

# Topics in HIV Medicine®

A publication of the International AIDS Society–USA

## Perspectives

Solid-Organ Transplantation in HIV-Infected Patients  
in the Potent Antiretroviral Therapy Era 73

*Michelle E. Roland, MD*

*Findings in Transplant Recipients in the Potent Antiretroviral Therapy Era • Special Clinical Considerations in HIV-infected Patients • Prospective Study in Transplantation*

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Substance Use Disorders in HIV-Infected Patients:  
Impact and New Treatment Strategies 77

*David A. Fiellin, MD*

*Alcohol • Cocaine • Opioids*

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Initiation of Antiretroviral Therapy: Implications of  
Recent Findings 83

*Michael S. Saag, MD*

*When to Initiate Therapy • Considerations in Selecting the Initial Regimen: Recent Findings • Results of Other Initial Therapy Studies*

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Diagnosis and Management of Body Morphology  
Changes and Lipid Abnormalities Associated With  
HIV Infection and Its Therapies 89

*David A. Wohl, MD*

*Body Morphology Changes • Lipid Abnormalities*

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The International AIDS Society–USA

## About This Issue

This issue features 4 *Perspectives* articles based on presentations from the International AIDS Society–USA (IAS–USA) continuing medical education courses held in Los Angeles, Atlanta, New York, and Chicago in February, March, and April 2004. Michelle E. Roland, MD discussed greater prospects for success in liver and kidney transplantation in HIV-infected patients brought about by improvements in antiretroviral therapy, opportunistic infection prophylaxis, and antirejection treatment. David A. Fiellin, MD reviewed new treatment strategies—both medication and counseling treatments—for alcohol, cocaine, and opioid dependencies in patients with HIV infection. Michael S. Saag, MD reviewed new findings regarding the timing and selection of initial antiretroviral regimens, many of which were presented at the 11th Conference on Retroviruses and Opportunistic Infections. Much of these new data were also considered by the IAS–USA panel in its development of 2004 recommendations for treatment of adult HIV infection published in the July 14, 2004, issue of the *Journal of the American Medical Association*. A reprint of this report will appear in the September/October issue of *Topics in HIV Medicine*. Finally, David A. Wohl, MD outlined strategies for diagnosing and managing body morphology changes and lipid abnormalities in HIV-infected patients on antiretroviral therapy.

## Topics in HIV Medicine®

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Recent Findings 83

*Michael S. Saag, MD*

Diagnosis and Management of Body Morphology  
Changes and Lipid Abnormalities Associated With  
HIV Infection and Its Therapies 89

*David A. Wohl, MD*

## Announcements

Guidelines for Authors and Contributors 95

Subscription Request Form 96

Educational Programs of the  
International AIDS Society–USA 97

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## Perspective

# Solid-Organ Transplantation in HIV-Infected Patients in the Potent Antiretroviral Therapy Era

*Improvements in antiretroviral therapy, opportunistic infection prophylaxis, and antirejection treatment have made solid-organ transplantation a potential option for HIV-infected patients. Preliminary experience in a small group of kidney and liver transplant recipients suggests that CD4+ cell counts and plasma HIV RNA level suppression can be maintained. As few opportunistic infections have been seen, a history of some opportunistic infection conditions may not be a contraindication to transplantation; this question is under investigation. Kidney graft rejection rates appear to be higher in HIV-infected patients, but one-year patient-survival and graft-survival rates appear to be similar to those in HIV-uninfected populations. A large multicenter study of the safety and efficacy of kidney and liver transplantation in HIV-infected patients is under way. Findings from this study should help to provide guidance in achieving optimal outcomes in this population. This article summarizes a presentation by Michelle E. Roland, MD, at the February and April 2004 International AIDS Society–USA courses in Atlanta, Los Angeles, and Chicago.*

HIV-infected persons traditionally have not been considered to be good candidates for solid-organ transplantation. The poor life expectancy associated with HIV disease prior to the advent of potent antiretroviral therapy motivated the decision to use scarce donor organs in patients with better prognoses. Further, there has been understandable concern over the potentially dangerous effects of posttransplantation immunosuppressive therapy in patients with HIV disease. A survey of US transplantation centers published in 1998 showed that only 9% and 5% of responding centers would consider HIV-infected patients with end-stage renal disease for cadaveric and living-donor transplantations, respectively. However, with the improved survival and clinical status of HIV-infected persons in the current treatment era, solid-organ transplantation is more frequently being considered and performed in such patients.

Recognition of the role of immune activation in HIV disease pathogenesis has also raised the possibility that immunosuppressive therapy may provide benefit rather than necessarily contributing to more rapid HIV disease pro-

gression in transplant recipients. Indeed, immunosuppressant drugs may exert antiviral effects, whether by reducing cellular targets for the virus, via direct antiviral effects (eg, cyclosporine, which appears to interfere with HIV gag processing), or through potentiation of antiretroviral drug activity (eg, mycophenolate mofetil interactions with nucleoside reverse transcriptase inhibitors [nRTIs]). All of these factors have contributed to interest in formal study of transplantation outcomes in HIV-infected patients and identification of patient characteristics that may help to achieve optimal outcomes.

## Findings in Transplant Recipients in the Potent Antiretroviral Therapy Era

Published information on HIV-infected transplant recipients in the pre-potent antiretroviral therapy era consists of case reports and case series of anecdotal experiences with varied results. In these reports, baseline characteristics and outcomes with regard to such HIV disease factors as CD4+ cell counts, HIV RNA levels, and opportunistic infection frequency and type generally are poorly defined. This early experience also does not reflect improvements in opportunistic infection prophylaxis and antirejection therapy that have occurred in recent years.

At the XIV International AIDS Conference in Barcelona in 2002, Dr Roland and colleagues first reported on the largest group of HIV-infected transplant recipients studied to date (Roland and Stock, *Transplantation*, 2003). The report included analysis of patients prospectively enrolled in an ongoing pilot multicenter transplantation study and retrospective review of patients from study transplant centers that used the same protocol for transplantation as centers in the ongoing study.

For the purposes of this analysis, patients were defined as “eligible” — those who met the study criteria for eligibility — and “ineligible.” Eligibility criteria included absence of history of opportunistic infection; CD4+ cell counts greater than 200/μL in kidney transplant recipients and greater than 100/μL in liver transplant recipients; and plasma HIV RNA levels below detection limits using ultrasensitive assays in kidney or liver recipients, or intolerance to antiretroviral therapy but predicted ability to achieve viral suppression posttransplantation in liver recipients.

Among the 45 eligible patients, 26 received kidney transplants and 19 received liver transplants. Eight patients were considered ineligible because of elevated HIV RNA level, low CD4+ cell count, history of opportunistic infection or neoplasm, or incompletely evaluated altered mental status. Among the eligible subjects, 92% of kidney recipients and 95% of liver recipients were men and the median ages of kidney and liver recipients were 45 and 43 years, respectively. Among the kidney recipients, 54% were African American, 42% were white, and 4% were Asian. Among the liver recipients, 79% were white, 11% were Hispanic, 5% were African American, and 5% were Asian. Median baseline CD4+ cell counts were 441/μL (range, 200-1054/μL) in kidney recipients and 280/μL (range, 103-973/μL) in liver recipients. Liver

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recipients had a range of HIV RNA levels of below 50 to 115,776 copies/mL, with a median below 50 copies/mL.

The results are summarized in Table 1. Median follow-up was 314 days. CD4+ cell counts were maintained and HIV RNA levels largely remained suppressed, with levels below 50 or 75 copies/mL maintained in the vast majority of patients. Two kidney recipients and 4 liver recipients died during follow-up. Of the 2 kidney recipients who died, one had an ischemic bowel episode and enterococcal sepsis 6 months after transplantation and the other developed staphylococcal sepsis 2 months after returning to dialysis after chronic rejection. Of the 4 liver recipients who died, one died with recurrent hepatitis C virus (HCV) infection 15 months after transplantation, one from postoperative pancreatitis, and one from *Rhizopus cavernous sinus* thrombosis, an uncommon posttransplantation or HIV-associated complication, 4.5 years after transplantation. The fourth patient died from a rejection episode. The patient was taking very low-dose immunosuppressant therapy because of pharmacokinetic interaction with his protease inhibitor (PI) treatment; however, when he later was put on an antiretroviral drug holiday, that information was not communicated to the transplant physicians, and the patient was thus left virtually without immunosuppressant therapy.

Opportunistic infections were infrequent: a liver transplant patient who died from recurrent HCV infection developed cytomegalovirus (CMV) esophagitis at a relatively high CD4+ cell count of 200/μL, and a kidney transplant recipient with diabetes mellitus developed candidal esophagitis, which was easily managed.

The rejection rate of 38% among kidney recipients is relatively high; additional follow-up in this cohort has shown even higher kidney rejection rates (approximately 70%), and the explanation for the high rate of rejection remains uncertain. Nevertheless, as shown in Table 2, patient survival rates and graft survival rates in this small cohort of patients are at least consistent with that observed at 1 year among patients in the United Network of Organ Sharing (UNOS) database. Among the ineligible patients, 2 with very advanced HIV dis-

**Table 1. Outcomes of Transplantation in 45 HIV-Infected Patients (26 Kidney Recipients, 19 Liver Recipients)**

<b>Median follow-up</b>	314 days (range, 3-1696)
<b>Deaths</b>	2 kidney recipients 4 liver recipients
<b>Opportunistic complications</b>	1 kidney recipient (Candida esophagitis) 1 liver recipient (cytomegalovirus esophagitis)
<b>CD4+ cell count, median (range)</b>	
Kidney recipients	Baseline: 441/μL Posttransplantation: 436/μL (3-975/μL)
Liver recipients	Baseline: 280/μL Posttransplantation: 218/μL (110-992/μL)
<b>Plasma HIV RNA, median (range)</b>	
Kidney recipients	Baseline: <50 copies/mL Posttransplantation: <50 copies/mL (50-533 copies/mL)
Liver recipients	Baseline: <50 copies/mL Posttransplantation: <50 copies/mL (<50-9600 copies/mL)
<b>Retransplantation</b>	1 liver recipient (small-for-size graft lesion)
<b>Additional graft loss</b>	3 kidney recipients (2 rejection, 1 thrombosis)
<b>Total rejection</b>	38% of kidney recipients 21% of liver recipients

ease died shortly after transplantation, one (ineligible because of undiagnosed HIV disease and a low CD4+ cell count) with *Mycobacterium avium* complex (MAC) disease and progressive multifocal leukoencephalopathy (PML) and the other (ineligible because of incompletely evaluated altered mental status) with PML alone. The 2 cases of PML in this setting is troubling, and the condition is considered an exclusion criterion for transplantation in the ongoing study. In 2 patients who were ineligible because of history of opportunistic infection, no recurrences were observed; one had a history of *Pneumocystis carinii* pneumonia (PCP; now named *Pneumocystis jiroveci* pneumonia) and CMV disease and another had a history of Kaposi's sarcoma and CMV disease. On the basis of these observations and other anecdotal experience, the ongoing study is now permitting enrollment of patients with histories of many opportunistic diseases. In other patients considered ineligible because of CD4+ cell counts just under the inclusion criteria or very low detectable HIV RNA levels, CD4+ cell counts were at least maintained and HIV RNA levels were well controlled.

