Perspectives

Management of Dyslipidemia and Other Cardiovascular Risk Factors in HIV-Infected Patients: Case-based Review

Many HIV-infected patients have dyslipidemia and other cardiovascular risk factors prior to acquiring infection. Both HIV infection itself and antiretroviral therapy can cause or worsen lipid abnormalities. Management of dyslipidemia in the HIV-infected patient requires awareness of the effects of antiretroviral agents on lipid profiles, including potential sex- and race-related effects, and interactions between lipid-modifying agents and antiretroviral agents. This article uses individual case histories to illustrate the decisions encountered in treating HIV infection and dyslipidemia. The article is based on a presentation on management of dyslipidemia and other cardiovascular risk factors in HIV infection made by Judith A. Aberg, MD, at the International AIDS Society–USA Los Angeles CME program in February 2006.

Case 1: Combined Dyslipidemia

A 52-year-old Hispanic man with HIV infection diagnosed in the past month has a CD4+ cell count of 238/µL and plasma HIV RNA level of 62,000 copies/mL. A lipid panel shows total cholesterol level of 162 mg/dL, triglyceride value of 468 mg/dL, and high-density lipoprotein (HDL) cholesterol (HDL-C) of 24 mg/dL, and the patient has additional coronary heart disease (CHD) risk factors of cigarette smoking and family history of premature disease (father died of myocardial infarction at age 56 years).

Antiretroviral therapy should be initiated in this patient before addressing the cardiovascular risk factors. It is important to recognize the effects that HIV infection itself can have on lipid metabolism. For example, it has long been recognized that triglyceride level increases markedly with HIV disease progression, likely reflecting persistence of an inflammatory state as well as wasting. One early study showed an increase in mean triglyceride value from 91 mg/dL in non-HIV infected subjects to 166 mg/dL in HIV infection and 231 mg/dL in people with AIDS, with increases in triglyceride level occurring in half of the HIV-infected patients. Total cholesterol value decreased from 190 mg/dL in non HIV-infected patients to 157 mg/dL in patients with AIDS (Grunfeld et al, *Am J Med*, 1989). Data from a Multicenter AIDS Cohort Study (MACS) cohort indicate that low-density lipoprotein cholesterol (LDL-C), total cholesterol, and HDL-C levels decrease with HIV infection. Initiation of antiretroviral therapy is associated with increases in LDL-C and total cholesterol values and persistence of reduced HDL-C level (Figure 1; Riddler et al, *JAMA*, 2003).

Genotypic analysis shows the presence of the K103N resistance mutation, and it is thus decided to start the patient on antiretroviral therapy with tenofovir/lamivudine/ritonavir-boosted fosamprenavir. A lipid panel at 4 weeks shows no marked change in lipid profile. At 24 weeks, the patient has an HIV RNA level below 400 copies/mL and a CD4+ cell count of 416/µL; the lipid panel values show total cholesterol of 245 mg/dL, HDL-C of 18 mg/dL, and triglyceride of 872 mg/dL, with LDL-C not being calculated due to the high triglyceride level. After a 4-week trial of diet and exercise, there are no changes in lipid levels. Does it make sense to:

(1) order direct enzymatic assay to determine if LDL-C is elevated before prescribing lipid-lowering agents,
(2) start lipid-lowering therapy with a statin,
(3) start lipid-lowering therapy with a triglyceride-lowering agent, or
(4) switch the ritonavir-boosted fosamprenavir to ritonavir-boosted atazanavir?

