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Perspectives

Telling Stories

Commentary

The International AIDS Society–USA

About This Issue

In this issue, 2 *Perspectives* articles are offered. First, Judith A. Aberg, MD, considers the impact of cardiovascular risk factors when managing HIV-infected patients in a case-based review adapted from her presentation at the International AIDS Society–USA Los Angeles CME Program in February 2006. Dr Hammer's *Perspectives* article is based on his presentation at the March 2006 International AIDS Society–USA course in New York, which examined the role of nucleoside analogue reverse transcriptase inhibitors in the backbone of antiretroviral regimens.

This issue also features a personal account of Dr David J. Malebranche's experience after a needle-stick injury in his residency in the *Telling Stories* section. Dr Peter L. Tenore closes the issue with a *Commentary* article, where he brings to light the lack of warning labels on Internet dating sites, which may promote unsafe-sex practices.

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Announcements

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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-

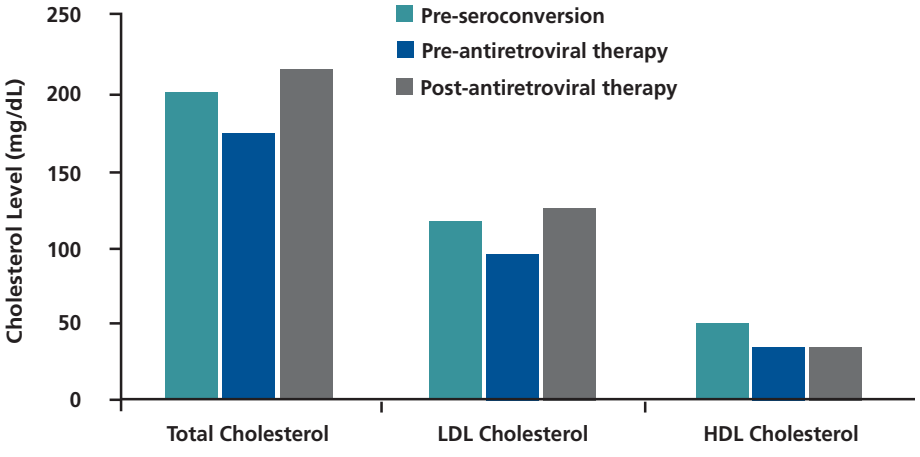

Figure **1**. Multicenter AIDS Cohort Study (MACS): Effect of HIV and treatment on cholesterol level. Total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol prior to HIV-seroconversion, before beginning antiretroviral therapy, and during antiretroviral 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

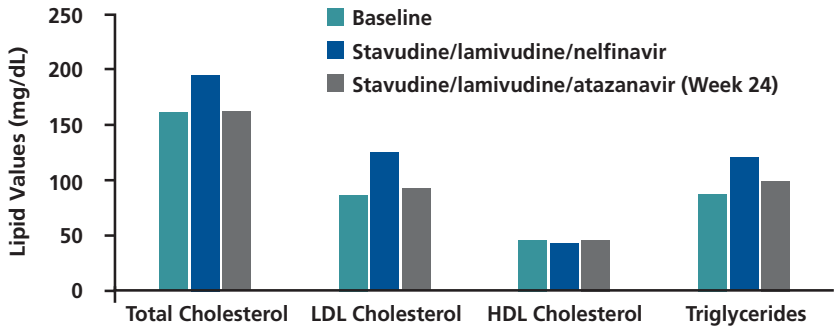

Figure 2. Total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride at baseline (008 entry), after treatment with stavudine/lamivudine and nelfinavir (044 entry), and 24 weeks after switching from nelfinavir to atazanavir (044 week 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.

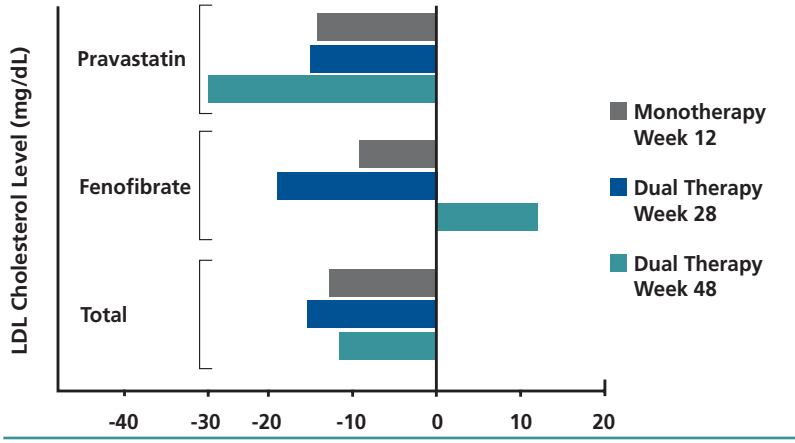

Figure **3**. Median change in low-density lipoprotein (LDL) cholesterol by initial randomized treatment with pravastatin alone and after addition of fenofibrate (pravastatin), with fenofibrate alone and after addition of pravastatin (fenofibrate); and for both monotherapies and both dual-therapy groups (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