Thus, the overall findings in both the eligible and ineligible patients indicate that in carefully selected patients, baseline immunologic and virologic values can be maintained and that opportunistic complications are infrequent; they also suggest that progression of HIV disease does occur in those patients with advanced disease.

Updated information is available from a group of 24 patients treated at the University of California San Francisco (UCSF), consisting of patients included in the above analysis and patients subsequently enrolled in the pilot multicenter study. Of these 24 patients, 14 were kidney recipients, 9 were liver recipients, and 1 received both organs. Four patients (17%) have a history of opportunistic infection (CMV disease, MAC, cryptococcosis, and Kaposi's sarcoma); 4 of the kidney recipients (29%) and 4 of the liver recipients (40%) have HCV coinfection. Median follow-up is 480 days (range, 8-1254 days). Two patients have died, one from recurrent HCV infection as mentioned above, and another (kidney recipient) from congestive heart failure.

No new AIDS-defining opportunistic infections have been observed. Overall,

**Table 2.** Patient and Graft Survival in Current Cohort\* Compared With 1-year Outcomes in United Network of Organ Sharing (UNOS) Database

	Current HIV cohort	UNOS database, 1-year rates
<b>Patient survival</b>		
Kidney recipients	92% of all recipients; 91% at 1 year (n=11)	94.8% deceased donor 97.6% living donor
Liver recipients	79% of all recipients; 92% at 1 year (n=12)	87.9%
<b>Graft survival</b>		
Kidney recipients	85% of all recipients; 71% at 1 year (n=14)	89.4% deceased donor 94.5% living donor
Liver recipients	79% of all recipients; 83% at 1 year (n=12)	81.4%

\*Data from current cohort from all patients and from those dying before 1 year or with at least 1 year of follow-up.

rejection has occurred in 10 (71%) of the kidney recipients, with no clear pattern in type or timing of rejection, and in 1 liver recipient. Graft loss has occurred in 1 kidney recipient (graft rejection) and in 1 liver recipient (retransplantation required due to a “small-for-size” graft lesion from a living donor). Evidence of recurrent HCV infection has been observed in 2 liver recipients and in none of the kidney recipients. The median CD4+ cell count in these patients decreased from 407/ $\mu$ L (range, 104–973/ $\mu$ L) to 255/ $\mu$ L (range, 8–902/ $\mu$ L); this decrease likely reflects the effects of immunosuppressant treatment for acute rejection episodes. The median HIV RNA level is below 75 copies/mL (range, < 75–9600 copies/mL).

### Special Clinical Considerations in HIV-Infected Patients

#### Viral Coinfection

Prior to the availability of effective antiviral therapy, hepatitis B virus (HBV) infection was a contraindication to transplantation, since reinfection is universally rapid and fatal in the absence of viral control. Current posttransplantation management of HBV infection relies on hepatitis B immune globulin and lamivudine treatment, but there is concern that many HIV-infected patients will have lamivudine-resistant HBV because the drug has been used in their antiretroviral regimens. However, there is

hope that adefovir or tenofovir can provide adequate control of lamivudine-resistant HBV in the posttransplantation period. Thus far, posttransplantation management of a very few patients with lamivudine-resistant HBV has been successful.

HCV coinfection is common in patients with HIV infection. Unfortunately, HCV infection is associated with relatively poor outcomes in HIV-uninfected transplant recipients, with universal infection of the transplant graft. HIV/HCV coinfection prompts additional concern since HCV disease has an accelerated natural history in the setting of HIV infection. Experience to date with transplantation in HIV/HCV-coinfected patients is variable, with some centers reporting very bad outcomes and some reporting outcomes similar to those in HIV-uninfected patients. Further study of this issue is needed. According to the current transplant study protocol, HCV treatment is not to be instituted preemptively in the posttransplantation period because there are no data to indicate that HCV clearance rates are improved by this practice and to minimize drug interactions and toxicity in the posttransplantation period. HCV treatment should be initiated if biopsy shows severe or progressive recurrent HCV disease, with the decision whether and when to treat being made by the treating physician. A nested randomized study of preemptive versus histologically

indicated therapy may be incorporated into the ongoing multicenter study.

Human papilloma virus (HPV)-related cervical and anorectal disease is more common in HIV-infected than HIV-uninfected persons, and there is concern that the incidence may increase with immunosuppression in the posttransplantation period. The ongoing study of transplantation includes a substudy of baseline and posttransplantation disease characteristics to ascertain the potential effect of iatrogenic immunosuppression on disease progression. Observations thus far in the small group of patients treated at UCSF suggest that progression rates are similar to those in patients not undergoing transplantation.

There is also considerable concern that posttransplantation immunosuppression could exacerbate Kaposi's sarcoma or other human herpesvirus-8-associated disease. Transplant-associated Kaposi's sarcoma in kidney recipients requires sacrifice of the kidney transplant to stop Kaposi's sarcoma progression. Thus far, transplantation has occurred in 2 patients who were known to have visceral (pulmonary) Kaposi's sarcoma, and these patients have had no recurrence of the disease. No new occurrence of Kaposi's sarcoma has been observed in transplant patients to date. The ongoing transplant study is now permitting enrollment of patients with a history of cutaneous Kaposi's sarcoma but not visceral disease, and this issue will be monitored closely in the study.

#### Immunosuppression-Related Issues

A number of transplant patients have developed metabolic complications, including insulin resistance, frank diabetes, hyperlipidemia, osteopenia, osteoporosis, and fracture. Iatrogenic immunosuppression, the antiretroviral treatment, and HIV infection itself can contribute to these abnormalities. The interactions among these conditions are unknown; these complications may occur at higher rates in the context of HIV infection and should be monitored carefully.

#### Drug Issues

Antiretroviral treatment interruptions in the posttransplantation period (eg, to permit organ function to stabilize or

for recurrent HCV infection) have resulted in minimal and delayed rebound of HIV RNA levels in some patients. This observation suggests that immunosuppressive therapies—in particular, cyclosporine and mycophenolate mofetil—may have direct or immune-mediated antiretroviral activity. Cyclosporine and tacrolimus may have different mechanisms of activity with regard to anti-HIV effects, and analyses are planned in the ongoing transplant study to attempt to determine whether different immunosuppressant regimens have different effects on virus levels in plasma and other viral reservoirs.

The pharmacokinetic interactions of hepatically metabolized antiretroviral and immunosuppressant drugs need to be characterized in the transplantation setting. The ongoing transplant study includes 12- to 24-hour pharmacokinetic evaluations of immunosuppressant drug, PI, and nonnucleoside reverse transcriptase inhibitor (NNRTI) levels at pretransplantation; at 2 and 12 weeks, 6 months, and 1, 2, and 5 years post-transplantation; and when there is a significant change in antiretroviral treatment or immunosuppressant treatment, or when an opportunistic infection occurs. It is already recognized that cyclosporine must be given at low doses when used together with PIs or PI/NNRTI combinations and at low to typical doses when used together with NNRTIs to achieve adequate plasma cyclosporine levels and adequate immunosuppression. Findings with tacrolimus and sirolimus have been similar to those with cyclosporine. PI and NNRTI concentrations are also affected by the coadministration of the immunosuppressants, but generally have remained within adequate therapeutic ranges. It remains unclear precisely how to integrate these observations into optimizing treatment, and it is hoped that the pharmacokinetic studies will provide guidance in this regard.

### Prospective Study in Transplantation

The ongoing multicenter prospective study has a target enrollment of 150 kidney transplant recipients and 125 liver transplant recipients (see Table 3).

**Table 3. Participating Centers of the Solid-Organ Transplant in HIV Multisite Study**

#### Kidney and Liver

- Beth Israel Deaconess Medical Center, Boston, MA
- Georgetown Medical Center, Washington, DC
- Mount Sinai School of Medicine, New York, NY (adult, both; pediatrics, kidney)
- University of California San Francisco (adult and pediatrics, both)
- University of Chicago (adult and pediatrics, both)
- University of Cincinnati
- University of Minnesota
- University of Pennsylvania
- University of Pittsburgh
- University of Virginia

#### Kidney

- Drexel University, Philadelphia, PA
- University of Maryland
- University of Miami
- Washington Hospital Center, Washington, DC

#### Liver

- Cedars-Sinai Medical Center, Los Angeles, CA
- Columbia University, New York, NY (adult and pediatrics)

Visit the study Web site, <http://spitfire.emmes.com/study/htr/> for further information, including contact information and listings of additional centers and changes.

Primary aims of the study are to assess the impact of iatrogenic immunosuppression on patient survival and to assess the impact of HIV infection and antiretroviral treatment on graft survival, including in the settings of HBV or HCV coinfection and HIV-associated nephropathy. Secondary aims include assessment of the effect of immunosuppressant therapy on CD4+ cell counts, HIV RNA levels, and opportunistic complications; exploration of the relationships among disease development, the host immune response, and viral evolution with regard to HBV, HCV, CMV, human herpesvirus-8, and HPV; assessment of the impact of HIV infection on alloimmune response and graft rejection rates; and analysis of pharmacokinetic interactions between immunosuppressant drugs and hepatically metabolized antiretroviral agents.

Initial experience in managing HIV-infected transplant recipients has highlighted the need for a multidisciplinary health care team to participate actively in patient monitoring and management, with excellent communication among team members being crucial to patient safety. Effective and timely communication is particularly important regarding medication changes and evaluation of symptoms and laboratory abnormalities.

*Presented in February and April 2004. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Roland in July 2004.*

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### Suggested Reading

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## Perspective

# Substance Use Disorders in HIV-Infected Patients: Impact and New Treatment Strategies

*Substance use disorders — including alcohol, cocaine, and opioid dependencies — are common in HIV-infected patients. Untreated substance use disorders result in poor HIV disease treatment outcomes; however, several new treatment strategies have emerged in recent years. Combined medication and counseling therapies are effective for alcohol and opioid dependencies, and counseling treatments are effective for cocaine dependence. Office-based treatment with buprenorphine offers the opportunity for coordinated treatment of HIV disease and opioid dependence. This article summarizes a presentation by David A. Fiellin, MD, in March 2004 at the International AIDS Society–USA New York course.*

Substance use is a common comorbidity with HIV infection. When untreated, substance use disorders can result in poor outcome of HIV disease treatment (Sullivan and Fiellin, *Am J Addict*, 2004). In considering the integration of substance use treatment into HIV care, it is important to recognize a number of principles of addiction medicine:

1. *Addiction is a chronic medical disorder that includes multifactorial genetic components, biologic changes due to exposure to addictive substances, and behavioral components.* Treatment for addictive disorders frequently must address both neurobiologic and behavioral components.
2. *Addictive substances work on common neurologic reward pathways that are highly conserved in evolution.* These pathways involve projections between the ventral tegmental area and the nucleus accumbens; in brief, most addictive substances stimulate the ventral tegmental area, resulting in release of dopamine and stimulation of the nucleus accumbens, which is experienced as euphoria or reward.
3. *Profound neurobiologic changes accompany the transition from use to abuse to dependence.* In addition to the acute response to exposure to the addictive substance, the increased intracellular cyclic adenosine monophosphate (AMP) and cellular excitation resulting from brain

cell exposure results in activation of a number of intracellular pathways that leads to altered gene expression associated with craving.