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines indicate that total choles-

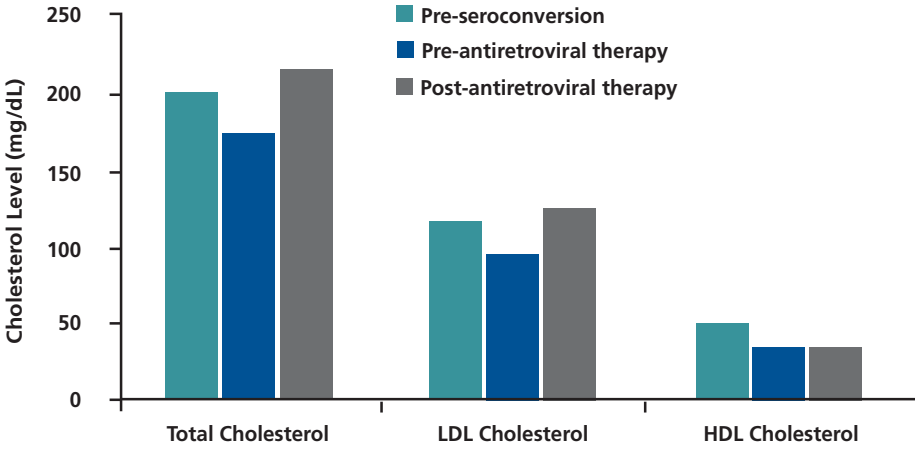

Figure **1**. Multicenter AIDS Cohort Study (MACS): Effect of HIV and treatment on cholesterol level. Total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol prior to HIV-seroconversion, before beginning antiretroviral therapy, and during antiretroviral therapy in the (MACS). Adapted from data in Riddler et al, *JAMA*, 2003.

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terol level of less than 200 mg/dL is desirable, HDL-C of 60 mg/dL or higher (in men) is protective, LDL-C less than 70 mg/dL is optimal, and triglyceride less than 150 mg/dL is normal. Pharmacologic options, beyond diet and exercise, for achieving lipid goals include statins, which act primarily to reduce LDL-C and total cholesterol level, and fibrates, which act to reduce triglyceride and increase HDL-C, as well as bile-acid sequestrants, ezetimibe, and niacin. Fish oil is also highly useful for improving triglyceride and other lipid measures. Concerns with statin therapy include risk for skeletal muscle and hepatic toxicity, risks for which are increased with combination of certain statins and fibrates. Additional concerns include potential drug interactions with antiretroviral agents.

The extremely high triglyceride level should be the first lipid target in this patient. It is important to note that quantitation of LDL-C is unreliable in the setting of very elevated triglyceride levels with commonly used methods of measurement. Ultracentrifugation is the reference standard for measuring LDL-C, but most laboratories use the Friedewald equation to calculate LDL-C (total cholesterol value – [HDL-C value + (0.20 × triglyceride level)]). A recent study assessing Friedewald equation results and direct enzymatic methods in HIV-infected patients showed that both methods were fairly accurate when triglyceride value was below 400 mg/dL (90% of results within 30 mg/dL and 32 mg/dL, respectively) and far less accurate when triglyceride was above 400 mg/dL (90% of results within 68 mg/dL and 120 mg/dL, respectively) (Evans et al, CROI, 2006). Overall, only 27% and 16% of results, respectively, were within 15 mg/dL when the triglyceride value was above 400 mg/dL. It was concluded that direct enzymatic methods are not more reliable than using the Friedewald equation and may offer no benefit over the latter approach when the triglyceride level is more than 400 mg/dL. Dr Aberg noted that since the current patient has elevated triglycerides and will require therapy to lower it, it makes sense to wait until there is response to this intervention before calculating or measuring LDL-C. Thus, statin treatment would not be used until it is determined whether LDL-C is elevated after triglyceride reduction.

Antiretroviral agents can affect triglyceride and other lipid levels. In a study assessing changes in lipid levels in non-HIV infected subjects, 5 days of administration of ritonavir-boosted lopinavir increased triglyceride value significantly (177 mg/dL) compared with atazanavir (131 mg/dL) or placebo (124 mg/dL), with no significant differences in total cholesterol, LDL-C, or HDL-C being observed. In another study, patients received stavudine/lamivudine with either nelfinavir or atazanavir; in those patients receiving nelfinavir, total cholesterol, LDL-C, and triglyceride values increased from baseline, with levels returning to near-baseline values after patients were crossed over to open-label atazanavir at 72 weeks (Figure 2; Murphy et al, CROI, 2003; Wood et al, *J Acquir Immune Defic Syndr*, 2004).