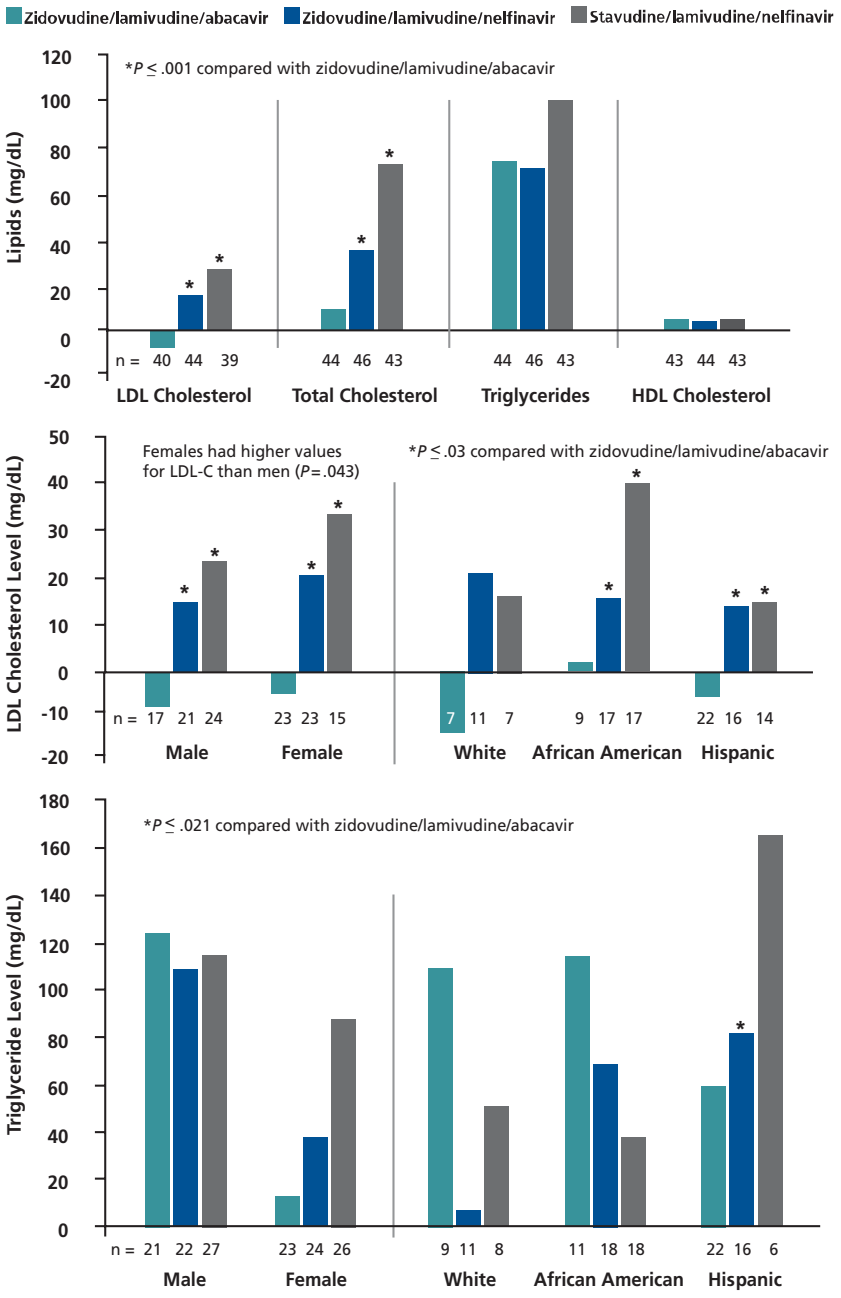

Figure **4**. Change in lipids at 96 weeks according to antiretroviral therapy regimen. Change in low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C; top). Change in LDL-C by sex and race or ethnicity (center). Change in 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.