4. *Detoxification does not equal treatment.* Acute detoxification alone—that is, getting the patient through the acute phase of withdrawal—typically does not result in prolonged abstinence. By analogy, treating diabetic ketoacidosis is not the same as treating diabetes. Treatment strategies for patients with substance use disorders should be considered long-term, ongoing processes. Typically, abstinence rates during acute detoxification are high and fall off dramatically at some point after treatment. The success during acute detoxification treatment should serve to suggest that rates of sustained abstinence could be improved with continuation of treatment beyond acute detoxification.
5. *Treatment outcomes are improved with increased counseling services.* This finding has been repeatedly confirmed. As an example, one study comparing patients receiving treatment with methadone alone, methadone plus standard counseling, and methadone plus enhanced counseling showed that treatment retention rates were 31%, 59%, and 81%, respectively. Urine toxicology results were negative for opiates at greater than 16 weeks in 0%, 28%, and 55% of patients, respectively (McLellan, *JAMA*, 1993).

The following reviews aspects of alcohol, cocaine, and opiate abuse epidemi-

ology and impact on HIV care and new treatment strategies for substance abuse and dependency. Although abuse of other substances, including methamphetamines, may be seen in patients who are HIV infected, this review focuses on these 3 commonly encountered substances.

## Alcohol

Epidemiologic data indicate that approximately 35% of the general population can be considered moderate alcohol drinkers. At-risk drinkers (ie, men who consume more than 2 drinks per day or more than 4 on a single occasion and women who consume more than 1 drink per day or more than 3 on a single occasion) and alcohol abusers (greater use than at-risk use) constitute approximately 20% of the population, and 5% of the population is alcohol-dependent. In the general medical-practice setting population, approximately 20% to 35% fall into at-risk and abuse categories and 5% to 10% are dependent (Fiellin et al, *Ann Intern Med*, 2000). Studies in HIV-infected populations have reported alcohol problems or alcohol use disorders in 22% to 60% of patients (Phillips et al, *J Gen Intern Med*, 2001; Petry, *Int J STD AIDS*, 1999; Cook, *J Gen Intern Med*, 2001) and rates of alcohol abuse or dependence of 12% to 41% (Lefevre, *J Gen Intern Med*, 1995; Dew et al, *Psychological Med*, 1997).

Alcohol abuse can negatively affect HIV disease and its treatment in a number of ways. Studies in vitro have indicated enhanced HIV replication with alcohol exposure (Bagasra, *Alcohol Clin Exp Res*, 1989; Cook et al, *J Investig Med*, 1997), and alcohol use is associated with decreased levels of a number of endogenous immunomodulators. Alcohol use is also associated with high-risk sexual behavior. Data from the Multicenter AIDS Cohort Study (MACS) in the pre-potent antiretroviral therapy era indicated an absence of an association between alcohol use and HIV disease progression (Kaslow, 1989). How-

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**Table 1.** Effect of Alcohol Use on Adherence to Antiretroviral Medication

<b>Drinking Behavior Type</b>		<b>Missed dose in 24 hours</b>	<b>Medicines off schedule in past week</b>
Hazardous	(n=32)	21%	53%*
Heavy	(n=17)	15%	59%*
Binge	(n=34)	17%	38%
None of above	(n=161)	12%	26%

\*P<0.05. Adapted from Cook et al, *J Gen Intern Med*, 2001.

ever, studies in the potent antiretroviral therapy era have demonstrated that alcohol problems are associated with reduced adherence to antiretroviral regimens (Fabris, *J Acquir Immune Defic Syndr*, 2000; Cook, *J Gen Intern Med*, 2001; Galvan, *J Stud Alcohol*, 2002) and that alcohol consumption is associated with higher plasma HIV RNA levels and lower CD4+ cell counts. (Palepu et al, *Addiction*, 2004). Adherence to antiretroviral regimens is a critical component in maintaining optimal suppression of viral replication. An example of the effect of alcohol use on adherence is provided by the data from a study by Cook and colleagues shown in Table 1; alcohol use was associated with reduced adherence to antiretroviral medications over the prior 24 hours, and heavier use was associated with significantly poorer weekly adherence.

Treatment strategies for alcohol abuse in patients considered at-risk drinkers include brief interventions—generally, 15-minute targeted interventions provided in the office setting that focus on consequences of alcohol abuse, including the potential impact on medication adherence and biochemical damage and symptoms, and recommendations regarding appropriate and inappropriate drinking levels. A meta-analysis of 12 randomized controlled trials has shown that heavy drinkers who receive a brief intervention are twice as likely to moderate their alcohol consumption as those receiving no intervention (Wilk, *J Gen Intern Med*, 1997). In Project TREAT (Trial for Early Alcohol Treatment), performed in 64 physician offices in Wisconsin, patients receiving a 15-minute physician intervention visit with a repeat visit 1 month

later showed significant reductions in mean number of drinks during the prior 7 days, mean number of episodes of binge drinking within the prior 30 days, percentage of excessive drinking within the prior 7 days, and days of hospitalization within the prior 6 months compared with control patients not receiving the intervention (Table 2; Fleming et al, *JAMA*, 1997).

Patients meeting criteria for alcohol abuse and dependence require more intensive treatment strategies, the mainstays of which are psychosocial treatments. The main treatments are motivational enhancement therapy, cognitive behavioral therapy, and 12-step facilitation; in each of these the patient attends individual or group counseling on a weekly basis. An example of the results achieved with these approaches comes from the National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity), in which 1726 patients were randomized to one of the 3 treatments. Results with the individual treatments were very similar; pooled outcomes for outpatients and inpatients are shown in Table 3 (*J Stud Alcohol*, 1997). Overall, of patients initiating treatment from the outpatient or inpatient setting, 35% remained abstinent, 25% consumed a small amount of alcohol on at least 1 occasion, and 40% relapsed to heavy or uncontrolled drinking during the first 12 months. In the outpatient-only arm, 19% maintained complete abstinence, 35% consumed a small amount of alcohol on at least 1 occasion, and 46% had a relapse. These findings indicate that physicians can expect that many of their patients will benefit from alcohol treatment programs.

A number of pharmacologic approaches to treatment of alcohol abuse and dependence are currently available or have shown promise in clinical investigation. However, there are few available data on the use of pharmacologic treatments in HIV-infected patients. Disulfiram is a well-described medication that appears to be most effective in highly motivated patients receiving directly observed therapy. There were initial promising results with the opioid antagonist naltrexone, but more recent

**Table 2.** Effect of Physician Brief Intervention in At-Risk Drinkers in Project TREAT: Baseline to 12 Months

	<b>Baseline</b>	<b>12 Months</b>
<b>Mean number drinks, prior 7 days*</b>		
Intervention	19.1	11.5
Control	18.9	15.5
<b>Mean number episodes of binge drinking, prior 30 days*</b>		
Intervention	5.7	3.1
Control	5.3	4.2
<b>Percent drinking excessively, prior 7 days*</b>		
Intervention	47.5%	17.8%
Control	48.1%	32.5%
<b>Days of hospitalization, prior 6 months*</b>		
Intervention	93	91
Control	42	146

\*P<001 for intervention versus control. Adapted from Fleming et al, *JAMA*, 1997.

**Table 3.** Pooled Results With Motivational Enhancement Therapy, Cognitive Behavioral Therapy, and 12-Step Facilitation in Project MATCH

	Outpatients	Inpatients
Abstinent	19%	35%
Non-abstinent	35%	25%
Relapse	46%	40%

Adapted from Project MATCH Research Group, *J Stud Alcohol*, 1997.

data suggest that it is not as effective as initial findings suggested. Acamprosate, which is widely used in Europe, tends to result in a 30% to 40% decrease in excessive drinking behavior; a large NIAAA trial combining acamprosate and naltrexone is under way. Promising results have been seen with neuroleptics such as topiramate, and odansetron has been found to be helpful in decreasing excessive drinking behavior in select patients.

## Cocaine

Epidemiologic data on cocaine use in HIV-infected patients are relatively sparse. Chaisson and colleagues found that 12% of 633 heterosexual injection drug users with HIV infection were using cocaine or heroin (*JAMA*, 1989). More recently, Samet and colleagues (in press) found that 25% of HIV-infected patients with alcohol problems were using cocaine.

Cocaine use is a well-established risk factor for acquiring HIV infection (Chaisson, *JAMA*, 1989). The effect of cocaine use on HIV disease progression is less clear, although it is known that cocaine suppresses T-cell activity and facilitates HIV replication. It is also

known that ongoing cocaine use is associated with decreased adherence to antiretroviral regimens.

Psychosocial treatments currently are the mainstay of therapy for cocaine use. Drug counseling and contingency management are the most promising counseling approaches. Results of the National Institute on Drug Abuse Collaborative Cocaine Treatment Study comparing patients receiving individual and group counseling, cognitive therapy and group counseling, supportive-expressive and group counseling, and group counseling alone are summarized in Table 4 (Crits-Cristoph, *Arch Gen Psychiatry*, 1999). These findings suggest somewhat better maintenance of abstinence with the combined individual and group counseling approach. At present, there are no established pharmacologic therapies. Early work on a potential vaccine is ongoing. Initial findings with use of disulfiram have been promising.

## Opioids

Heroin use is clearly on the rise in the United States. Data from the National Household Survey on Drug Abuse indicate that 2.4 million Americans used

heroin in 1997 and that there were 410,000 new users between 1996 and 1998. Prescription opioid abuse is also rising; data from the Drug Abuse Warning Network indicate that oxycodone abuse increased by 68% (from 6,429 to 10,825 reports) between 1999 and 2000 and that hydrocodone abuse increased by 31% (from 14,639 to 19,221 reports) over the same period. Prescription opioid abuse with controlled-release oxycodone often occurs when the pill matrix is broken to allow the contents to be snorted or swallowed, resulting in immediate drug exposure and euphoric reward.

It is estimated that approximately 1 million Americans have heroin dependency, and 2 to 2.5 million have prescription opioid dependency. According to Office of National Drug Control Policy data for 1999, an estimated 810,000 to 1 million persons in the United States had opioid dependency, but only some 170,000 to 200,000 were receiving effective treatment strategies.

