Impact of Antiretroviral Medications on Fasting Lipid Parameters

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It is widely accepted that metabolic disease in human immunodeficiency virus (HIV) develops at the intersection of traditional risk factors and HIV-specific contributors, but in observational studies it is difficult to dissect the contribution of the two. This review describes the metabolic impact of antiretroviral medications recommended in the first-line treatment in HIV-infected naive patients. At a clinical level, coronary heart disease screening and management will continue to be of paramount importance in the long-term management of HIV-positive patients on antiretroviral therapy.

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KEY WORDS

Coronary heart disease • Human immunodeficiency virus • Antiretroviral therapy • Dyslipidemia

Although the initial research on coronary heart disease (CHD) in patients with human immunodeficiency virus (HIV) focused on the relationship between dyslipidemia associated with antiretroviral therapy (ART) and cardiovascular risk, a broader appreciation of the complex interplay between traditional risk factors and HIV infection has emerged more recently.

Currently, it is widely accepted that metabolic disease in HIV develops at the intersection of traditional risk factors (such as tobacco use, obesity, and genetic predisposition) and HIV-specific contributors (including ART exposure, chronic inflammation, and immune activation), but in observational studies it is difficult to dissect the contribution of the two; HIV-positive status may simply serve as a marker for differences in the prevalence of traditional risk factors such as smoking.

Pathogenesis

Dyslipidemia associated with ART exposure may induce a predominance of small, dense low-density lipoprotein (LDL) particles with accompanying elevated triglycerides and reduced high-density lipoprotein (HDL) cholesterol. Morphologic and functional studies of the earliest stages of atherogenesis in human and animal models indicate that the key initiating step is subendothelial accumulation of apolipoprotein B (apoB) lipoproteins. Hepatic apoB lipoproteins are secreted as very low-density lipoproteins, which are converted in the circulation to atherogenic LDL.[1]

Riddler and colleagues[2] demonstrated in the Multicenter AIDS Cohort Study that this atherogenic profile was more pronounced in patients undergoing protease inhibitor (PI)–containing regimens when compared with patients treated with non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Awareness of adipose tissue as an inflammatory and endocrine organ has improved understanding of the connections between adipose tissue dysfunction and the development of diseases associated with systemic inflammation, including insulin resistance and cardiovascular disease.

Pathogenesis of cardiometabolic diseases relies also in perturbation of adipose tissue, both in the presence of lipodystrophy or in the absence of clinically apparent fat changes. Awareness of adipose tissue as an inflammatory and endocrine organ has improved understanding of the connections between adipose tissue dysfunction and the development of diseases associated with systemic inflammation, including insulin resistance and cardiovascular disease.[3]

PIs and NNRTIs may activate adipocyte nuclear transcription factors with downstream effects leading to lipohypertrophy[4]; nonetheless, a direct impact of highly activated antiretroviral therapy on visceral fat is still unproven and no clinical studies have ever proven benefit from switching antiretroviral drug classes. In this context, we question the role of ART on lipid metabolism.[5-13]