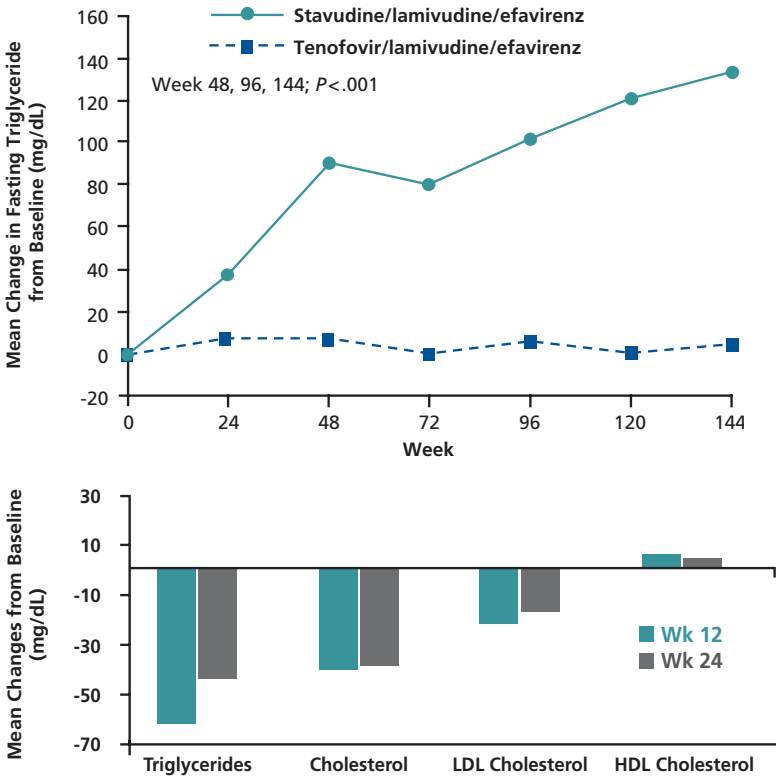

Figure **5**. Top: Mean change in fasting triglyceride (95% confidence interval) according to treatment in Gilead 903 study (top). Adapted from Gallant et al, *JAMA*, 2004. Bottom: Mean change in fasting lipids after substituting tenofovir for stavudine. HDL-C indicates high-density lipoprotein cholesterol;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

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Suggested Reading

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Perspective

Nucleoside Analogue Reverse Transcriptase Inhibitor Options: A Re-examination of the Class

The main options for dual nucleoside (or nucleotide) analogue reverse transcriptase inhibitors (nRTIs) as a component of initial antiretroviral therapy regimens are tenofovir/emtricitabine, zidovudine/lamivudine, and abacavir/lamivudine as fixed-dose combinations. Resistance to nRTIs can limit usefulness of many of the drugs in the class. Investigation of triple nRTI regimens has shown that zidovudine/lamivudine/abacavir does not provide benefits compared with dual nRTIs plus efavirenz and that others (tenofovir/lamivudine/abacavir and didanosine/lamivudine/abacavir) are associated with very high virologic failure rates. Further, 4-nRTI regimens are under investigation. The article summarizes a presentation on nRTIs made by Scott M. Hammer, MD, at the International AIDS Society–USA course in New York in March 2006. The original presentation is available as a Webcast at www.iasusa.org.

Dual nRTIs in Initial Treatment

The audience at the International AIDS Society–USA course in New York in March 2006 was posed the following question: When initiating therapy in an antiretroviral therapy-naive person with no other illnesses, and with normal laboratory results and drug-susceptible virus, which of the following dual nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) components (to be combined with nonnucleoside reverse transcriptase inhibitors [NNRTIs] or a protease inhibitor [PI]) do you choose:

(1) zidovudine/lamivudine as a fixed-dose combination (FDC)
(2) abacavir/lamivudine FDC
(3) tenofovir/lamivudine
(4) tenofovir/ didanosine
(5) tenofovir/emtricitabine FDC
(6) stavudine/didanosine
(7) abacavir/tenofovir
(8) zidovudine/didanosine

The majority of audience responders selected tenofovir/emtricitabine as an FDC (57%) and most of the remainder (28%) selected zidovudine/lamivudine, with these choices being fairly representative of current use patterns in US treatment centers. The use of tenofovir/emtricitabine as a component of initial treatment has been partly motivated by results of the Gilead 934 trial (Gallant et al, *N Engl J Med*, 2006). The trial showed that tenofovir/emtricitabine/efavirenz (n = 244) was associated with a significantly greater rate of reduction of plasma HIV RNA level to below 400 copies/mL at 48 weeks than zidovudine/lamivudine/efavirenz (n = 243; 84% vs 73%, respectively, $P = .002$).

Findings of interest with regard to resistance in this trial included the absence of the characteristic K65R tenofovir-associated resistance mutation in the tenofovir/emtricitabine group. It is also of interest that the characteristic M184V/I lamivudine-associated resistance mutation, which also occurs with emtricitabine, was less common in the tenofovir/emtricitabine group, adding to other observations that there is a lower frequency of M184V mutations with emtricitabine versus lamivudine in the setting of early virologic failure. It is very likely that the difference in virologic outcome with the 2 regimens is not related to any difference in intrinsic potency, but rather to better tolerability of the tenofovir/emtricitabine/efavirenz regimen, resulting in a smaller proportion of patients being discontinued from study treatment due to adverse events.

Discontinuation due to adverse events occurred in 4% of the tenofovir/emtricitabine arm versus 9% of the zidovudine/lamivudine arm, with anemia alone resulting in discontinuation of 6% of patients in the zidovudine/lamivudine arm. A nonrandomized substudy of this trial also showed greater loss of limb fat in the zidovudine/lamivudine group.