Data on the prevalence of opioid use in HIV-infected patients is largely confined to data on injection drug use. According to the Centers for Disease Control and Prevention (CDC), the number of injection drug users living with AIDS increased from 48,244 to 88,540 between 1993 and 1999 (CDC, *HIV/AIDS Surveillance Report*, 2000). It is estimated that 25% of the roughly 40,000 new HIV infections per year occur through injection drug use (CDC, *HIV Prevention Strategic Plan Through 2005*, 2001).

Opioid use is associated with poorer HIV disease treatment outcomes. Injection drug users are less adherent to antiretroviral regimens (Roca, *J Infect*, 1999; Poundstone, *AIDS*, 2001) and HIV-infected injection drug users are less likely to receive antiretroviral treatment (Celentano, *JAMA*, 1998; Strathdee, *JAMA*, 1998; Turner, *J Gen Intern Med*, 2001). Often, potent antiretroviral therapy is delayed until active opioid use is addressed. This has usually required referral of patients to off-site treatment programs; however, as discussed below, the availability of buprenorphine presents options for dependency treatment in the HIV specialty setting.

The most effective treatment strate-

**Table 4.** Abstinence Outcome According to Treatment in the National Institute on Drug Abuse Collaborative Cocaine Treatment Study

Consecutive months abstinent	Individual and group counseling (n=121)	Cognitive therapy and group counseling (n=119)	Supportive-expressive and group counseling (n=124)	Group counseling (n=123)
1	71%	54%	60%	58%
2	48%	36%	32%	42%
3	38%	23%	18%	27%

Adapted from Crits-Christoph et al, *Arch Gen Psychiatry*, 1999.

gies for opioid dependence are pharmacologic approaches combined with psychosocial treatment. (O'Connor and Fiellin, *Ann Intern Med*, 2000). Pharmacologic options consist primarily of methadone and buprenorphine; levomethadyl acetate (LAAM) is no longer available in the United States because of concerns over cardiac toxicity (QT prolongation and episodes of torsade de pointes). Figure 1 shows results of a trial comparing low- and high-dose methadone, buprenorphine, and LAAM, all combined with counseling, in patients with opioid dependence (Johnson, *NEJM*, 2000). Rates of both treatment retention and opioid-negative urine toxicology compare well with rates observed with high-dose methadone, which can be considered the standard treatment in this setting.

The importance of opioid dependency treatment with regard to HIV disease is illustrated by a study reported by Metzger and colleagues (*J Acquir Immune Defic Syndr*, 1993). During an 18-month follow-up of initially HIV-seronegative patients, 22% of 103 injection opioid users who were receiving no treatment became HIV-seropositive, compared with 3.5% of 152 patients receiving methadone treatment.

With regard to drug-drug interactions that may arise when treating dependency and HIV infection, there are numerous interactions between methadone and antiretroviral agents. Methadone disposition is not affected by concomitant nucleoside reverse transcriptase inhibitor treatment. However, the zidovudine area under the concentration-time curve (AUC) is reduced with concomitant treatment, and blood levels of didanosine (minimal effect with enteric formulation of didanosine) and stavudine are reduced. With regard to nonnucleoside reverse transcriptase inhibitors (NNRTIs), both efavirenz and nevirapine are associated with a 50% reduction in methadone AUC. For protease inhibitors, ritonavir, indinavir, and saquinavir inhibit methadone metabolism in vitro; however, ritonavir has no effect on methadone metabolism in vivo. Methadone concentrations are reduced by nelfinavir (40%) and lopinavir/ritonavir (32%); nelfinavir

use has not been associated with clinical opioid withdrawal symptoms, but the use of lopinavir/ritonavir has been. The interaction of methadone and atazanavir currently is being studied.

**Buprenorphine.** Buprenorphine is a partial agonist at the  $\mu$  receptor that has a unique pharmacologic profile. The agent is characterized by a ceiling effect in intrinsic opioid activity (Figure 2), reducing the potential for respiratory depression and death associated with full agonist use. The drug has low abuse and diversion potential. The currently available formulation consists of a sublingual tablet in a 4-to-1 ratio with the opioid antagonist naloxone. The buprenorphine component is well absorbed sublingually and the naloxone component is not; if the pill is ground and injected, an opioid-dependent patient will experience an immediate withdrawal from the naloxone.

Currently, there is limited informa-

tion on drug-drug interactions between buprenorphine and antiretroviral agents. The agent undergoes N-dealkylation mediated by the cytochrome P450 3A4 isoenzyme, and there is thus potential for interaction with NNRTIs and protease inhibitors. Preliminary information, however, indicates that there is no decrease in buprenorphine concentrations with coadministration of efavirenz. Results from cohorts of HIV-infected patients in France, where the medication has been available since 1996, indicate that buprenorphine treatment is associated with increased adherence to potent antiretroviral therapy and that patients experience appropriate increases in CD4+ cell count and reductions in viral load while receiving this medication (Carrieri et al, *Drug Alcohol Depend*, 2000; Moatti et al, *AIDS*, 2000).

Buprenorphine was approved in October 2002 for office-based treatment of opioid dependency, including

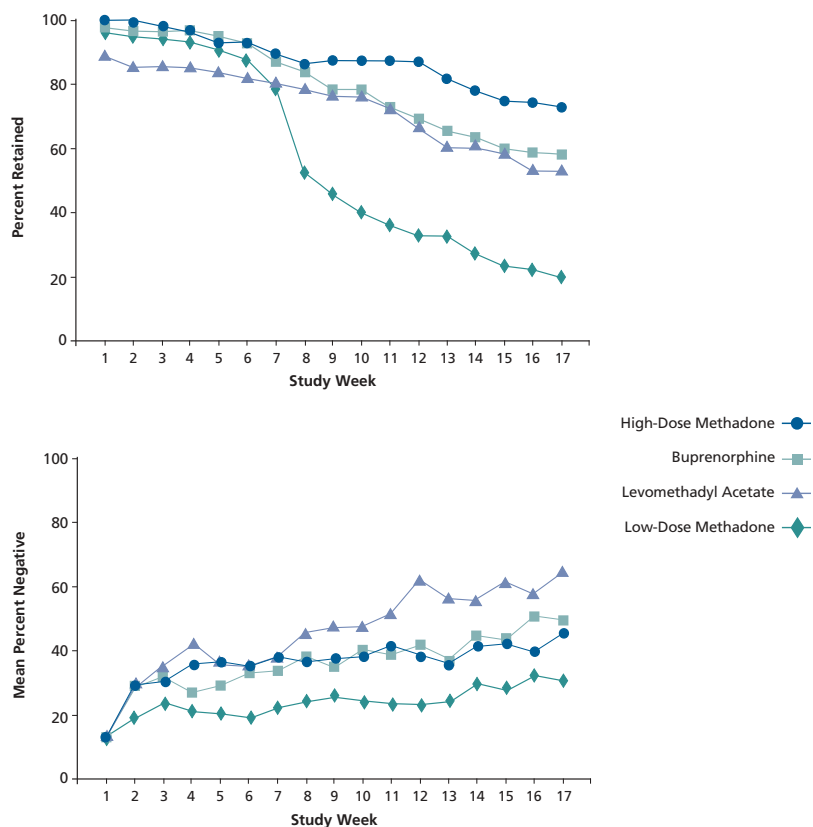
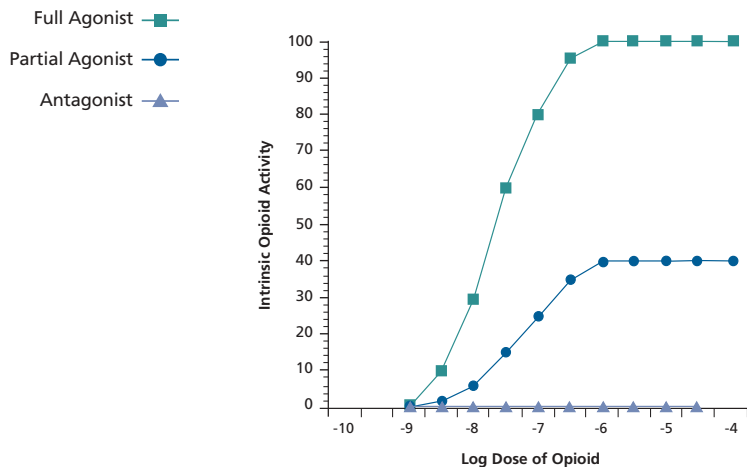


Figure 1. Treatment retention rates (top) and opioid-negative urine toxicology results (bottom) according to treatment in opioid-dependent patients. Adapted from Johnson et al, *N Engl J Med*, 2000.



**Figure 2.** Intrinsic opioid activity of methadone (full agonist), buprenorphine (partial agonist), and naltrexone (antagonist). Adapted from *Use of Buprenorphine in the Pharmacologic Management of Opioid Dependence: A Curriculum for Physicians, 2001*.

treatment in HIV specialty settings. The Drug Addiction Treatment Act of 2000 created the pathway by which physicians can prescribe buprenorphine (Fiellin and O'Connor, *N Engl J Med*, 2002).

The requirements for prescribing buprenorphine in the office setting are that it be prescribed by a licensed physician who is board certified in addiction medicine and has the capacity to refer patients for counseling. At this time, no more than 30 patients can be under the care of an individual physician or a group practice, but legislative efforts are under way to lift this restriction. The prescriber must successfully complete an approved 8-hour training. As of November 2003, there were 3159 physicians who had undergone the 8-hour training program required in the absence of certification in addiction medicine. Currently, there are approximately 3500 to 4000 physicians who have been trained, but relatively few are HIV care providers. An initiative is under way to provide training sessions targeted to HIV care providers.

Buprenorphine information, including copies of the Drug Addiction Act of 2000, waiver notification forms, a listing of buprenorphine trainings, a buprenorphine physician locator map, and frequently asked questions, can be found at <http://buprenorphine.samhsa.gov>. Questions about buprenorphine and training sessions can be answered

by calling 1-866-BUP-CSAT Monday through Friday, 8:30 AM to 5:00 PM Eastern time, or via email at [info@buprenorphine.samhsa.gov](mailto:info@buprenorphine.samhsa.gov).