The Data Collection on Adverse Events of Anti-HIV Drugs Study

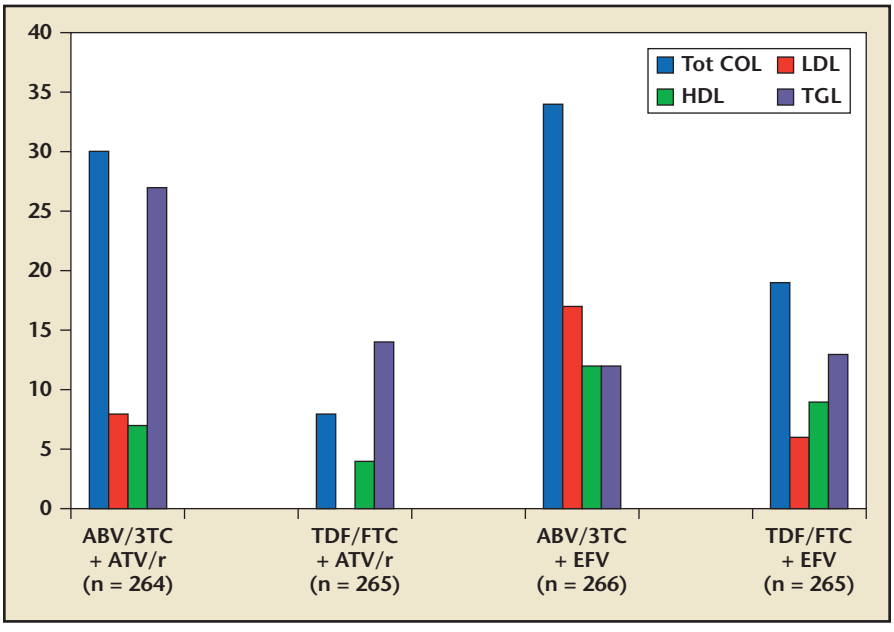
The largest prospective study of cardiovascular risk with ART is the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.[5]

Of 23,437 participants, 345 (1.5%) developed a first myocardial infarction (MI) with an incidence of 3.7 per 1000 person-years. Of these, 29% were fatal, representing 10% of all deaths in the study. Incidence of MI increased directly with longer exposure to ART (relative risk [RR] 1.16; 95% confidence interval [CI], 1.09-1.23 per year of exposure; $P < .0001$) for up to 6 to 7 years of exposure. Information on longer-term associations is unavailable. Importantly, this relative association between exposure to ART and increased risk of MI was comparable irrespective of age or sex. In further analyses evaluating the impact of individual antiretroviral drug classes, the RR of PI therapy was also 1.16 (95% CI, 1.10-1.23; $P < .001$), whereas the annual RR for NNRTI-based therapy was not significant (RR 1.05; 95% CI, 0.98-1.13).[6]

Although the risk of MI remained significant in relation to duration of PI-based ART, this risk was approximately halved in analyses that controlled for increased total cholesterol levels and lower HDL cholesterol levels. This suggests that not only PIs, but also ART in general, may impact CHD by inducing lipid abnormalities contributing to traditional, modifiable risk factors, and also with a direct toxic mechanism that may be related to cumulative or current exposure to a specific drug.

In the D:A:D cohort the statistical power to analyze association between a single drug exposure and CHD cannot be reached before 30,000 patient-years of follow-up. This makes physicians gain confidence in drug safety only after a drug has been on the market for many years. In order to get early safety data, which is particularly important for new drugs, clinicians

Figure 1. Nucleoside reverse transcriptase inhibitor-induced mean changes in lipids (mg/dL) from baseline at week 96. Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) vs abacavir/lamivudine (ABV/3TC) in association with efavirenz (EFV) or atazanavir/ritonavir (ATV/r). COL, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TGL, triglycerides. Data from Sax PE et al.[14]