In another experience, 162 patients with hyperlipidemia on other antiretroviral therapy regimens (34% receiving lopinavir/ritonavir) were switched to ritonavir-boosted atazanavir as part of an early access program. After 6 months, total cholesterol level was reduced by 12%, LDL-C by 10%, and triglyceride by 18%, and HDL-C was increased by 3% (all statistically significant changes). Almost one-third of patients who were receiving lipid-lowering therapy were able to discontinue such therapy after the switch to ritonavir-boosted atazanavir.

With regard to therapeutic options to reduce triglyceride level, a study reported at the 2006 CROI showed that fish oil significantly reduced the median triglyceride level from 665 mg/dL to 362 mg/dL and that fenofibrate treatment also resulted in a reduction, from 694 mg/dL to 338 mg/dL (Gerber et al, CROI, 2006). The addition of fish oil to fenofibrate, or vice versa, significantly further reduced the median triglyceride level to 279 mg/dL from 377 mg/dL with either alone. After a total of 18 weeks of treatment with either and then both, median triglyceride had been reduced by 65%. Another recent study showed that niacin treatment resulted in median decreases of 24 and 8 mg/dL in total cholesterol level (median baseline value, 253 mg/dL), 30 and 19 mg/dL in non-HDL-C (median baseline level, 217 mg/dL), and 176 and 153 mg/dL in triglyceride level (median baseline value, 478 mg/dL) and median increases of 3 and 5 mg/dL in HDL-C (baseline 34.5 mg/dL) at 24 and 48 weeks, respectively (Dubé et al, International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 2005).

Since the patient had elevated triglyceride prior to starting fosamprenavir/ritonavir, and there are limited data on switching from a protease inhibitor

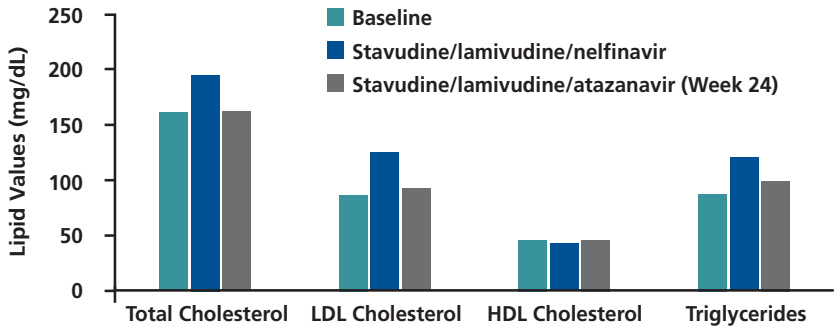

Figure 2. Total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride at baseline (008 entry), after treatment with stavudine/lamivudine and nelfinavir (044 entry), and 24 weeks after switching from nelfinavir to atazanavir (044 week 24). Adapted from data from Murphy, CROI, 2003; and Wood, *J Acquir Immune Defic Syndr,* 2004.

(PI), it was decided to start the patient on triglyceride-lowering therapy with fenofibrate. After 8 weeks, his total cholesterol level decreased to 206 mg/dL and triglyceride decreased to 342 mg/dL, and HDL-C increased to 28 mg/dL. LDL-C was calculated at 110 mg/dL. The patient's viral load remained undetectable and his CD4+ cell count was above 500/µL. The patient still is considered at high-risk for coronary heart disease, and his LDL-C still is therefore too high. Statin treatment should be considered to reduce the LDL-C.