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## Perspective

# Initiation of Antiretroviral Therapy: Implications of Recent Findings

*A number of reports related to initiation of antiretroviral therapy have been reported recently. Available data continue to support the practice of not starting therapy for asymptomatic patients who have CD4+ cell counts above 350/μL, and consideration for initiating antiretroviral therapy below this point, but before the count drops to 200/mL. In terms of initial regimens, some data suggest better virologic response rates with nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens than with protease inhibitor-based regimens. The differences are likely due to better tolerability of NNRTI-based regimens. Small studies in treatment-naïve patients have shown poor virologic outcome in patients receiving certain regimens, such as abacavir/lamivudine/tenofovir or didanosine/lamivudine/tenofovir, yet better outcomes in patients treated with abacavir/lamivudine/zidovudine/tenofovir. These findings appear to be explained by the differing effects of the reverse transcriptase K65R mutation on different drugs. Other recent studies suggest fewer metabolic adverse effects with emtricitabine-containing treatment than with stavudine-containing treatment, comparable virologic outcomes with once-daily and twice-daily abacavir regimens; comparable virologic outcomes with once-daily and twice-daily lopinavir/ritonavir regimens, and an association between didanosine 400 mg/tenofovir regimens and declines in CD4+ cell counts despite viral suppression. This article summarizes a presentation on initiation of antiretroviral therapy by Michael S. Saag, MD, at the International AIDS Society–USA course in New York in March 2004.*

New data have become available since early 2004 that impact the strategies for initiating antiretroviral therapy in HIV-infected individuals. Information continues to support initiating therapy for asymptomatic patients somewhere between 200 and 350 CD4+ cells/μL, but when, in this range, is the optimal time to start remains undefined. Despite this uncertainty, waiting until the CD4+ count drops below 200 cells/μL is clearly too late.

With regard to the best regimen to use as initial therapy, results of several trials in antiretroviral-naïve and antiretroviral-experienced patients identify specific drugs or combinations to strongly consider and some regimens to definitely avoid. The following summarizes some of these new data and how they may impact current clinical practice.

### When to Initiate Therapy

The optimal time to initiate antiretroviral therapy in HIV-infected individuals

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remains imprecisely defined beyond the currently accepted and well-established CD4+ cell count threshold levels. Treatment should be started in all patients with symptomatic disease regardless of CD4+ count. Natural history data continue to show that disease progression is slow in patients with CD4+ cell counts greater than 350/μL, suggesting that treatment can be delayed in asymptomatic patients in this setting. The probability of AIDS-free survival according to baseline CD4+ cell count in the ART Cohort Collaboration, now involving tens of thousands of patients, is shown in Figure 1 (Eggers et al, *Lancet*, 2003).

The use of viral load as a marker of when to initiate therapy remains controversial. In the Antiretroviral Therapy (ART) Cohort Collaboration, accelerated disease progression occurred in patients with plasma HIV RNA levels greater than 5 log<sub>10</sub> (100,000) copies/mL. However, it is possible that more frequent monitoring of patients with higher CD4+ cell counts who have elevated viral load values may be preferable to starting therapy simply based on viral load values alone.

Unfortunately, the issue of when to initiate therapy is not one typically

faced with individuals presenting with HIV infection in many clinics. For example, at the University of Alabama at Birmingham 1917 Clinic, the median CD4+ cell count at first contact is approximately 100/μL; only 15% of patients present with CD4+ counts above 350 cells/μL. Among those patients presenting with higher CD4+ cell counts, the majority are pregnant women who were tested for HIV as part of their prenatal evaluations.

It is tragic that HIV infections are not being identified earlier in the disease course, because there is higher mortality among patients starting therapy with CD4+ counts below 200 cells/μL. The failure to identify patients and start their treatment earlier in their disease course in current practice argues against simple voluntary testing and argues for the provision of opt-out testing as a strategic national approach to minimize mortality and potentially to reduce the number of new infections.

### Considerations in Selecting the Initial Regimen: Recent Findings

#### Tolerability and Virologic Effectiveness

Most antiretroviral regimens used as initial treatment are relatively equipotent in terms of their virologic activity. One exception to this tenet is illustrated by the results of the AIDS Clinical Trials Group (ACTG) 5095 study, wherein a triple-nucleoside reverse transcriptase inhibitor (nRTI) regimen did not perform as well as regimens anchored with a nonnucleoside reverse transcriptase inhibitor (NNRTI) agent (Gulick, *NEJM*, 2004). In other studies, however, careful evaluation of the trial results suggests that differences in outcomes are attributable to subtle differences in tolerability among the regimens used. This is especially true in asymptomatic patients, in whom adverse effects such as nausea, cramping, headache, and

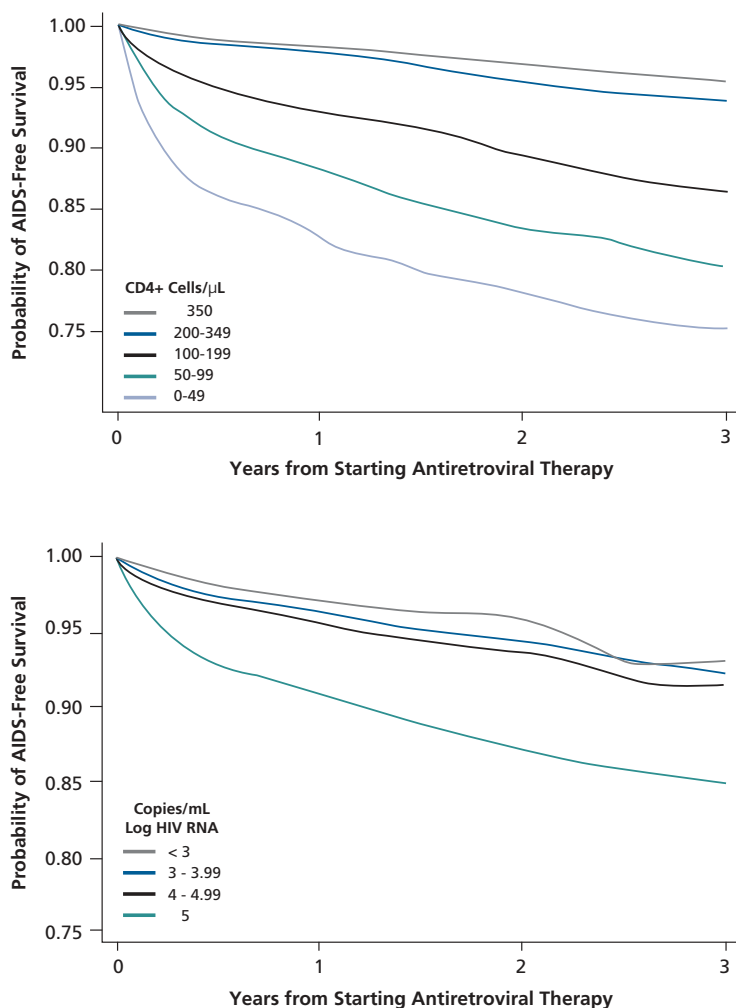


Figure 1. AIDS-free survival by CD4+ count (cells/μL) (top) and plasma log<sub>10</sub> HIV RNA (bottom) at baseline in the ART Cohort Collaboration. Adapted in part from data in Egger et al, *Lancet*, 2003.

general dysphoria can have a profound impact on their attitudes toward taking medication.

Most patients base their daily decisions about taking medication on how they feel rather than on potential long-term consequences. For those patients experiencing even subtle toxicities, the association of a missed dose of medication with feeling better due to the absence of adverse effects serves to reinforce the behavior of missing doses. Outcomes assessed by intent-to-treat analyses in clinical trials of initial regimens are influenced by a number of factors, the most critical of which is whether the patient actually took the assigned medication. Recent studies demonstrate that the highest virologic response rates (in terms of reduction of

plasma HIV RNA to less than 50 copies/mL at 24 weeks by intent-to-treat analyses) are observed with NNRTI-based regimens, particularly efavirenz-based regimens, rather than with protease inhibitor (PI)-based regimens. In several studies, efavirenz-based regimens achieved HIV RNA response rates of less than 50 copies/mL at 48 weeks (intent-to-treat analyses) reaching or exceeding 80%. In contrast, no randomized controlled study of a PI-based regimen has been reported (intent-to-treat analysis) to produce such a virologic response rate greater than 70%. It is likely that this difference in efficacy reflects overall poorer tolerability of PIs, since as-treated analyses of groups receiving PI-based treatment tend to show successful virologic responses in

more than 90% of patients. Among relatively equipotent regimens, those that are better tolerated produce better treatment outcomes. Therefore, a key consideration of initial therapy is short- and long-term tolerability.

### Tenofovir-Containing Triple-nRTI Regimens and the K65R Mutation

Although the ACTG 5095 study demonstrated inferior activity of the triple-nRTI regimen of zidovudine/lamivudine/abacavir compared with an efavirenz-based regimen, the overall activity of the triple-nRTI regimen was comparable to results of PI-containing regimens by intent-to-treat analyses. However, this does not mean that all triple-nRTI regimens have similar effectiveness. A recent study (TONUS) showed poor virologic outcome with the triple-nRTI combination of once-daily abacavir/lamivudine/tenofovir (Landman et al, 11th CROI, 2004). In this study, HIV RNA level was not reduced to below 400 copies/mL in the majority of patients by week 12, and virologic failure occurred in 12 of 36 patients at week 24. The conclusion from this study was that there might be an unanticipated interaction between abacavir and tenofovir.

In follow-up to this concept, Jemsek and colleagues (11th CROI, 2004) evaluated a once-daily regimen of didanosine/lamivudine/tenofovir in 20 treatment-naïve patients. Virologic results in this study were also surprisingly dismal: only approximately 25% had a decrease of greater than 1 log<sub>10</sub> in plasma HIV RNA after 12 weeks and approximately 20% of patients had an increase in plasma HIV RNA level. Such poor responses were not expected with triple-nRTI combinations. Genotypic analysis showed that half of the patients had the M184V lamivudine-associated resistance mutation and half had the M184V mutation plus the K65R resistance mutation. Phenotypic analysis showed reduced susceptibility to lamivudine in each of 19 patients tested, to didanosine in 6 patients (associated with the M184V and K65R mutations), and to abacavir in 6 patients (associated with the M184V and K65R mutations). There was no reduced susceptibility to zidovudine, tenofovir, or stavudine.

A subanalysis of the TONUS study (Landman et al, 11th CROI, 2004)

**Table 1.** Proportions of patients receiving abacavir/lamivudine/zidovudine/tenofovir who had HIV RNA levels below 400 copies/mL and below 50 copies/mL at 24 weeks in study COL40263 (intent-to-treat observed analysis).

Subgroup	Proportion with Response
Pretreatment HIV RNA <100,000 copies/mL	
Decline to <400	84%
Decline to <50	79%
Pretreatment HIV RNA >100,000 copies/mL	
Decline to <400	74%
Decline to <50	60%
Overall	
Decline to <400	79%
Decline to <50	67%

Based on data presented by Elion et al, 11th CROI, 2004.

explored potential reasons why some triple-nRTI regimens are not performing as would have been expected. Thirty-two of 37 patients had adequate minimum plasma concentrations of all 3 drugs at week 4. Analysis of intracellular nRTI triphosphate (the active metabolite) levels using direct liquid tandem mass spectroscopy was performed in 14 patients at week 4, including 1 patient in whom treatment was failing virologically. The triphosphate metabolite of at least 1 drug was found in all

patients and triphosphate metabolites of all 3 drugs were found in 8 patients. Therefore, this study did not provide full evidence that the poor virologic results were associated with reduced triphosphate levels.