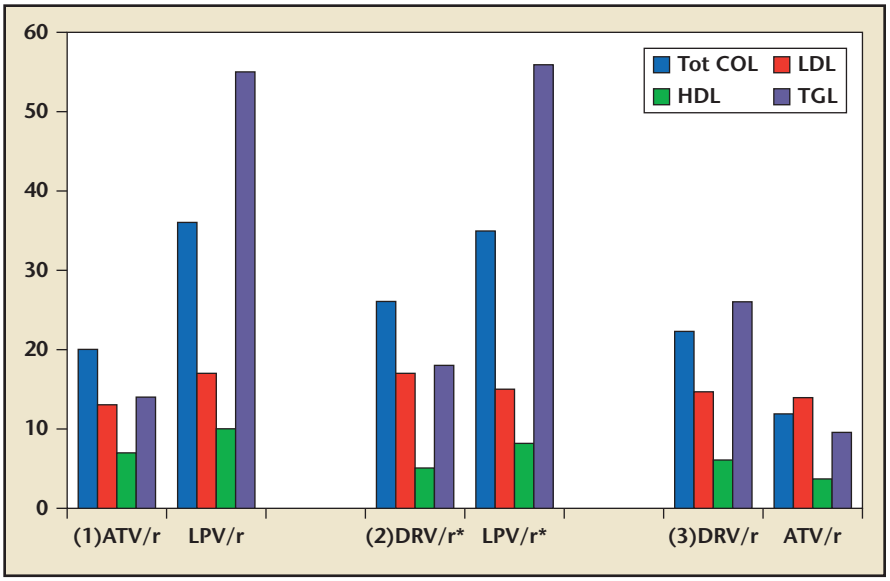


Figure 2. Protease inhibitor/ritonavir-induced mean changes in lipid (mg/dL). (1) Adapted from CASTLE at week 96; sample size: n = 440 (ATV/r; n = 440), n = 443 (LPV/r). (2) Adapted from ARTEMIS at week 96; sample size: n = 343 (DRV/r), n = 346 (LPV/r). (3) Adapted from METABOLIK at week 48; sample size: n = 34 (DRV/r), n = 31 (ATV/r). *Median value. ARTEMIS, Antiretroviral Therapy with TMC114 Examined in Naïve Subjects; ATV/r, atazanavir/ritonavir; CASTLE, Comparison of Atazanavir/Ritonavir in Naive Subjects in Combination with Tenofovir-Emtricitabine Versus Lopinavir/Ritonavir in Combination with Tenofovir-Emtricitabine to Assess Safety and Efficacy; COL, cholesterol; HDL, high-density lipoprotein; DRV/r, darunavir/ritonavir; LDL, low-density lipoprotein; LPV/r, lopinavir/ritonavir; METABOLIK, Metabolic Evaluation in Treatment-Naives Assessing the Impact of Two Boosted Protease Inhibitors on Lipids and Other Markers; TGL, triglycerides. Data from Molina JM et al,[15] Mills AM et al,[16] and Aberg JA et al.[17]

still rely on the impact of single agents and drug classes on blood glucose and lipids as assessed in randomized controlled trials.

Measurement of fasting lipid concentrations has become a standard component of clinical trials; it assesses new antiretroviral drugs and is a major driver for drug discovery for new agents harboring minimum metabolic impact. Metabolic variables are captured in national and international guidelines that weigh antiretroviral class specific; therefore, we present the impact of the currently used antiretroviral according to drug class classification. The metabolic impact of antiretroviral switch studies is also analyzed.

Nucleoside Reverse Transcriptase Inhibitors

Tenofovir disoproxil fumarate/emtricitabine and abacavir/lamivudine are the NRTIs that represent the backbone for initial treatment of naive patients.

Changes in lipid levels during ART are drug specific and not class specific…

recommendations on metabolic impact, particularly in first-line regimens. Guideline recommendations for first-line treatment of naive patients are shown in Table 1. The expected changes in lipid levels during antiretroviral therapy are summarized in Table 2.[14-17]

Changes in lipid levels during ART are drug specific and not

A head-to-head comparison of lipid impact of these two drugs was explored in the AIDS Clinical Trials Group (ACTG) 5202 study[14] in association with either open-label efavirenz or atazanavir/ritonavir. Both at 48 and 96 weeks of observation, abacavir/lamivudine—when compared with tenofovir disoproxil fumarate/emtricitabine—displayed a higher increase from baseline of total cholesterol, LDL, HDL, and triglycerides, both in association with atazanavir/ritonavir or efavirenz.

This result postulated not just a neutral impact of tenofovir disoproxil fumarate with regard to lipid profile, but a so-called statin-like phenomenon, which implies a reduction of lipid plasma level in patients entering tenofovir disoproxil fumarate regimens and lipid worsening in studies switching from tenofovir disoproxil fumarate (Figure 1).

PIs

Treatment with boosted PIs may substantially increase lipid parameters and insulin resistance. Starting from the introduction of atazanavir/ritonavir, PI-based regimens are generally believed to have more favorable lipid effects than older PIs, especially when compared with lopinavir/ritonavir.