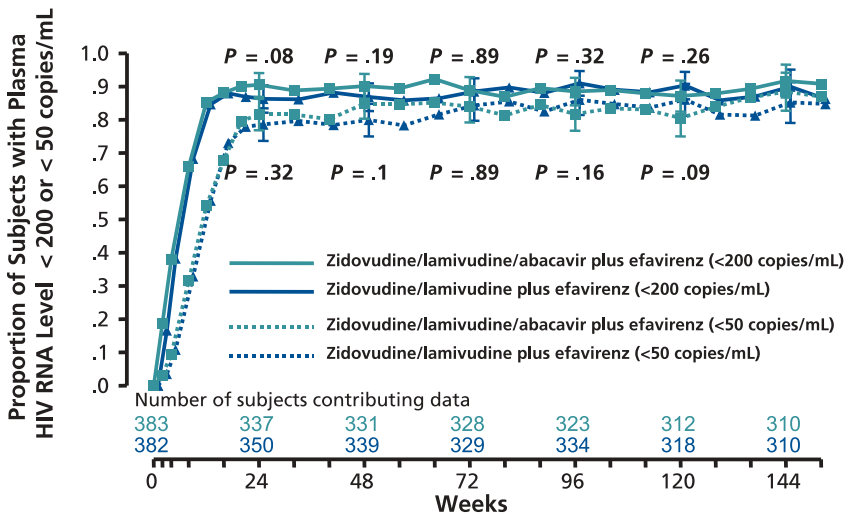

Figure **1**. Proportions of patients with suppression of plasma HIV RNA level to less than 200 copies/mL and less than 50 copies/mL by treatment on intent-to-treat analysis in ACTG A5095. Adapted from Gulick et al, *JAMA*, 2006.

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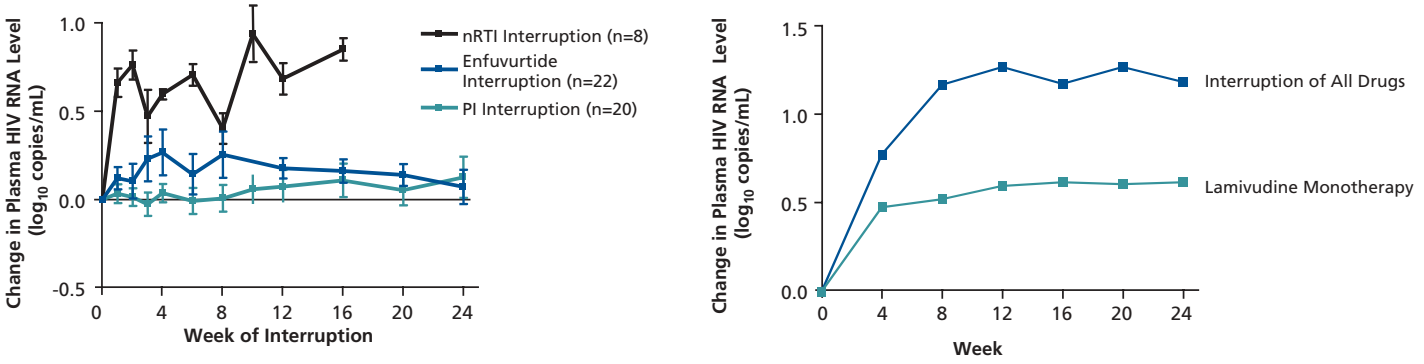

Figure **2**. Effect of partial treatment interruptions (n=53) on viral load in patients with resistance to interrupted drugs (left). Adapted from Deeks et al, *J Infect Dis*, 2005. Complete treatment interruption vs continuation of lamivudine alone in patients (n=50) with multi-drug resistant virus (right). Adapted from Castagna et al, *AIDS*, 2006. nRTI indicates nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; PI, protease inhibitor.

nRTI Resistance

Resistance mutations selected by nRTIs are listed in the International AIDS Society–USA Drug Resistance Mutations summary (Johnson et al, *Top HIV Med*, 2006). There is a high degree of cross-resistance within the nRTI class. For example, the K65R mutation is associated with cross-resistance among all the current nRTIs except zidovudine, and the thymidine analogue-associated mutations (TAMs) associated with zidovudine resistance, the codon 69-insertion complex, and the codon 151-complex can each confer cross-class resistance.

There are 2 principal mechanisms of nRTI resistance, and these mechanisms can interact to further alter susceptibility patterns (Clavel and Hance, *N Engl J Med*, 2004). In brief, nRTI resistance can occur via mutations in reverse transcriptase that interfere with the incorporation of the active nucleoside analogue form into the growing DNA; such mutations include the M184V or I and K65R mutations. Resistance can also occur via adenosine triphosphate (ATP)-mediated excision of the anti-retroviral nucleoside that would otherwise terminate elongation of the viral DNA chain. TAMs permit ATP to bind to reverse transcriptase, where the ATP molecule can excise the incorporated nucleoside analogue from the viral DNA. As noted in Table 1, the presence of TAMs can antagonize the K65R mutation, whereas the presence of M184V or K65R mutations, which result in decreased analogue incorporation, results in reduced zidovudine monophosphate excision and reduced zidovudine resistance.

Other Distinguishing Features of Dual nRTIs

Table 2 lists some defining characteristics of 3 commonly used dual nRTI options for combination with a PI or NNRTI in initial treatment. With regard to the inclusion of zidovudine/lamivudine given the results of Gilead 934, the combination continues to be widely used on the basis of individual choice and on the strength of the wealth of experience in using the combination. Advantageous features of the 3 combinations listed include the fact that each is available as an FDC. The tenofovir/emtricitabine combination is active against hepatitis B virus, providing an advantage in coinfected patients.

