV have generally been small, short, and uncontrolled, but have shown safety and success rates similar to reports in uninfected subjects.[92,93]

The effect of smoking cessation on the rates of subsequent CV events was reported for a large cohort in the D:A:D study.[94] Among those who stopped smoking, the incidence of MI and other CV events began to decrease within the first year, with a further decrease thereafter. This pattern is similar to what is seen in quitters without HIV infection, making smoking cessation a very desirable therapeutic goal.

Conclusion

Persons living with HIV are now older and at increased risk for CV events. The presence of HIV approximately doubles CV risk, as does either diabetes or hypertension.[2] Lipid abnormalities are common among individuals with HIV infection, and their lipids are abnormally atherogenic, because of several inter-related factors. Although clinical trial data with lipid-lowering drugs is not yet available for those with HIV, guidelines recommend that they be treated aggressively with statins. Simvastatin and lovastatin are contraindicated with PIs because of drug−drug interactions. Studies indicate that statins are underused in the setting of HIV,[59,62,63] perhaps because HIV specialists might not have the expertise to manage CV risk, and because cardiologists do not have expertise in HIV or appreciation of CV risk in this unique population.

Disclosures

Dr Waters has received remuneration from pharmaceutical companies for participating in clinical trial committees of investigational cholesterol drugs. Dr Hsue has received honoraria from Gilead and Merck.

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