

## Perspective

# Metabolic Complications of Antiretroviral Therapy

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*HIV-infected patients receiving long-term antiretroviral treatment experience a number of metabolic abnormalities, including lipid abnormalities, dysregulation of glucose metabolism, body-fat redistribution, mitochondrial abnormalities, and bone abnormalities, as well as the sequelae of these disorders. These complications can be severe and life threatening, disrupt adherence to antiretroviral therapy, limit options in therapy, and profoundly affect quality of life. Risk for such complications should be considered in selection of antiretroviral therapy, and patients should be monitored for the occurrence of abnormalities and changes in risk factors. This article summarizes a presentation by Donna E. Sweet, MD, on the metabolic complications of long-term antiretroviral therapy at the IAS–USA course in New York in March 2005.*

Many advances have been made in understanding the pathogenesis and progression of HIV disease, developing effective antiretroviral agents and regimens, learning how best to use these regimens for prolonged maximal viral suppression, lowering the pill burden of regimens, and managing many acute adverse effects of treatment. The problems for many patients on long-term effective antiretroviral therapy are the long-term metabolic complications of treatment. Much work remains to be done in identifying how best to avoid these complications and how to effectively treat them when they cannot be avoided.

## Clinical Implications of Metabolic Abnormalities

HIV-infected patients receiving long-term antiretroviral therapy exhibit a number of metabolic complications, including lipid abnormalities, dysregulation of glucose metabolism, body-fat redistribution, mitochondrial abnormalities, and bone abnormalities, as well as the sequelae of these disorders. The etiology of these abnormalities remains largely undefined, and it is unclear whether they represent individual or multiple syndromes. The prospect of patients ultimately experiencing these abnormalities influences the timing of initiation of antiretroviral therapy, since the risk of long-term toxicity must be considered against the virologic and immunologic benefits of early treatment. The risk of these abnormali-

ties should also influence the choice of initial therapy, and the selection should be individualized as much as possible based on risk factors for the abnormalities. The metabolic derangements have an impact on adherence to therapy, which threatens efficacy, and their presence may limit options in salvage therapy. Specific strategies to minimize the occurrence of these abnormalities, such as simplification of regimens, need to be developed to preserve the efficacy of antiretroviral treatment.

## Lipodystrophy

Lipodystrophy, including lipoatrophy (wasting) and lipohypertrophy (accumulation), has occurred in an estimated 40% to 50% of patients on long-term treatment, and the morphologic changes have a substantial impact on patient quality of life. The lack of a standardized case definition for lipodystrophy complicates characterization, diagnosis, and tracking of the disorder. The etiology of the abnormalities remains unknown, although it appears to be multifactorial and influenced by specific antiretroviral drugs, host factors such as age and genetics, and HIV disease stage. Because there are probably multiple causes of fat redistribution, it is unlikely that a single uniform treatment approach will be successful. Management strategies for lipodystrophy include exercise and diet, switching of antiretroviral drugs, anabolic steroids, testosterone, recombinant human growth hormone, metformin and glitazone treatment, lipid-lowering therapy, and plastic surgery. The benefits of most of these strategies remain largely unproven.

With regard to risk associated with particular nucleoside reverse transcriptase inhibitors (NRTIs), a number of studies have shown that the use of an NRTI backbone of didanosine/stavudine is associated with greater fat loss than is zidovudine/lamivudine (eg, the AIDS Clinical Trials Group [ACTG] 384 study) or abacavir/lamivudine (eg, Strategies for Management of Antiretroviral Therapy–Terry Bein Community Programs for Clinical Research on AIDS [SMART-CPCRA] study 065C). A recent report from the metabolic substudy in the FIRST study showed reductions in total and regional fat in patients receiving didanosine/stavudine but not in those receiving abacavir/lamivudine over 32 months (Shlay et al, XV Int AIDS Conf, 2004). Increases in body cell mass and fat were observed in both treatment groups through month 12. However, overall changes from month 0 to 32 for the didanosine/stavudine and abacavir/lamivudine treatment arms, respectively were  $-0.08$  kg/month and  $+0.08$  kg/month in total body fat,  $-0.18$  cm/month and  $+0.10$  cm/month in hip circumference,  $-0.21$  cm<sup>2</sup>/month and  $+0.05$  cm<sup>2</sup>/month in mid-arm skinfold fat area, and  $-0.62$  cm<sup>2</sup>/month and  $+0.62$  cm<sup>2</sup>/month in waist skinfold fat area ( $P < .05$ ).

A number of studies on drug switching were reported at the recent Conference on Retroviruses and Opportunistic Infections. In brief, findings in these studies indicate that substituting a protease inhibitor (PI) with a nonnucleoside reverse transcriptase inhibitor (NNRTI) appears safe, decreases insulin resistance, usually reduces triglyceride levels, has inconsistent effects on total cholesterol and high-density lipoprotein (HDL) cholesterol levels, and has no consistent effects on fat gain or loss. Other findings indicated that abacavir substitution for stavudine results in increased subcutaneous adipose tissue (SAT) but no change in visceral adipose tissue (VAT).