There has been concern about cumulative renal toxicity with tenofovir, especially given the serious toxicity observed with its related forerunner adefovir when given at high doses. Although serious renal toxicity concerns with tenofovir have not been raised by clinical trial data, there have been reports of tenofovir-related renal dysfunction in clinical experience and in Investigational New Drug (IND) safety reports. It is now recommended that calculated creatinine clearance and urinalysis results, as well as serum-creatinine level, be obtained at baseline in any patient starting tenofovir. In addition to decreased renal function at baseline, risk factors for renal dysfunction in patients receiving tenofovir include diabetes and lower CD4+ cell count.

With regard to nRTI-associated mitochondrial toxicity, the results of a recent study in a transgenic mouse model in cardiac tissue showed mitochondrial damage with zidovudine and stavudine and not with lamivu-

Table **1**. Mechanisms of nRTI Resistance

TAMs: M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N	M184V	K65R
Confer zidovudine resistance via zidovudine monophosphate excision	Confers lamivudine resistance via decreased lamivudine triphosphate incorporation	Confers nonzidovudine nRTI resistance via decreased analogue incorporation
Antagonize K65R	Decreases zidovudine resistance via decreased zidovudine monophosphate excision	Decreases zidovudine resistance via decreased zidovudine-monophosphate excision

nRTI indicates nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; TAMs, thymidine analogue-associated mutations.

dine (Lewis et al, *AIDS*, 2006). The deoxynucleotide-carrier molecule that is responsible for normal transportation of nucleotide triphosphates into mitochondria was overexpressed in the mouse model, resulting in reduplication of mitochondrial cristae. The addition of zidovudine or stavudine resulted in loss of cristae, amorphous deposits, and destruction of the mitochondria, whereas no such damage was observed when lamivudine was added. These findings indicate that selective transport of zidovudine and stavudine triphosphates into the mitochondria may be responsible for the greater toxicity observed with these 2 nRTIs. Abacavir has been discontinued in 5% to 8% of patients because of hypersensitivity in clinical trials. The hypersensitivity reaction is associated with the human leukocyte antigen (HLA)-B5701 haplotype.

Triple or Quadruple nRTIs?

Available data do not indicate that use of triple nRTIs is a beneficial strategy for initial treatment. The results of AIDS Clinical Trials Group (ACTG) A5095 showed that the combination of zidovudine/lamivudine/abacavir was inferior to dual-nRTI-plus-efavirenz regimens. However, the zidovudine/lamivudine/abacavir regimen is still considered an alternative in such settings as intolerance of or resistance to PIs or NNRTIs. The trial also showed no difference in virologic response between the regimens of zidovudine/lamivudine/abacavir plus efavirenz and zidovudine/lamivudine plus efavirenz, with no differences being observed in proportions of patients with suppression of plasma HIV RNA level to less than 200 copies/mL or less than 50 copies/mL (Figure 1) or time to first virologic failure among all patients or among those with baseline plasma HIV RNA level above or below 100,000 copies/mL (Gulick et al, *JAMA*, 2006).

Other studies have shown very high virologic failure rates (eg, 50% to 90%) with the triple nRTI regimens of tenofovir/lamivudine/abacavir and didanosine/lamivudine/abacavir. These regimens should not be used. The high virologic failure rates are not related to such factors as antagonism at the reverse transcriptase activity level, pharmacokinetic interactions affecting serum drug levels, or interference in intracellular phosphorylation of 1 or more of the nRTIs. Rather, failure is related to a low genetic barrier to resistance and increased likelihood of "convergent" resistance involving mutations to the component drugs, with the mechanism appearing to be lack of uniform distribution of the different drugs to target cells. This finding emphasizes the importance of achieving rapid, profound suppression of viral replication with drug combinations and of ascertaining such an effect in vivo. A study of the evolution of the M184V and K65R mutations in patients receiving tenofovir/lamivudine/abacavir in the TONUS trial used both bulk sequencing and clonal sequencing to detect minor variants in the viral population (Delaunay et al, *J Virol*, 2005). The study showed that: (1) M184V evolves more quickly than K65R; (2) the 2 mutations first appear on separate viral genomes on clonal analysis; and (3) the mutations converge on the same genomes over time. The findings emphasize that bulk sequencing cannot be relied upon to provide a complete picture of viral resistance, with minor variant detection being essential to understanding the dynamics of resistance mutation evolution within the total viral population.

The potential use of quadruple nRTI regimens remains under investigation. A recent small study comparing the quadruple nRTI regimen of zidovudine/lamivudine/abacavir/tenofovir with zidovudine/lamivudine/efavirenz showed similar rates of viral suppression to less than 50 copies/mL at 48 weeks in intent-to-treat analysis (67% vs 68%) and in on-treatment analysis (100% vs 98%; Moyle et al, *Antivir Ther*, 2006).