The Comparison of Atazanavir/Ritonavir in Naive Subjects in Combination with Tenofovir-Emtricitabine Versus Lopinavir/Ritonavir in Combination with Tenofovir-Emtricitabine to Assess Safety and Efficacy (CASTLE) study was an international, multicenter, open-label, 96-week noninferiority randomized trial of atazanavir/ritonavir, 300/100 mg/d, versus lopinavir/ritonavir, 400/100 mg twice daily, each in combination with fixed-dose of tenofovir disoproxil fumarate/emtricitabine. Mean changes from baseline in fasting total cholesterol, non-HDL cholesterol, and triglycerides at week 96 were significantly higher with lopinavir/ritonavir.[15]

Additionally, darunavir, when compared with lopinavir in the Antiretroviral Therapy with TMC114 Examined in Naive Subjects (ARTEMIS) study, showed less impact on

TABLE 1

Guideline Recommendations for First-line Treatment of Naive Patients

	International Antiviral Society	US Department of Health and Human Services	European AIDS Clinical Society	World Health Organization
TDF/FTC or 3TC	X	X	X	X
ABC/3TC			X	
ZDV/3TC				X
EFV	X	X	X	X
NVP				X
RPV			X	
ATV/r	X	X	X	
DRV/r	X	X	X	
LPV/r				
RAL	X	X	X	
ELV		X		
DTG		X		

3TC, lamivudine, ABC, abacavir; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; ELV, elvitegravir; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate, ZDV, zidovudine.

triglycerides and total cholesterol elevation. Moreover, median levels of lipid parameters for darunavir/ritonavir consistently remained below National Cholesterol Education Program cut-off levels.[16]

In a pilot study, Aberg and colleagues[17] described metabolic outcomes of darunavir/ritonavir-based therapy compared with atazanavir/ritonavir-based therapy in treatment-naive patients. Small changes in lipid parameters from baseline to weeks 12 and 48 were observed in both arms. At week 48, no clinically relevant differences between arms were noted for changes in any lipid parameter, fasting glucose level, or insulin sensitivity (Figure 2).

Integrase Strand Transfer Inhibitors

Three integrase strand transfer inhibitors are now available for clinical use: raltegravir, dolutegravir, and elvitegravir. Lipid profiles of these drugs were studied in registrational trials.

The Raltegravir Versus Efavirenz Regimens in Treatment-Naive HIV-1–Infected Patients: 96-Week Efficacy, Durability, Subgroup, Safety, and Metabolic Analyses (STARTMRK) study was a phase 3 noninferiority trial of a raltegravir-based regimen versus an efavirenz-based regimen, both in combination with fixed doses of tenofovir disoproxil fumarate/emtricitabine.[18] The analyses of fasting lipid levels at week 240 identified a significantly lower increase in serum triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol in comparison with baseline raltegravir versus efavirenz recipients. In addition, a higher percentage of patients required lipid-lowering medications in the efavirenz group during follow-up.

GS-236-0102, a phase 3 study, was designed to assess safety and efficacy of elvitegravir/cobicistat/emtricitabine /tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for treatment of naive patients. This is the first head-to-head single-tablet regimen study.[19]

Both the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and the efavirenz/emtricitabine/tenofovir disoproxil fumarate treatment groups displayed no change in baseline triglyceride concentration, although HDL cholesterol concentration increased more in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group than in the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate group. Increases in total cholesterol and LDL cholesterol concentrations were also greater with efavirenz/