Findings to date on studies of the effects of rosiglitazone in lipodystrophy indicate that it may not be effective in

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increasing subcutaneous fat in patients with lipoatrophy alone but may increase fat mass in those with both insulin resistance and lipoatrophy. Treatment with this agent improves insulin sensitivity, hyperinsulinemia, and adiponectin levels, but may result in increased total and low-density lipoprotein (LDL) cholesterol levels. Further studies with newer glitazones are needed to define subpopulations of patients most likely to benefit from such treatment.

### Dyslipidemia and Coronary Heart Disease

Traditional cardiovascular risk factors contribute to cardiovascular disease in HIV-infected patients and these risk factors need to be managed aggressively. HIV-infected patients appear to be at increased risk of coronary heart disease (CHD), as well as for diabetes and hypertension, both major risk factors for CHD. Antiretroviral therapy appears to accelerate the progression of insulin resistance and dyslipidemia. A recent study has indicated that HIV infection alone, prior to initiation of therapy, is associated with increased cholesterol levels and an adverse effect on insulin sensitivity (El-Sadr et al, *HIV Med*, 2005). HIV-mediated inflammation may also play a role in accelerated CHD. Treatment of risk factors for CHD is complicated by drug-drug and drug-disease interactions in HIV-infected patients. Further studies are needed to understand the pathogenesis of dyslipidemia and cardiovascular disease in HIV-infected patients.

Some of the data indicating an increased risk of cardiovascular disease in the HIV-infected population include a Veterans Administration study showing cardiovascular disease rates of 11.8 per 1000 person-years in HIV-infected patients, compared with 8.1 per 1000 person-years in HIV-uninfected individuals matched for age and sex. In the Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) study, conducted in 11 cohorts in Europe, Australia, and the United States, 126 cases of myocardial infarction (MI), 28% of which were fatal, were found in 36,479 person-years of observation. The relative risk for MI in HIV-infected patients on long-term therapy was 1.26 per year of therapy; a recent update after an additional year of follow-up indicates a relative risk of 1.17 per year of antiretroviral therapy (Sabin et al, 12th CROI, 2005). Another study has reported that patients with AIDS have a relative risk of 10.4 for stroke. Another has suggested that carotid artery intima media thickness, a surrogate marker for coronary disease, is greater and increases more rapidly in HIV-infected patients than in age-matched controls.

Recommendations for treating dyslipidemia in HIV-infected patients to reduce cardiovascular risk include following the National Cholesterol Education Panel (NCEP) recommendations for the general population, including institution of diet and exercise and smoking cessation. Drug-drug interactions and liver toxicity in association with HIV-hepatitis B or C virus coinfection need to be taken into careful consideration when selecting

lipid-lowering drug therapy. For drug therapy, statin treatment may consist of pravastatin 40 mg or atorvastatin 5 or 10 mg; higher doses of atorvastatin may be needed if patients are taking efavirenz. Low-dose fluvastatin may also be considered, with careful dose titration; fluvastatin should not be used if the patient is taking saquinavir/ritonavir or nelfinavir. Simvastatin and lovastatin should be avoided until further pharmacokinetics studies are performed to identify drug interactions. Fenofibrate 160 mg may also be used to treat dyslipidemia. Other agents under study in the HIV-infected population include niacin, fish oil, and ezetimibe. A recent study indicated that fish oil taken 3 times daily produced a large decrease in triglycerides in hypertriglyceridemic patients, although levels remained elevated above normal (Wagh, *Expert Rev Cardiovasc Ther*, 2004). For patients in whom hyperlipidemia is present before beginning antiretroviral therapy, regimens containing atazanavir, tenofovir, or efavirenz may be appropriate to have less effect on lipid profiles. As shown in Figure 1, both atazanavir-based and efavirenz-based therapies resulted in stability or an increase in appendicular and truncal fat on dual energy x-ray absorptiometry scan and increased SAT and VAT on computed tomography in the BMS-034 study (Noor et al, XV Int AIDS Conf, 2004).