Residual Activity of nRTIs in the Context of Resistance: Treatment Interruption Studies

Recent findings on the strategy of structured treatment interruption (STI) of antiretroviral therapy are reviewed in the contribution by Dr Benson in this issue. In brief, STIs should not be part of antiretroviral therapy strategies in most settings according to currently available data.

Data from studies of nRTI interruption indicate that the agents possess residual activity in vivo despite the presence of nRTI resistance mutations, supporting the rationale for continuing treatment with or recycling these agents at later stages of treatment when full viral suppression cannot be achieved with available options.

For example, as shown in Figure 2,

Table **2**. Characteristics of Recommended Dual nRTI Options in Initial Antiretroviral Therapy

Regimen	Features	Differential toxicity concerns	Resistance mutations
Tenofovir/emtricitabine	FDC, once daily Both drugs active against HBV	Renal dysfunction — increased risk with diabetes, lower CD4+ cell count, or decreased renal function at baseline	M184V, K65R
Zidovudine/lamivudine	FDC, twice daily	Anemia, mitochondrial dysfunction	M184V, TAMs
Abacavir/lamivudine	FDC, once daily	Hypersensitivity reaction (HLA-B5701)	M184V, K65R

FDC indicates fixed-dose combination; HBV, hepatitis B virus; HLA, human leukocyte antigen; nRTI, nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; TAMs, thymidine analogue-associated mutations.

cessation of nRTI treatment in the setting of nRTI resistance nevertheless resulted in a marked increase in viral load, whereas discontinuation of the entry inhibitor enfuvirtide or PI treatment in the context of resistance had little effect on viral load.

As also shown in Figure 2, the continuation of lamivudine alone while stopping all other drugs in patients with resistance including the M184V lamivudine resistance mutation nevertheless resulted in a markedly smaller increase in viral load than did the stopping of all drugs, likely reflecting residual antiviral activity or a viral fitness defect conferred by the M184V mutation.

Conclusion

The leading dual nRTI options as components of NNRTI- or PI-based regimens (in the absence of drug resistance) are tenofovir/emtricitabine, zidovudine/lamivudine, and abacavir/lamivudine as FDCs. Triple nRTI regimens are not recommended, but zidovudine/lamivudine/abacavir can be considered in select circumstances and zidovudine/lamivudine/tenofovir is under study. The observation of very high virologic failure rates with some triple nRTI combinations underscores the need to understand the complexity of in vivo evolution of resistance. Quadruple nRTI regimens remain experimental.

Presented by Dr Hammer in March 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Hammer in October 2006.

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Telling Stories

Eye of the Needle

David J. Malebranche, MD, MPH

On a humid September night in New York City, crimson-colored blood trickled down the length of my finger and splashed against a cold grey sink basin. Betadine® and Hibiclens® soap washed over the tiny wound that had resulted from an unlucky combination of fatigue and carelessness. It was a solid-bore needle.

This was the beginning of my first inpatient hospital ward month of my second year of internal medicine residency; my first month as the resident in charge; and my first time as the captain of a team caring for a very sick group of 20 patients with AIDS. I was responsible for supervising 1 intern, 2 fourth year medical students, and 2 third year medical students. Our service was busy, and the days were filled with spiking fevers, lumbar punctures, blood cultures, and arterial blood gases. The year was 1997, and although HIV protease inhibitors had been available for more than a year, people were still dying at an incredible rate from complications related to HIV.

That particular evening, I had just returned from my continuity clinic in Queens and was doing chart rounds on our inpatient service, a daily resident ritual to ensure that nothing was missed on our complex patients before we went home for the night. This time I was by myself—my interns and students had already gone home after rounding with a covering resident, and I was more tired than usual after a long day of attending to both hospital and clinic responsibilities. It was 9:00 pm, and I desperately just wanted to go home and curl up in my bed like a child.

While reviewing our patients' developments over the day, I came across the chart of a 30-something-year-old man with AIDS, a T-cell count of 40/mL, and a HIV-1 RNA level of 400,000 copies/mL. He was also co-infected with hepatitis B and C viruses and had a history of past admissions for a multitude of opportunistic infections. Now the patient had unexplained fevers, despite being on appropriate antibiotic therapy for pneumonia. The previous team had placed a femoral central line because they were unable to get peripheral intravenous access. Unfortunately, it had not been changed in approximately a week, and femoral lines are notorious locations for iatrogenic infections.

I decided to replace the old central line, as it could explain his persistent fevers, and I feared that he would become septic overnight. Entering his room, I was fully prepared to persuade him that changing the line was necessary at that moment. To my surprise, I found him awake and resting, and to his surprise, he found me rounding late and wanting to address the issue immediately. I explained the situation to him, and he agreed to let me change his central line that night. His only request was that I place the new line in the opposite femoral vein from the one it was already in. He fully understood the increased potential for infection in the groin as opposed to subclavian or internal jugular lines, but he didn't like the idea of an obviously fatigued resident physician poking a needle into his neck at 9:00 pm in the evening. Smart man.