TABLE 2

Expected Changes in Lipid Levels During Antiretroviral Therapy

Antiretroviral Class	Drug	Effect			
		Total Cholesterol	Triglycerides	HDL Cholesterol	LDL Cholesterol
NNRTIs	Nevirapine	↑	↓	↑	↑
	Efavirenz	↑	↑	↑	↑
	Etravirine	↑	↑	↑	No change
	Rilpivirine	No change	No change	No change	No change
NRTIs	Stavudine	↑	↑	↓	↑
	Zidovudine	↑	↑	↑	No change
	Lamivudine	↑	↑	↑	No change
	Abacavir	No change	No change	↓	No change
	Abacavir/lamivudine	↑	↑	↑	No change
	Abacavir/lamivudine/ zidovudine	↑	↑	↑	No change
	Didanosine	No change	↑	↓	No change
	Emtricitabine	↑	↑	↑	No change
	Tenofovir	No change	No change	No change	No change
IIs	Raltegravir	No change	No change	No change	No change
PIs	Indinavir	↑	↑	No change	↑
	Nelfinavir	↑	No change	No change	↑
	Saquinavir	↑	↑	↓	↑
	Lopinavir/ritonavir	↑	↑	No change	↑
	Fosamprenavir	↑	↑	No change	↑
	Atazanavir	No change	No change	No change	No change
	Darunavir/ritonavir	↑	↑	No change	↑
	Ritonavir (full dose)	↑	No change	No change	↑
Fusion/entry inhibitors	Enfuvirtide	No change	No change	No change	No change
	Maraviroc	No change	No change	No change	No change

HDL, high-density lipoprotein; II, integrase inhibitor; LDL, low-density lipoprotein; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

emtricitabine/tenofovir disoproxil fumarate than with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.[19]

GS-236-0103 compared elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate with atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate as an initial therapy for HIV-1 infection. At week 96, increases from the baseline in metabolic measures did not differ substantially between groups, with the exception of fasting triglyceride concentration.[20] These results support that total cholesterol and LDL cholesterol concentration levels are not increased in a boosted integrase inhibitor regimen, contrary to what was expected from boosted PIs.

The SPRING-2 trial is a phase 3, randomized, double-blind, non-inferiority study in treatment-naive adults infected with HIV-1. It compared dolutegravir with raltegravir, both given with coformulated tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudine; no significant changes in lipid profiles were shown in either treatment group (Figure 3).[21,22]

NNRTIs

Rilpivirine has recently been approved for the treatment of naive HIV-patients. The Rilpivirine Versus Efavirenz with Tenofovir and Emtricitabine in Treatment-Naive Adults Infected with HIV-1 (ECHO)/Rilpivirine Versus Efavirenz with Two Background Nucleoside or Nucleotide Reverse Transcriptase Inhibitors in