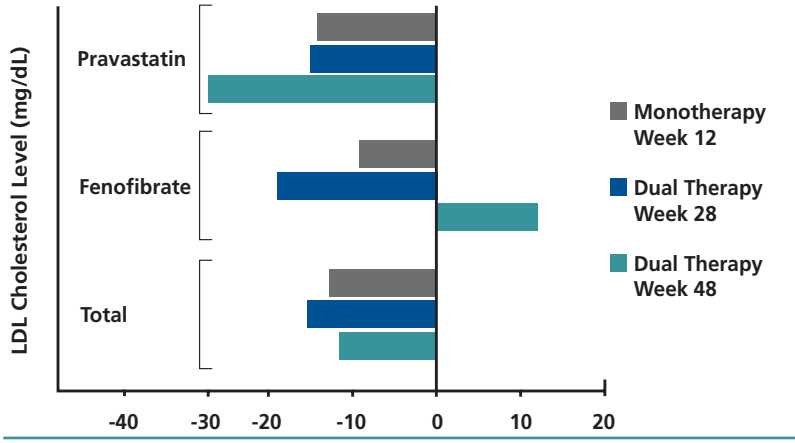

Figure **3**. Median change in low-density lipoprotein (LDL) cholesterol by initial randomized treatment with pravastatin alone and after addition of fenofibrate (pravastatin), with fenofibrate alone and after addition of pravastatin (fenofibrate); and for both monotherapies and both dual-therapy groups (total). Adapted from Aberg et al, *AIDS Res Hum Retroviruses*, 2005.

We evaluated the ability of pravastatin (40 mg) fenofibrate (200 mg), or the combination to bring hypercholesterolemic HIV-infected patients to lipid targets of LDL-C less than 130 mg/dL or less than 100 mg/dL if there were at least 2 additional coronary heart disease risk factors, triglyceride less than 200 mg/dL, and HDL-C greater than 40 mg/dL (Aberg et al, *AIDS Res Hum Retroviruses*, 2005). Prevastatin was selected on the basis of its better pharmacokinetic interaction with PIs (its levels decrease rather than increase in concomitant administration). All patients had LDL-C of 130 mg/dL or greater and triglyceride of 200 mg/dL or greater. With single-agent treatment, all 3 targets were reached by 3% of patients overall, including 5% of patients with pravastatin and 1% with fenofibrate. With dual-agent treatment, 10% of patients reached all 3 targets; the achievement rate of 16% in patients who started on fenofibrate and then added pravastatin was statistically significantly greater than the 7% achievement rate in patients starting on pravastatin and then adding fenofibrate. As suggested by these findings, sequencing of a statin and a fibrate in patients with elevated triglyceride may make a difference in LDL-C response. With reduction of triglyceride during fibrate treatment, there typically is an increase in LDL-C, as shown for the current study in Figure 3; when a statin is given first, some of the reduction in LDL-C achieved is subsequently lost during fibrate treatment.

Potential drug interactions between statins and PIs need to be considered in selecting treatment. In general, there is a low potential for interaction of PIs with fibrates and with the statins fluvastatin and pravastatin. Statin-fibrate combinations and atorvastatin pose greater risk and should be used with caution with PIs. Lovastatin and simvastatin should not be used with PIs. Examples of drug interactions include: an increase of atorvastatin area-under-the-concentration-time curve (AUC) of 347%, an increase of

Table **1**. Insulin-Sensitizing Agents Used in HIV Infection

Thiazolidinediones

↑ Subcutaneous fat 23 ± 10%; ↓ VAT 21 ± 8%[1]
↑ Leg subcutaneous fat; improved insulin sensitivity[2]
↓ Insulin levels; no effect on SAT or VAT[3]
↑ Subcutaneous fat, ↓ 2 hour OGTT 34 mg/dL[4]

Metformin

↓ Insulin and visceral fat[5,6]
↓ Waist circumference; weight loss[6]
↓ Waist circumference, SAT, VAT, TAT, ↓ 2 hour OGTT by 20 mg/dL but 32% gastrointestinal adverse events[4]