After obtaining consent, I prepped the area around his groin in a sterile fashion, felt for a pulse, and numbed the area with lidocaine. After inserting the finder-needle medial to his artery and getting a flash of dark, non-pulsatile blood, I inserted the guidewire and threaded the catheter in his vein. I was relieved to get the guidewire and catheter through, as this is the hardest part of central-line placement, and I was too tired to try numerous times. After making sure all 3 ports were working, I began sewing the line into place on his skin. I checked in with him periodically throughout the procedure to make sure he was doing okay, and he consistently reassured me that he was fine. Suddenly I felt a tiny bee sting on my left index finger. I closed my eyes, imagining that what I had just felt was just a resident's hypersensitivity when performing a procedure. It wasn't.

I knew I had stuck myself, but at the moment I was more concerned with how my patient would feel if he saw me go into a panic in front of him. So I calmly completed securing the central line, placed a protective seal over the catheter-insertion site, and disposed of the central-line kit. I left his bedside and stood in front of the room's sink basin, carefully removing my gloves. As I squeezed my index finger and saw my own blood trickle out, visions of solid-bore needles versus open-bore needles began dancing in my head. Solid-bore needlesticks were considered to have a much lower risk for HIV transmission than open-bore ones according to the medical literature, and I repeated this fact to myself in the hope that it would ring true for my situation as well. I put on a bandage after cleansing the pin-size wound, said good night to my patient, wrote a brief procedure note, and went back to my apartment. Denial was my middle name.

The next day I didn't mention the incident to the team during morning rounds, I merely told them that I changed the central line and broadened the patient's antibiotic coverage to include hospital-acquired skin infections. After resident morning report, I told my chief resident, a former infectious diseases fellow, about what happened, hoping he would simply reassure me that it was just a solid-bore needle and I would be fine. Instead, he recommended that I go to occupational health for an urgent evaluation and suggested that I start taking antiretroviral medications as soon as possible. Back then, the standard time frame for initiating HIV post-exposure pro-

phylaxis was within 48- to 72- hours of exposure in order to get the benefit documented in the current medical literature.

Reluctantly, I went to occupational health, had my initial blood work done, and began taking a post-exposure prophylaxis regimen of zidovudine 300 mg twice a day, lamivudine 150 mg twice a day, and indinavir 800 mg 3 times a day. I would be taking a total of 10 pills daily for the next 4 weeks, and the indinavir needed to be ingested on an empty stomach and with at least 1.5 liters of water daily to prevent kidney stones. Several of our patients took this regimen, so I knew it was good for slowing down progression of HIV, and I was hopeful that the drugs would prevent my seroconversion without major side effects.

I resumed my duties as resident for that month, but with the added burden of taking HIV medications daily, on top of my patient care, teaching, and supervising responsibilities. I saw my patients, rounded with my intern, guided my third and fourth year medical students to the best of my abilities, and took each and every pill I was supposed to without missing a dose, as if my life depended on it—and in a way, it did. Headaches, fatigue, and a persistent sense of nausea with a metallic taste in my mouth did not leave me for the entire month. Ice cold bottles of Evian® water became my best friends and worst enemies. I could appreciate the irony of my situation: a resident physician who encouraged patients living with AIDS to adhere to their medications now had to take these very same medications while providing care to them.

September 1997 was undoubtedly the most difficult month during my 3 year residency, and the one that taught me the most about being a patient. Six months after that incident, my tests for HIV and hepatitis B and C viruses were all negative, and have remained so to this very day. But that wasn't the point. During those 28 days, I woke up each morning wondering how these strange medications that were causing me to feel ill could actually be the same ones preventing me from contracting HIV. In theory, it was easy to write a prescription, hand it to a patient, and tell him or her to take a medication and watch out for certain side effects. It was quite another thing to actually take these medications myself out of necessity and experience their side effects on a daily basis. I was also getting a glimpse into a month in the life of those living with HIV taking these medications, and the perseverance and strength required to maintain one's physical and mental health while doing so. Their lives do depend on it.

The whole situation made me realize that "compliance" is a funny word in the medical profession. In more politically correct terms, we call it "adherence," and given recent advancements allowing people with HIV to take 1 pill a day for their entire regimen, talk of "compliance" may soon fall out of style. In Webster's dictionary, compliance is defined as "the ability or process of yielding to changes in pressure without disruption of structure or function" or "the process of complying with a regimen of treatment." Prior to September 1997, I had no concept of what compliance was, except for the pejorative labels of "non-compliant" that often pepper our patients' charts when describing their reluctance to do what we as medical providers tell them to. If I had been honest with the occupational physician at my last visit, she perhaps would have called me non-compliant because I threw out the final 4 pills I was supposed to take to complete my month of post-exposure prophylaxis. And according to definitions of "complying with a regimen of treatment," maybe I was. My rationale for throwing out those final pills was that I wanted to enjoy a movie that evening without feeling nauseated. Is that really so "non-compliant?" Even if I didn't take those final 4 pills, I saw myself as actually being compliant as noted by Webster's first definition of the word. I yielded to the pressure of having to take medications for that month, and was able to maintain the structure of functioning as a resident for the sake of my patients, my team, and perhaps most importantly, myself.