Assessment of viral resistance suggested a major role of the combined K65R and M184V/I mutations in poor virologic outcomes. Genotypic analysis in 11 of the 12 patients with virologic failure (plasma HIV RNA never <400 copies/mL or a rebound of >0.7 log<sub>10</sub>

after suppression to below this level) showed the presence of the K65R plus M184V/I mutations in 9 patients (82%) and the M184V/I mutation alone in 2 patients. Among the 10 patients assessed with detectable HIV RNA levels but not virologic failure, 7 (70%) had the K65R plus M184V/I mutations, 2 had the M184V/I mutation alone, and 1 had wild-type virus. Changing treatment was successful in reducing HIV RNA levels to below 50 copies/mL in 14 patients with the K65R plus M184V/I mutations; some of the successful regimens were 4-drug regimens and many contained zidovudine. These data suggest that the failure noted among some triple-nRTI regimens may be due to rapid evolution of resistance rather than low plasma drug levels or poor intracellular processing of the drugs into active moieties.

The association of the K65R mutation with viral resistance and poor virologic response to these regimens receives support from an additional study examining the once-daily, 4-drug combination of abacavir/lamivudine/zidovudine/tenofovir (COL40263; Elion, 11th CROI, 2004). Although it might be expected that this abacavir/tenofovir-containing combination would also yield poor virologic outcomes, results of the study indicate otherwise. As shown in Table 1, 79% of the 56 patients studied had HIV RNA levels below 400 copies/mL and 67% had levels below 50 copies/mL at week 24.

Rates of early virologic response were better with the zidovudine-containing 4-drug regimen than with the abacavir/lamivudine/tenofovir regimen assessed in the TONUS study (ESS30009) among patients with baseline HIV RNA levels less than or greater than 100,000 copies/mL (Table 2). Baseline genotypic analysis showed that of isolates from 8 nonresponders to the 4-drug regimen, 1 had the K103N resistance mutation, 1 had a T215V/F reversion, and 6 had wild-type virus. Analysis of isolates from the 8 nonresponders at the last study visit (time of withdrawal from the study or last visit after 24 weeks) showed the K65R mutation in only 1 patient, 1 or more thymidine analogue mutations (TAMs) in 2 patients, and 1 or more TAMs plus the M184V/I mutation in 3 patients; 2 of the isolates were wild-type virus. These data

**Table 2.** Comparison of early HIV RNA response with abacavir/lamivudine/tenofovir in study ESS30009 and with abacavir/lamivudine/zidovudine/tenofovir in study COL40263. Based on early virologic nonresponse criteria used in ESS30009: (1) Less than 2-log copies/mL decline from baseline by week 8 and HIV RNA of 50 copies/mL or higher by week 8, and (2) 1-log copies/mL or greater increase above nadir at or before 8 weeks.

Subgroup	Early HIV RNA Response
Pretreatment HIV RNA <100,000 copies/mL	
ESS30009	56%
COL40263	83%
Pretreatment HIV RNA >100,000 copies/mL	
ESS30009	32%
COL40263	52%
Overall	
ESS30009	51%
COL40263	76%

Based on data presented by Elion et al, 11th CROI, 2004.



suggest a potential protective effect of zidovudine on the development of the K65R mutation.

An analysis by Parikh and colleagues (11th CROI, 2004) indicated that the prevalence of the K65R mutation in patients who have had genotypic testing increased from 0.4% in 1998 to 3.6% in 2003 and that the combined presence of the K65R and M184V/I mutations changes susceptibility to nRTIs compared with the presence of either mutation alone. As shown in Table 3, the combination of the 2 mutations reduces susceptibility to abacavir, didanosine, and lamivudine, but appears to result in hypersusceptibility to zidovudine. The effect of the K65R mutation on nRTI activity appears to be explained by a combination of decreased nRTI incorporation into viral DNA and decreased excision of the nRTI from the growing DNA chain, according to a study reported by White and colleagues (11th CROI, 2004). Decreased incorporation results in increased resistance, whereas decreased excision results in increased susceptibility, since the drug is not being removed as readily from the growing chain. The balance between these 2 competing effects results in the net susceptibility. This study showed that the presence of the next nucleotide to be added in the chain and its concentration both have an effect on excision efficiency, with higher concentrations of the next nucleotide resulting in reduced excision. Although most nRTIs experienced slightly decreased or no change in excision in the presence of K65R, zidovudine-monophosphate excision was dramatically decreased at physiologic concentrations of the next nucleotide. Overall, for most nRTIs, the K65R mutation acts to increase resistance by decreasing nRTI incorporation, with this effect being counterbalanced to varying degrees by the effect of the mutation in increasing the nRTI stability after incorporation (decreased excision). Virus with the K65R mutation may also have reduced replication capacity in association with reduced incorporation of the natural nucleotides. In the case of zidovudine, the increase in stability more than offsets the decreased incorporation, increasing the susceptibility of K65R virus to zidovudine compared

**Table 3. Effect of Reverse Transcriptase M184V and K65R Mutations on Susceptibility\* to Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors**

	<b>K65R</b>	<b>M184V</b>	<b>K65R + M184V</b>
<b>Abacavir</b>	4.2	2.8	11
<b>Didanosine</b>	2.7	1.8	3.4
<b>Lamivudine</b>	60	>100	>100
<b>Tenofovir</b>	2.4	0.4	1.0
<b>Zidovudine</b>	1.1	0.9	0.6

\*Expressed as fold change. Adapted from Parikh et al, 11th CROI, 2004.

with the established clinical cutoff value for the drug (Table 4). Susceptibility is preserved (ie, is below clinical cutoffs) for stavudine and abacavir, and susceptibility is reduced for tenofovir, didanosine, lamivudine, and zalcitabine.

It is known that TAMs reduce nRTI susceptibility by increasing nucleotide excision; the opposition of this effect to that of reverse transcriptase with the K65R mutation may help explain the relative lack of virus with both TAMs and the K65R mutations.

### Results of Other Initial Therapy Studies

#### Emtricitabine

Emtricitabine (formerly FTC) is a recently approved nRTI, which is very similar to lamivudine. The FTC-301A study compared the effects of once-daily emtricitabine and twice-daily stavudine each in combination with once-daily didanosine/efavirenz in 571 treatment-

naive patients (Saag et al, *JAMA*, 2004). The emtricitabine regimen was associated with a statistically significant higher rate of virologic response (<50 copies/mL) at 48 weeks (78% vs 59%). A recent report (Powderly, 11th CROI) on metabolic outcomes with the 2 regimens indicated that the stavudine-containing regimen was associated with more adverse effects in terms of body-fat loss and a substantially greater increase in fasting triglyceride levels than the emtricitabine regimen. The emtricitabine regimen was also associated with a significantly greater increase in high-density lipoprotein (HDL) cholesterol level.

#### Once-Daily Versus Twice-Daily Abacavir

Study CNA30021—which compared once-daily and twice-daily abacavir each combined with lamivudine/ efavirenz in 39 treatment-naive patients—indicated comparable virologic response rates

**Table 4. Effect of Reverse Transcriptase K65R Mutation on Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitor Binding and Incorporation, Stability, and Susceptibility**

	<b>Binding/ incorporation</b>	<b>Stability</b>	<b>Net susceptibility in cell culture (versus clinical cutoff)</b>
<b>Zidovudine</b>	↓	↑↑	Hypersusceptible
<b>Stavudine</b>	↓	—	Susceptible
<b>Tenofovir</b>	↓↓	↑ / —	Reduced susceptibility
<b>Didanosine</b>	↓↓	—	Reduced susceptibility
<b>Abacavir</b>	↓↓	↑	Susceptible

↓,↓↓ indicates decreased; ↑,↑↑, increased; —, no effect. Data from White et al, 11th CROI, 2004.

with the 2 regimens (Craig, 11th CROI, 2004). Although the group receiving twice-daily abacavir had a somewhat longer time to treatment response, plasma HIV RNA levels were at or below 50 copies/mL in both groups after approximately 25 weeks during the 48-week study.

### **CD4+ Cell Count Decline Despite Undetectable HIV RNA Level**

A retrospective analysis of data from 302 patients receiving antiretroviral regimens containing didanosine and tenofovir has provided a potential explanation for the observation of CD4+ cell count declines in patients with HIV RNA levels below assay detection limits (Negredo, 11th CROI, 2004). All patients in the analysis had HIV RNA levels below detection limits. Significant decreases in CD4+ cell, CD8+ cell, and total lymphocyte counts were observed only among those patients receiving both didanosine 400 mg and tenofovir 300 mg; approximately 50% of these patients had CD4+ cell count declines of more than 100/ $\mu$ L at 48 weeks. It is known that tenofovir acts to increase didanosine levels; didanosine levels in patients receiving the 400 mg dose were elevated during treatment and decreased significantly after didanosine dose reduction. Thus, the CD4+ cell count decline appears to be associated with lymphocyte toxicity from elevated didanosine levels rather than reduced virologic effect. The didanosine dose should be decreased to 250 mg when given in combination with tenofovir.

### **Once-Daily Versus Twice-Daily Lopinavir/Ritonavir**

A study comparing once-daily and twice-daily lopinavir/ritonavir, each with tenofovir/emtricitabine in 190 treatment-naive patients, showed little difference between the once-daily and twice-daily regimens in terms of treatment response (plasma viral load <50 copies/mL) at 48 weeks (Gathe, 11th CROI, 2004). Response rates were 70% in the once-daily group and 64% in the twice-daily group (difference, 6.4%; 95% confidence interval, -7.3% to 20.1%). Response rates with the PI-based regimens did not exceed 70%

when the data were analyzed on an intent-to-treat basis.

### **Boosted Atazanavir After Early Virologic Failure**

The BMS 045 trial compared atazanavir 300 mg/ritonavir 100mg; atazanavir 400 mg/saquinavir 1200 mg; and lopinavir 400 mg/ritonavir 100 mg, each combined with tenofovir and 1 nRTI in patients who had received 1 or 2 prior antiretroviral regimens. (De Jesus et al, 11th CROI, 2004) The atazanavir/ritonavir regimen was comparable to the lopinavir/ritonavir regimen in reducing plasma HIV RNA levels at 48 weeks (mean reductions of 1.93 log<sub>10</sub> and 1.87 log<sub>10</sub>, respectively). The reduction with atazanavir/saquinavir (1.55 log<sub>10</sub>) was not as great as with lopinavir/ritonavir (statistically significant in a time-averaged difference estimate). The ritonavir-boosted atazanavir regimen appears to provide better virologic activity than regimens with unboosted atazanavir. Further, the BMS045 study showed reductions in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels with both of the boosted atazanavir regimens, suggesting the potential for reduced metabolic adverse effects; however, HDL cholesterol also was reduced. Although the boosted atazanavir regimen has yet to be examined in a trial of initial therapy, these findings have prompted some practitioners to use ritonavir-boosted atazanavir when atazanavir is being used in initial antiretroviral regimens. The antiviral activity is likely to be similar in antiretroviral-naive patients treated with this regimen, but the absence of lipid effects still needs to be demonstrated in the treatment-naive population, since most of the patients evaluated in the BMS 045 study were coming off of a ritonavir-containing regimen.