Metformin + thiazolidinedione

Not much data; potential for drug interactions

Comparison of rosiglitazone and metformin in AIDS Clinical Trial Study 5082

Both ↓ insulin; rosiglitazone ↑ LDL-D and ↓ HDL-C

With use of stringent toxicity monitoring and dose reduction algorithms

12 of 26 patients in metformin group underwent dose reduction or premature discontinuation of study drug (diarrhea was the most common etiology; elevated lactate above 2 times the upper limit of normal was uncommon)

4 of 25 patients in the rosiglitazone group underwent dose reduction or premature discontinuation of study drug

[1]Gelato et al, *J Acquir Immune Defic Syndr*, 2002; [2]Hadigan et al, *Am J Clin Nutr*, 2003; [3]Sutinen et al, *Antivir Ther*, 2003; [4]van Wijk et al, *Ann Intern Med*, 2005; [5]Saint-Marc et al, *AIDS*, 1999; [6]Hadigan et al, *Am J Clin Nutr*, 2003.

ACTG indicates AIDS Clinical Trials Group; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

simvastatin AUC of 3059%, and a decrease in pravastatin (which is minimally metabolized via the cytochrome P450 system) AUC of 50% when each is combined with ritonavir-boosted saquinavir; increases in atorvastatin AUC of 74% and simvastatin AUC of 505% when combined with nelfinavir; and increases in atorvastatin AUC of 588% and in pravastatin AUC of 30% when combined with ritonavir-boosted lopinavir. (Fichtenbaum et al, *AIDS*, 2002; Hsyu et al, *Antimicrob Agents Chemother*, 2001; Carr et al, ICAAC, 2000.

Case 2: Dyslipidemia, Diabetes, Hypertension

The patient is a 48-year-old African American woman receiving stavudine/lamivudine/lopinavir/ritonavir. She switched from efavirenz to ritonavir-boosted lopinavir because of intolerable dreams on the former. Her CD4+ cell count nadir was 156/μL. Her current HIV RNA level is below 50 copies/mL and CD4+ cell count is 497/μL. She has a history of diabetes for 4 years, hypertension for 8 years, and a family history of coronary heart disease and diabetes. Current medications consist of sulfonylurea, hydrochlorothiazide (HCTZ), and atenolol. Her blood pressure is 142/90 mm Hg; her body weight is 162 pounds, waist circumference 39 inches, and body mass index 28.5 kg/m^2. She has a 20-year history of 1 pack per day cigarette smoking. Her lipid values are as follows: total cholesterol 295 mg/dL, LDL-C 191 mg/dL, HDL-C 33 mg/dL, and triglyceride 355 mg/dL. Serum creatinine level is 1.0 mg/dL. Fasting blood sugar value is 128 mg/dL. She eats fast food occasionally, and is sedentary due to "bad knees."

With regard to control of blood glucose, an insulin-sensitizing agent should be used in the current patient. Table 1 summarizes findings of studies of glitazones and metformin in HIV-infected patients, with available data not suggesting any decisive advantages for use of one over the other. Although rosiglitazone appears to be generally better tolerated than metformin, it is associated with adverse effects on lipids, suggesting that use of metformin may be preferable in the current patient. However, although the frequency of elevated lactate with metformin does not appear to be high, the potential for such an adverse reaction in a patient also receiving stavudine should also be considered. It is also important to note that the US Food and Drug Administration (FDA) issued a warning in January 2006 that rosiglitazone and the rosiglitazone/metformin combination has been associated with macular edema; the effect is reversible when medication is discontinued.