Many people living with HIV are compliant every day in this sense of the word, yielding to the physical, social, and emotional pressure of being diagnosed with a terminal condition, yet continuing to function productively every day in society while on these medications. I was only able to be this "compliant" because I had a good role model who allowed me to replace his central line late that September evening when he felt sick, even though he could have easily refused the procedure until the next morning. A small, solid-bore needle showed me what it was like to walk in his shoes, even if only for a month. And for that, I am eternally grateful.

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Commentary

Internet Sex and Dating Sites Need Warnings

For this issue's Commentary column, Peter L. Tenore, MD, discusses risk for infection with HIV or acquisition of sexually transmitted diseases associated with the use of the Internet to find sexual partners and presents results of an informal survey to determine whether Internet sites used to find sexual partners provide warnings about sexually transmitted diseases and HIV. He also calls for the operators of such sites to add warnings to their sites.

The Internet is emerging as a potential risk factor for HIV and sexually transmitted disease (STD) transmission, notably pornographic Web sites and dating sites that cater to users seeking sexual partners. Users of these sites may be at higher risk for infection with HIV and STDs. In a study of 4507 individuals who use the Internet to find sexual partners, McFarlane and co-workers noted that young adults 18- to 24-years-old underwent significantly less STD and HIV testing than their older counterparts, indicating that young adults "may be at significantly greater risk for STDs than their peers who do not seek sex partners online." The authors state there is an urgent need for online "sexual health promotion.[1]"

A Centers for Disease Control and Prevention (CDC) study of 544 women reporting sex with partners found via the Internet showed a higher number of total lifetime partners and suboptimal condom use, concluding that the Internet has the "potential to spread STDs or HIV with even greater efficiency than ever before imagined," and that "this population needs to be recognized and targeted with STD and HIV education and prevention efforts.[2]"

Pornographic Web sites are widespread on the Internet, as evidenced by their income generation of more than $900,000 yearly in the US. Investigating a gay male population, Kendall concluded that pornography undermines safer sexual practices.[3] In a study of 986 sexually active men, He and coworkers showed that viewing pornography correlated with the high-risk activity of having multiple sexual partners and that 78% of subjects never used condoms.[4] The danger associated with the high-risk sexual behaviors depicted on these Web sites is underscored by recent reports of HIV seropositivity in the adult film industry.[5]

We wished to determine if opening pages for sites that promote high-risk or unprotected sexual activity provide any readily visible health warnings regarding the potential for HIV and STD transmission. During a 10-day period, working online for 10 minutes per day, we reviewed the opening screens of adult Web sites and Internet dating Web sites servicing those seeking sexual partners. Sites were not entered, as our interest was in the opening pages. The opening screens usually have links to other similar sites that can be reached in seconds, making it simple to view a great deal of sexually explicit material in a short time. Typically, opening screens demonstrated frontal nudity with thinly-veiled, unprotected, high-risk sexual behavior, often with multiple partners, and enticement to use a credit card to pay to enter the Web site for more explicit images. Three or 4 sites per day were viewed for a total of 39 opening screens. Opening screens were examined for health advisories. In no case was any information regarding the risks of contracting HIV or STDs given on the opening screens. There was no information on risk-reduction behavior, condom use, the potential danger of HIV and STD transmission, and there were no health advisories at all.

Given the magnitude of morbidity and mortality caused by HIV in our society, the absence of health warnings seems an obvious omission of important information that should be read-ily available to Internet users. In the March 2004 edition of the *International Journal of STD and AIDS*, Green perused 8 "popular" pornographic Web sites in detail, from opening page to entering the sites, to determine "whether or not safer sex messages and/or condom usage were included." He noted that "not a single one of the Web sites' home pages contained written warnings to the viewing public of any sort about HIV/AIDS and/or the advisability of safe sex," and concluded that "Internet pornography does not consistently contain messages or present visual images supporting a safer sex message.[6]"

Given the increased risk for HIV and STDs inherent in the behaviors implicitly encouraged by Internet dating and pornographic Web sites, the number of HIV-infected individuals in the adult film industry itself, and the absence of health awareness information in opening screens of these sites, the potential for excess HIV and STD transmission should be recognized. The medical community should take steps to communicate the dangers of high-risk activity to the individuals involved in the production of these Web sites and point out the importance of appropriate health advisories that are easy to identify on the opening screens. Just as the tobacco industry prints health advisories on their products, and restaurants post advisories on the potential dangers of alcohol in pregnancy, it would be prudent for Internet sex-oriented sites to consider similar actions in a good-faith effort to promote better health for users of those sites.

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The Albert Einstein College of Medicine of Yeshiva University methadone clinics provide substance abuse care to some 3500 opiate-dependent patients in 10 clinics in Bronx, NY. Full services for HIV-infected individuals, including medical care, substance abuse treatment with methadone and other modalities, and psychiatric services are provided. HIV and STD transmission information and the need for risk-reduction are consistently reinforced by specific caseworkers dedicated to this topic.

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2001. Available at http://www.icmje.org. Accessed June 24, 2003.

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