### **Conclusion**

The timing and choice of the initial antiretroviral regimen continues to be refined. As discussed in the recently published 2004 guidelines on antiretroviral therapy by the International AIDS Society–USA panel (Yeni et al, *JAMA*, 2004), not much has changed in the

decision process of when to initiate therapy. On the other hand, optimal choices regarding the type of initial regimen to use are becoming clearer. Assuming equal potency, the choice of initial regimens should focus on the tolerability of the regimen, especially with regard to subtle, perhaps intermittent, intolerances that lead to missed doses. Once-daily dosing schedules and lower pill burden remain important considerations in the choice of initial therapy as well. In this regard, fixed-dose combinations of abacavir/lamivudine and tenofovir/emtricitabine have just been approved by the US Food and Drug Administration for once-daily administration.

Finally, recent studies demonstrate in full relief the importance of conducting clinical trials to fully elucidate the utility of newer treatment combinations. Very few investigators or clinicians predicted the poor responses noted among the tenofovir/abacavir or the didanosine/lamivudine/tenofovir combinations. Similarly, the potential protective effect of zidovudine on the appearance of the K65R mutation could only be fully established through carefully performed clinical trials. Although the data for the “best” regimen for initial therapy will continue to evolve, the ultimate “best regimen” is what is best for each individual patient and this remains a function of good physician-patient communication.

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## Perspective

# Diagnosis and Management of Body Morphology Changes and Lipid Abnormalities Associated With HIV Infection and Its Therapies

*Body-shape changes and lipid abnormalities are common metabolic disorders in HIV-infected persons. It is likely that numerous factors contribute to body-morphology changes, including antiretroviral therapy, HIV infection itself, and immune reconstitution under antiretroviral therapy. A recent large cross-sectional investigation, the Fat Redistribution and Metabolism (FRAM) study, suggests that lipoatrophy is the most common feature of body-shape changes. Recent findings suggest modest benefit in reversing fat wasting by switching to abacavir from stavudine or zidovudine but no benefit from rosiglitazone treatment or switching from protease inhibitor to nonnucleoside reverse transcriptase inhibitor therapy. Human growth hormone treatment reduces fat accumulation, but treatment is expensive and gains in this regard are lost when treatment is stopped. Guidelines for treating lipid abnormalities in the non-HIV-infected population generally apply to HIV-infected persons; however, drug-drug interactions and overlapping toxicities between HIV and lipid therapies must be recognized. Although antiretroviral agents can raise lipid levels, there are data to suggest that in the case of cholesterol, HIV therapy reverses HIV infection-induced reductions of all cholesterol subsets. There are conflicting data regarding whether there is increased cardiovascular morbidity and mortality in the HIV-infected population. On balance, it appears that cardiovascular disease due to HIV-associated lipid disorders currently is a relatively infrequent problem, but one that is increasing in magnitude. This article summarizes a presentation by David A. Wohl, MD, at the February 2004 International AIDS Society–USA course in Atlanta.*

Metabolic abnormalities in HIV-infected persons include lipodystrophy (ie, fat loss and fat accumulation) and lipid abnormalities that may pose risk of cardiovascular disease. A variety of factors may contribute to HIV-associated metabolic abnormalities; it has yet to be precisely determined to what relative degrees these abnormalities are due to HIV infection itself or to drugs used in treating HIV disease.

## Body Morphology Changes

### Case Presentation

A 37-year-old HIV-infected man on antiretroviral therapy presented with a complaint of progressive thinning of the face and legs and development of a “beer belly.” He has a 7-year history of HIV infection. His initial therapy was zidovudine/lamivudine/indinavir; stavudine was substituted for zidovudine after rapid development of anemia. His

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nadir CD4+ cell count was 364/μL, and his pretreatment plasma HIV RNA level is unknown. The indinavir regimen was modified to twice daily with ritonavir boosting 18 months ago. Currently, the patient has an HIV RNA level below assay detection limits and a CD4+ cell count of 1064/μL. Which among the following is a reasonable approach to addressing the body changes?

- Change stavudine to tenofovir or abacavir.
- Change indinavir/ritonavir to a nonnucleoside reverse transcriptase inhibitor (NNRTI) or atazanavir.
- Attempt to obtain human growth hormone therapy.
- Start treatment with metformin or a peroxisome proliferator-activated receptor (PPAR)-γ agonist (eg, rosiglitazone or pioglitazone).
- Stop antiretroviral treatment with the plan to restart it when the CD4+ cell count reaches a predetermined level (eg, 350/μL).

- Reassure the patient and forge on with the current successful regimen.

## Discussion

Body morphology changes in HIV-infected persons include fat accumulation (lipohypertrophy) and fat loss (lipoatrophy). Fat accumulation includes dorsocervical fat accumulation (“buffalo hump”), visceral adiposity, and breast enlargement. Fat loss includes facial-fat and limb-fat loss. The Fat Redistribution and Metabolic Changes (FRAM) study has provided cross-sectional data on metabolic alterations in a large group of HIV-infected patients (Grunfeld, 2002 IAC; Gripshover, 10th CROI, 2003; Saag, 10th CROI, 2003; Zolopa, 10th CROI, 2003). Characteristics of a randomly selected population of more than 800 men and 350 women with HIV infection, of whom 14% were not receiving antiretroviral therapy, were compared with those of control subjects aged 33 to 45 years from a prospective cardiovascular disease cohort in the Coronary Artery Risk Development in Young Adults (CARDIA) database. Evaluations consisted of a self-report questionnaire, physical exam, dual energy x-ray absorptiometry (DEXA) scans, magnetic resonance imaging, computed tomography scans, and laboratory analyses.

Preliminary findings in HIV-infected men indicated that lipoatrophy is the main component of body morphology changes that distinguishes the HIV-infected group from the control group. Notably, despite clinical impressions to the contrary, those who reported fat loss did not have more central fat gain than control-group subjects, nor did they have increased visceral fat accumulation. There was no difference in the prevalence of buffalo hump between groups, but the size of the fat accumulation was significantly greater in the HIV-infected group than in the control

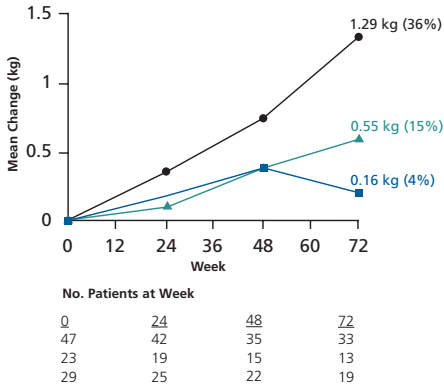


Figure 1. Changes in limb fat measured by dual-energy x-ray absorptiometry over 18 months in patients in the MITOX study who switched to abacavir at week 0 (circles) or week 24 (triangles) or who remained on stavudine- or zidovudine-containing regimens (squares) via on-treatment analysis. Adapted from Smith et al, 2nd IAS, 2003 and Martin et al, AIDS, 2004.

group. Findings in HIV-infected women indicated the presence of less peripheral fat than in control-group subjects (Shevitz, 2nd IAS, 2003). In contrast to what was observed in men, central lipoatrophy was inversely associated with peripheral lipoatrophy in women, and women without lipoatrophy had more upper trunk fat and more visceral adipose tissue than did controls. Some of the findings in men, such as the similarity in frequency of buffalo hump between patients and control-group subjects, do not appear to agree with the clinical experience of HIV care practitioners. A prospective follow-up of the FRAM study is under way that may help clarify the evolution of the body changes in HIV-infected men and women.

As noted, a variety of factors appear to play a role in body-shape changes. Available data support a direct role of nucleoside reverse transcriptase inhibitors (nRTIs), especially stavudine, in fat wasting, and a probable synergistic interaction with protease inhibitors (PIs) in this regard; evidence of a direct role of PIs in fat wasting is less clear. Cohort studies indicate that the duration of HIV disease is associated with body-shape changes, and other data indicate a potential role of immune reconstitution in these changes by showing a relation-

ship between body-shape changes and low CD4 + cell count nadirs. A potential role of genetic predisposition is suggested by findings indicating that patients' body mass index (BMI) is predictive of the tendency to gain or lose fat and possible racial and ethnic differences in the incidence of body-shape abnormalities.

Approaches under investigation for the treatment of fat accumulation include antiretroviral switching, exercise and diet, anabolic steroids, recombinant human growth hormone, metformin, PPAR- $\alpha$  agonists (glitazones), and plastic surgery. Approaches to fat loss, which can be considered the hallmark of the body-shape changes observed in HIV-infected patients, include antiretroviral switching, glitazones, and plastic surgery. A number of recent studies have examined some of these approaches to lipoatrophy. Switching of antiretroviral agents, which may be the approach best supported by currently available data, was assessed in the MITOX study, in which patients with peripheral lipoatrophy switched from stavudine or zidovudine to abacavir in their antiretroviral regimens. As shown in Figure 1, DEXA-measured limb-fat changes at 18 months increased by 36% in those switching to abacavir at week 0 and by 14% in those switching at week 24 (Smith, 2nd IAS, 2003). Subjects remaining on stavudine or zidovudine had a negligible 4% increase. The improvements observed with switching to abacavir are modest but at least indicate the potential for preventing worsening of fat loss.

The potential use of glitazones to treat HIV-associated lipoatrophy was suggested by the effects of the early glitazone troglitazone in producing peripheral fat gains in individuals with congenital lipoatrophy. A small randomized, placebo-controlled trial in 27 HIV-infected patients with insulin resistance and lipoatrophy indicated that treatment with rosiglitazone produced an overall significant increase in percentage of body fat at 3 months, as measured by bioelectrical impedance analysis (BIA; Hadigan et al, *Ann Intern Med*, 2004). Patients remaining on rosiglitazone or beginning rosiglitazone after 3 months reported greater satisfaction with body shape at 6 months. The amount of subcutaneous fat increased,

but there was little difference in limb fat. However, in a larger randomized, placebo-controlled trial (ROSEY study) in 108 patients, all of whom had lipoatrophy (mostly men, all white; Carr et al, *Lancet*, 2004), rosiglitazone treatment was not associated with improvements in DEXA-measured limb fat compared with placebo at 48 weeks. On this study, however, both the treatment and the control groups exhibited modest increases in limb fat — a finding that has yet to be explained. These negative results have dampened enthusiasm for the use of glitazones in this setting.