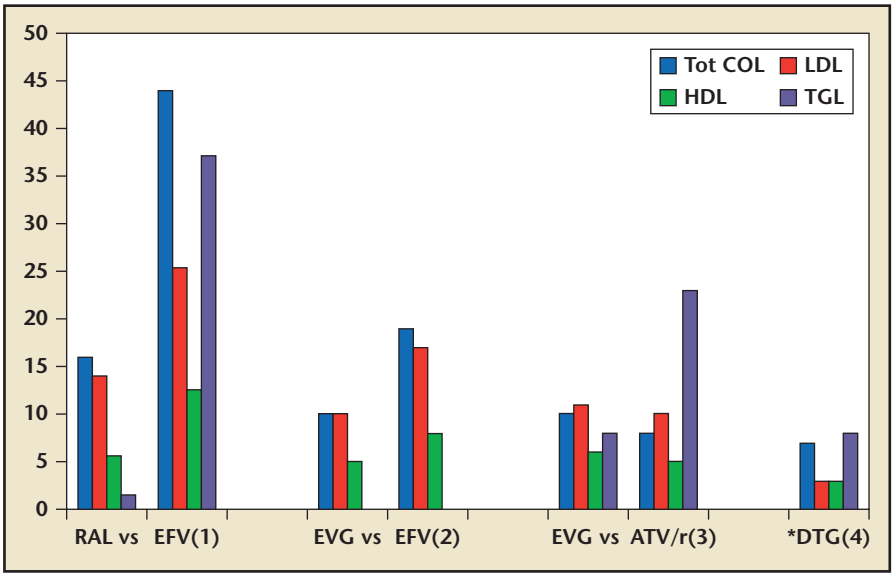


Figure 3. Integrase strand transfer inhibitor-induced mean changes in lipid (mg/dL). (1) Adapted from STARTMRK at week 240; sample size: n = 207 (RAL), n = 187 (EFV). (2) Adapted from GS-236-0102 at week 48; sample size: n = 348 (EVG), n = 352 (EFV). (3) Adapted from GS-236-0103 at week 48; sample size: n = 353 (EVG), n = 355 (ATV/r). (4) Adapted from SPRING-2 at week 48; sample size: n =403 (DTG). *Data on lipid changes of the antiretroviral drug (RAL) in comparison with DTG in SPRING-2 study are not available. ATV/r, atazanavir/ritonavir; COL, cholesterol; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAL, raltegravir; STARTMRK, Raltegravir Versus Efavirenz Regimens in Treatment-Naive HIV-1–Infected Patients: 96-Week Efficacy, Durability, Subgroup, Safety, and Metabolic Analyses; TGL, triglycerides. Data from Rockstroh JK et al,[18] Sax PE et al,[19] DeJesus E et al,[20] Raffi F et al,[22] and Tivicay US package insert.[27]

Treatment-Naive Adults Infected with HIV-1 (THRIVE) registration trial data showed that rilpivirine was associated with minimal changes from baseline in mean total cholesterol, LDL cholesterol, and triglycerides, and a small increase in HDL cholesterol through 96 weeks of treatment, whereas the comparator arm including efavirenz resulted in increases in all lipid parameters. Differences between arms were statistically significant at week 96 for all metabolic parameters.[23]

Etravirine is not approved for treatment in naive HIV-infected patients. The Etravirine (ETR) Shows Fewer Neuropsychiatric Adverse Events than Efavirenz (EFV) in Treatment-naive HIV-1 Infected Patients (SENSE) study was designed to evaluate the safety and preliminary efficacy of first-line etravirine versus the standard of care, efavirenz. The metabolic analyses at week 48 showed a larger mean increase in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in randomized patients on efavirenz in comparison with randomized patients on etravirine. An additional negative effect was found for abacavir/lamivudine when compared with tenofovir/emtricitabine (Figure 4).[24]

CC Chemokine Receptor 5 Antagonists

Maraviroc is the first approved CC chemokine receptor 5 antagonist. A post hoc analysis of the lipid data in the Maraviroc Versus Efavirenz in Treatment-Naive Patients (MERIT) study showed that, among patients with baseline dyslipidemia, maraviroc was associated with significant improvements in lipid parameters over 96 weeks when compared with efavirenz.[25]

Conclusions

Taking all these studies together, we can assume a progressive advantage in metabolic parameters is conferred with new drugs that were brought to market after 2009 when compared with older ones. Nevertheless, this lipid-friendly attitude does not necessary translate to a CHD risk reduction in HIV-infected patients.

It is important to underline that the impact magnitude of ART on cardiovascular risk, in absolute terms, is mediated by the underlying cardiovascular risk that is determined by both modifiable and unmodifiable factors. The recently published 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults[26] emphasized that lifestyle modification (eg, adhering to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion both prior to and in concert with the use of cholesterol-lowering drug therapies.

A post hoc analysis of the lipid data in the MERIT study showed that, among patients with baseline dyslipidemia, maraviroc was associated with significant improvements in lipid parameters over 96 weeks when compared with efavirenz.

Given that the most important risk factor for CHD is age, it can be assumed the improved lipid profile of new ART may not avoid the increased risk associated with improved life expectancy of patients with HIV. Therefore, CHD screening and management will continue to be of paramount importance in the long-term management of HIV-positive patients on ART.