With regard to lipid abnormalities, Figure 4 shows the greater increases in

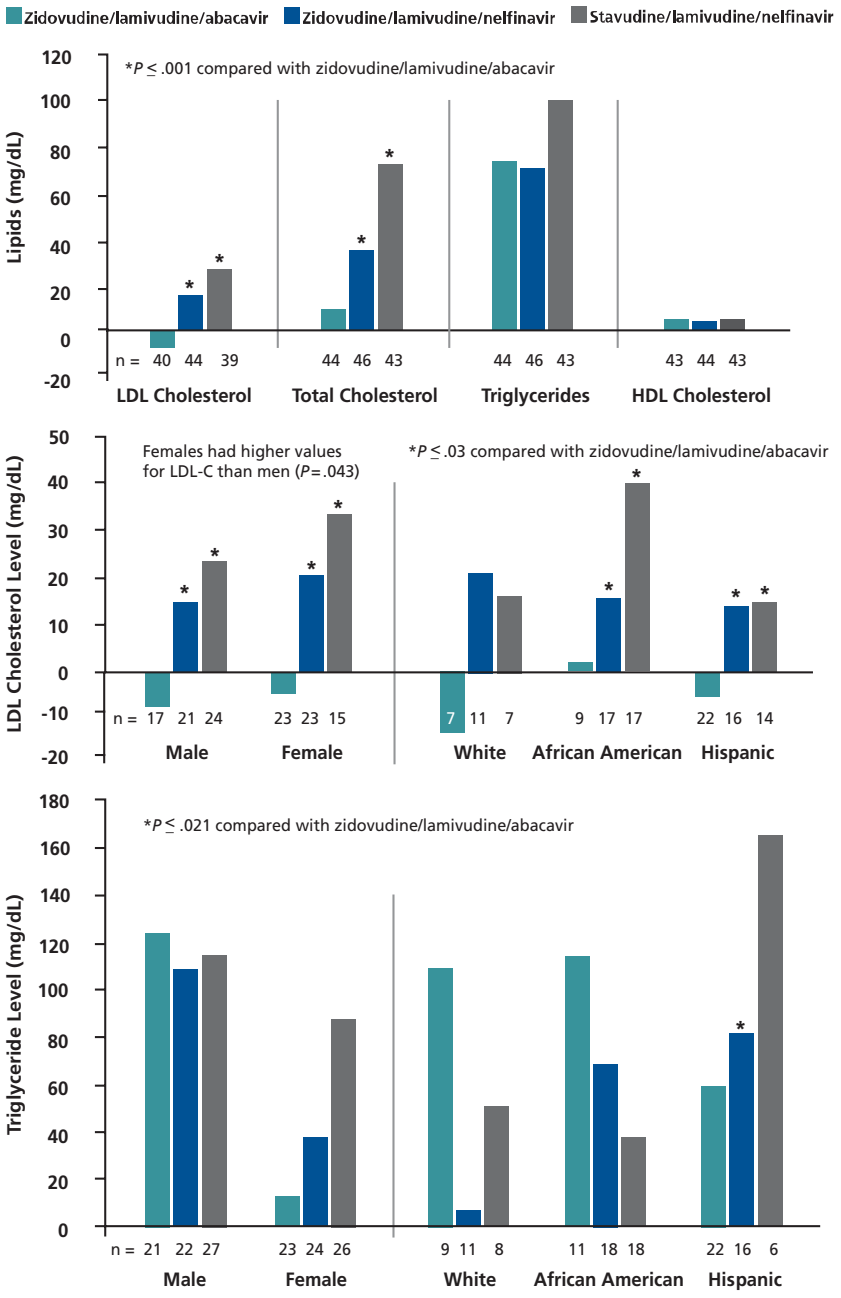

Figure **4**. Change in lipids at 96 weeks according to antiretroviral therapy regimen. Change in low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C; top). Change in LDL-C by sex and race or ethnicity (center). Change in TG by sex and race or ethnicity (bottom). Adapted from data from Kumar et al, *HIV Med*, 2006.