Studies using human growth hormone indicate that such treatment can reduce dorsocervical fat accumulation and visceral adiposity. Results of one study are shown in Figure 2 (Kotler, *JAIDS*, 2004). However, the treatment is expensive and rarely covered by third-party payors, and it is associated with numerous adverse effects including abnormal glucose metabolism, arthralgias, and carpal tunnel syndrome. In addition, body-shape abnormalities often return upon cessation. Moreover, since the agent is lipolytic, fat wasting can be worsened in

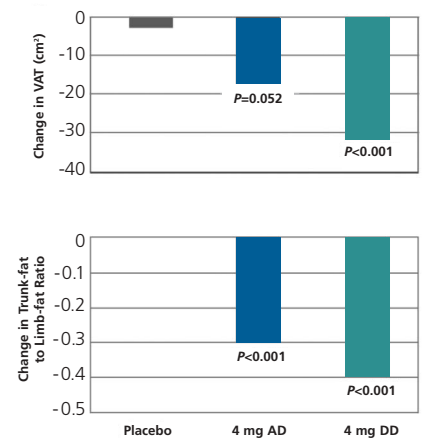


Figure 2. Changes in computed tomography measurement of visceral adipose tissue (VAT) and trunk-fat to limb-fat ratio measured by dual-energy x-ray absorptiometry in patients receiving recombinant human growth hormone treatment (intent-to-treat analysis). P values for change from baseline to week 12 compared with placebo group. DD indicates daily; AD, alternate days. Adapted from data in Kotler et al, *JAIDS*, 2004.

patients with both lipoatrophy and lipohypertrophy.

With regard to other potential approaches involving modification of antiretroviral therapy, one small study has suggested that switching from PI to NNRTI treatment has little effect on lipodystrophy (Garcia-Benayas, 5th Inter Workshop on ADR and Lipodystrophy, 2003). BIA and anthropometric assessment at 48 weeks in patients switching from a PI to nevirapine or efavirenz showed no changes in weight, BMI, lipodystrophy index, and other measures, and mild worsening of calf and triceps skin folds.

Among cosmetic approaches to lipoatrophy, poly-lactic acid injections have attracted considerable attention in some locales. Injection of the compound into subcutaneous tissue can result in improved appearance in cases of facial lipoatrophy. A recent report indicates that even in experienced hands, the procedure may be associated with serious adverse events in addition to pain and bruising in the injection area. In a study in 100 patients, an anaphylactic reaction to injection occurred in one patient and a facial nerve palsy occurred in another. However, this 2% serious adverse event rate is not so different from the adverse event rate seen with botulinum toxin injections. Poly-lactic acid injections are widely available in Europe, and there is interest in having the procedure approved for use in the United States.

### Case Conclusion

The chosen approach in the case outlined above was to stop antiretroviral treatment, given that the patient's CD4+ cell count nadir was relatively high, and to restart it when the CD4+ cell count began to decrease toward 350/ $\mu$ L. Since the patient's pretreatment HIV RNA level is not known, the patient will be monitored for degree of viral rebound. The patient agreed with this approach. Had he expressed anxiety over stopping treatment, it is likely that the substitution of abacavir or tenofovir for stavudine would have been selected as the management option; in this case, the patient would have been informed that although dramatic improvement in the body morphology

was unlikely to occur at least in the short term, the approach would provide continued effective antiretroviral treatment and would likely prevent the lipodystrophy from worsening.

## Lipid Abnormalities

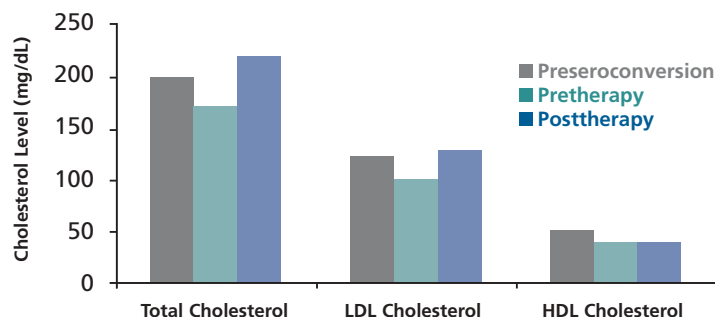
### Case Presentation

A 47-year-old man is newly diagnosed with HIV infection. His CD4+ cell count is 210/ $\mu$ L and his plasma HIV RNA level is 125,000 copies/mL. He agrees to initiate antiretroviral therapy. The patient smokes a pack of cigarettes per day, and does not have diabetes or hypertension. His father had a myocardial infarction (MI) at age 53 years. The patient's fasting lipid profile shows total cholesterol of 235 mg/dL, low-density lipoprotein (LDL) cholesterol of 141 mg/dL, high-density lipoprotein (HDL) cholesterol of 33 mg/dL, and triglyceride level of 290 mg/dL. In accordance with published guidelines and based on clinical efficacy and convenience, the patient is started on efavirenz/zidovudine/lamivudine and receives dietary counseling. A few weeks later, the patient is started on bupropion to assist in smoking cessation. At 4 months, the patient has a CD4+ cell count of 375/ $\mu$ L and HIV RNA level of less than 50 copies/mL. He has stopped taking bupropion, but his cigarette consumption is down to a half pack per day. His total cholesterol has increased to 248 mg/dL, LDL cholesterol to 147 mg/dL, and triglyceride level to 355 mg/dL; his

HDL cholesterol has increased to 38 mg/dL. Should the patient be put on lipid-lowering medication?

### Discussion

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III provides guidelines for initiating lipid-lowering therapy in adults based on assessment of coronary risk (*JAMA*, 2001). In the absence of evidence to the contrary, these guidelines should be used in HIV-infected individuals. The LDL cholesterol level at which initiation of drug treatment is recommended and the target LDL cholesterol level are determined by number of coronary risk factors and level of 10-year risk for coronary disease as determined by the Framingham risk calculator. Although this patient has no clinically evident coronary disease, he has multiple risk factors, including older age, cigarette smoking, low HDL cholesterol, and family history of premature coronary disease. The Framingham point-scoring risk calculation shows the patient to have a 10-year coronary risk of approximately 25%, indicating that treatment should be considered at an LDL cholesterol level of 130 mg/dL or higher with a target of less than 100 mg/dL. It is important to note that based on studies of HIV-uninfected persons, the NCEP guidelines are being revised and will likely lower the threshold for lipid-lowering therapy initiation, a recommendation that will have implications for HIV-infected patients with dyslipidemia.



**Figure 3.** Total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol levels prior to HIV seroconversion (left, gray), prior to initiation of antiretroviral therapy (middle, green), and after initiation of therapy (right, blue) in patients in a Multicenter AIDS Cohort Study (MACS) cohort. Adapted from Riddler et al, *JAMA*, 2003.

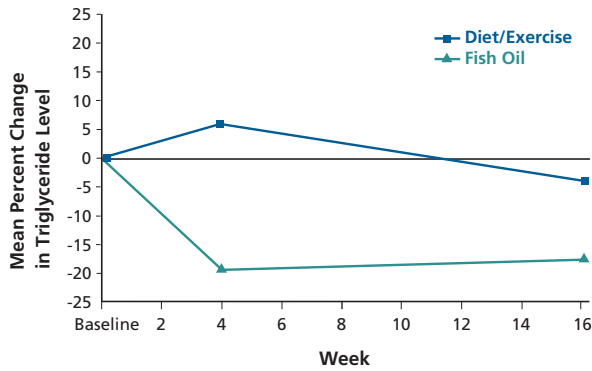


Figure 4. Effects of omega-3 fatty acids (fish oil) versus diet/exercise on triglyceride levels. Adapted with permission from Wohl et al, 11th CROI, 2004.

Manipulation of the antiretroviral regimen to include agents that may have less pronounced effects on blood lipids might be possible; however, changing the current regimen may not be desirable, since it continues to exert virologic control. Institution of lipid-lowering treatment is thus a reasonable approach.

Studies in healthy volunteers and HIV-infected patients have shown that antiretroviral drugs can raise lipid levels. However, it should also be noted that data from a Multicenter AIDS Cohort Study (MACS) indicate that HIV infection itself may be associated with decreases in total and LDL cholesterol. As shown in Figure 3, measurements of nonfasting blood samples from patients prior to HIV seroconversion, after infection but prior to potent antiretroviral therapy, and after the start of antiretroviral therapy suggest a decrease in cholesterol levels after seroconversion and an increase with potent antiretroviral therapy (Riddler, *JAMA*, 2003).

The effects of increased lipids on cardiovascular morbidity and mortality in the HIV-infected population remain incompletely defined. A retrospective analysis of the Veterans Administration database indicates that rates of hospital admission and death due to cardiovascular disease remained generally unchanged in HIV-infected patients between 1993 and 2001 (Bozzette, *N Engl J Med*, 2003). However, prospective data from a US and European cohort (D:A:D Study) indicate a significant association of rates of MI with years of combination antiretroviral therapy. On balance, available data appear to indicate that HIV-associated cardiovascular

disease is a relatively infrequent but probably growing problem and that patients with lipid risk factors should receive appropriate lipid-lowering therapy.

#### Case Conclusion

The patient was informed of his coronary risk status and was started on atorvastatin therapy to reduce LDL cholesterol level, with the statin selected to minimize the potential for harmful drug-drug interactions with antiretroviral drugs via cytochrome P450 isoenzyme metabolism. Recent data do indicate that efavirenz can induce the metabolism of atorvastatin and simvastatin, likely reducing the efficacy of these lipid-lowering agents (Gerber et al, 11th CROI, 2004). In practice this interaction may require cautious titration of the dose of atorvastatin if a suboptimal response is seen at starting doses. Statin treatment was well tolerated. The patient stopped smoking and lost 7 pounds with moderate exercise (walking every other day, taking stairs instead of the elevator) and dietary changes (fewer sweets, more fruits and vegetables). After 8 weeks, his LDL cholesterol level had been reduced to 123 mg/dL. Statin therapy rather than fibrate therapy was selected in this patient because of the patient's elevated LDL cholesterol level and the fact that reducing LDL cholesterol is the primary goal of lipid-lowering therapy in hypercholesterolemic patients. However, the patient also has an elevated triglyceride value. It has been demonstrated that omega-3 fatty acids can produce marked reduc-

tions in triglyceride levels in HIV-infected patients (Figure 4); given the patient's elevated triglyceride level, omega-3 fatty acid administration is also an option in this case.

#### Summary

HIV-associated body-shape changes are a vexing problem for which etiologies remain elusive and therapeutic options remain limited. Avoidance of or substitution for stavudine when possible appears to be a prudent measure to prevent or reduce lipoatrophy. Lipids are an important consideration when crafting antiretroviral therapies. The risk of coronary disease among HIV-infected persons appears to be relatively low at present but also appears to be increasing. The NCEP Adult Treatment Panel III guidelines for lipid lowering ([www.nhlbi.nih.gov/guidelines/cholesterol](http://www.nhlbi.nih.gov/guidelines/cholesterol)) should be used in assessing an HIV-infected patient's need for lipid-lowering treatment.

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