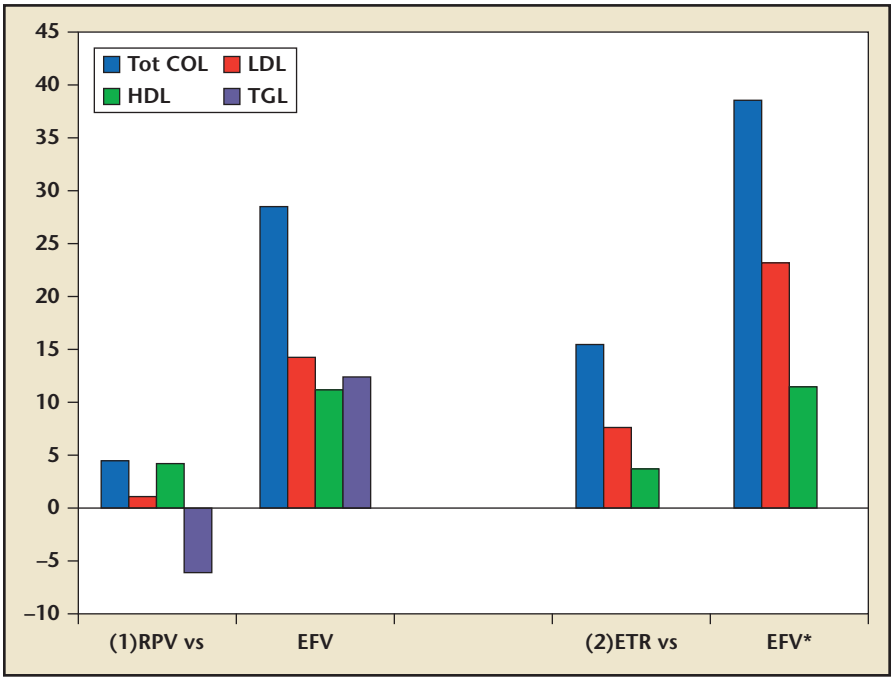


Figure 4. Non-nucleoside reverse transcriptase inhibitor-induced mean changes in lipid (mg/dL). (1) Adapted from ECHO and THRIVE study at week 96; sample size: n = 686 (RPV), n = 682 (EFV). (2) Adapted from SENSE study at week 48; sample size: n = 79 (ETR), n = 78 (EFV).*Data on changes in fasting triglyceride parameters are not available. COL, cholesterol; ECHO, Rilpivirine Versus Efavirenz with Tenofovir and Emtricitabine in Treatment-Naive Adults Infected with HIV-1; EFV, efavirenz; ETR, etravirine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RPV, rilpivirine; SENSE, Etravirine (ETR) Shows Fewer Neuropsychiatric Adverse Events than Efavirenz (EFV) in Treatment-naive HIV-1 Infected Patients; TGL, triglycerides; THRIVE, Rilpivirine Versus Efavirenz with Two Background Nucleoside or Nucleotide Reverse Transcriptase Inhibitors in Treatment-Naive Adults Infected with HIV-1. Data from Cohen CJ et al[23] and Fätkenheuer G et al.[24]

We support a rapidly changing paradigm of statin use in the general population. Initially offered as lipid-lowering agents to reach fixed cut-off goals of LDL cholesterol, statins were then used to reduce progression of vascular damage associated with coronary disease. More recently, according to 2013 ACC/AHA Guidelines, statins are extensively recommended at higher doses to those most likely to benefit. Future studies will allow us to understand the benefit of this more aggressive statin approach in an HIV setting. ■

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MAIN POINTS

- The initial research on coronary heart disease (CHD) in patients with human immunodeficiency virus (HIV) focused on the relationship between dyslipidemia associated with antiretroviral therapy (ART) and cardiovascular risk; it is widely accepted that metabolic disease in HIV develops at the intersection of traditional risk factors and HIV-specific contributors.
- Protease inhibitors and ART may impact CHD by inducing lipid abnormalities contributing to traditional, modifiable risk factors, in addition to having a direct toxic mechanism that may be related to cumulative or current exposure to a specific drug.
- The most important risk factor for CHD is age; therefore, it can be assumed the improved lipid profile of new ART may not overcome the increased risk associated with improved life expectancy of patients with HIV. CHD screening and management are of paramount importance in the long-term management of HIV-infected patients on ART.

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