LDL-C and total cholesterol values over 96 weeks with regimens of zidovudine/lamivudine/nelfinavir and stavudine/lamivudine/nelfinavir compared with zidovudine/lamivudine/abacavir. Women had greater increases in LDL-C on these 2 regimens than had men, and a marked increase in LDL-C in African American patients was observed with the stavudine/lamivudine/nelfinavir regimen. Triglyceride level was raised more with zidovudine/lamivudine/abacavir and zidovudine/lamivudine/nelfinavir in men than in women, and was increased most by the stavudine/lamivudine/nelfinavir regimen in women. Whereas triglyceride level was raised more by zidovudine/lamivudine/abacavir in white patients and African American patients, it was raised more by stavudine/lamivudine/nelfinavir in Hispanic patients (Kumar et al, *HIV Med*, 2006). Figure 5 shows outcomes in the Gilead 903 study indicating very little change in triglyceride levels with tenofovir/lamivudine/efavirenz compared with large and significant increases at 48, 96, and 144 weeks with stavudine lamivudine/efavirenz (Gallant et al, *JAMA*, 2004). Subsequent switching from stavudine to tenofovir in the regimen resulted in significant reductions in triglyceride, LDL-C, and total cholesterol and a significant increase in HDL-C at 12 and 24 weeks after the switch (Suleiman et al, ICAAC, 2004). In the case of the current patient, it may make most sense to replace stavudine with tenofovir and to begin statin therapy to further reduce LDL-C.

With regard to blood pressure control, it should be noted that interactions between PIs and calcium-channel blockers have been observed. For example, one study has shown that ritonavir-boosted indinavir statistically significantly increases amlodipine AUC (89.8%) and diltiazem AUC (26.5%), with increases in median PR interval occurring with both antihypertensive agents (Glesby et al, *Clin Pharmacol Ther*, 2005). In the current patient and other African American patients with diabetes, it is preferable to use an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker for blood pressure control and to prevent HIV-associated or diabetic nephropathy.

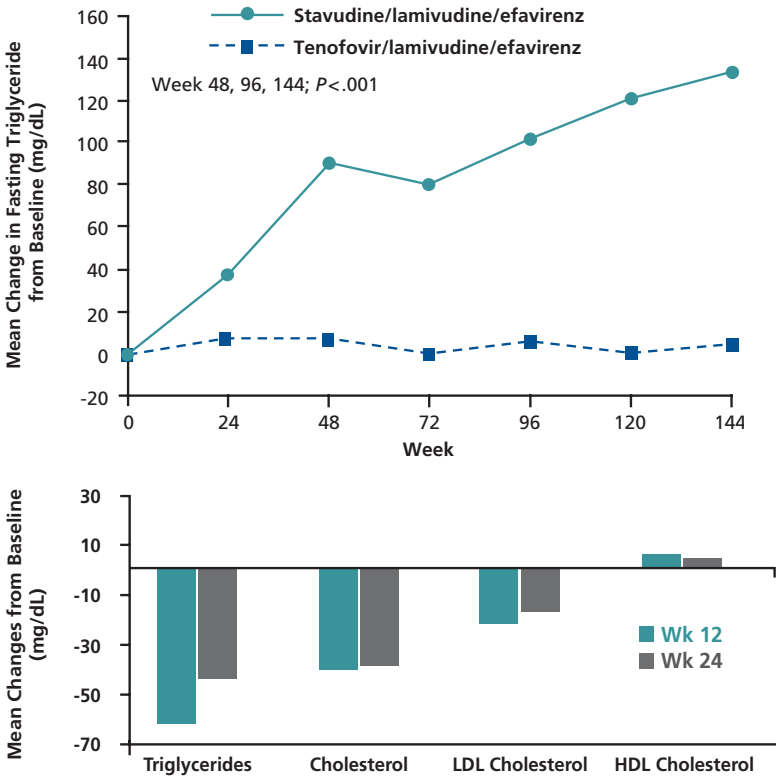

Figure **5**. Top: Mean change in fasting triglyceride (95% confidence interval) according to treatment in Gilead 903 study (top). Adapted from Gallant et al, *JAMA*, 2004. Bottom: Mean change in fasting lipids after substituting tenofovir for stavudine. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Adapted from Suleiman et al, ICAAC, 2004.

Presented in February 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Aberg in September 2006.

Financial Disclosure: Dr Aberg has received grants and research support from Berlex, Bristol-Myers Squibb, Gilead, Merck, and Pfizer. She has also served as a scientific advisor to Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, and Glaxo SmithKline.

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