With regard to the effects of anabolic steroid treatment on lipid profiles and fat distribution, a recent 12-week study in 32 patients indicated that oxandrolone with exercise caused worsening in lipid

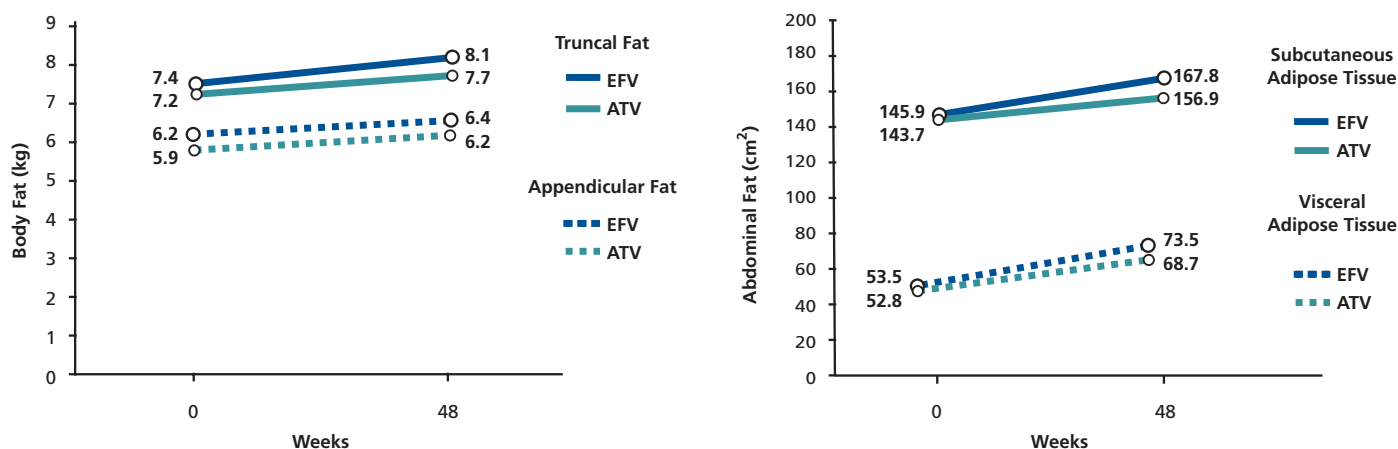


Figure 1. Changes in body fat (left) on dual energy x-ray absorptiometry (DEXA) and in abdominal fat (right) on computed tomography (CT) over 48 weeks of efavirenz-based (EFV) or atazanavir-based (ATV) treatment in the BMS-034 study. Adapted with permission from Noor et al, XV Int AIDS Conf, 2004.

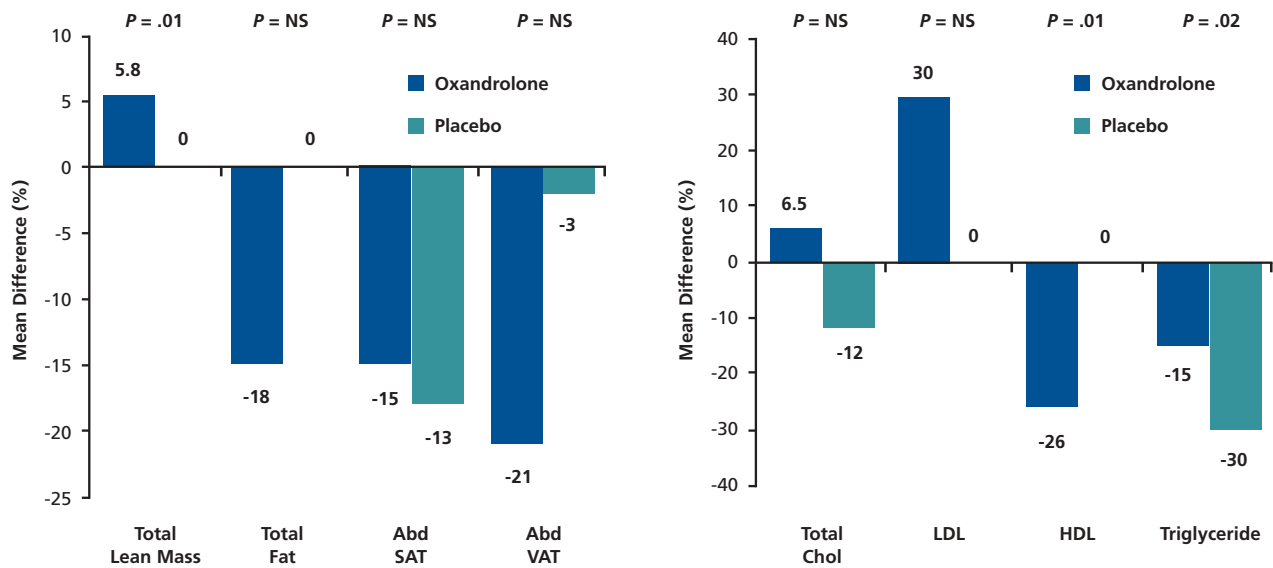


Figure 2. Changes in body fat and lipid measures over 12 weeks with oxandrolone treatment plus exercise (oxandrolone) or exercise alone (placebo). Abd SAT indicates abdominal subcutaneous adipose tissue; Abd VAT, abdominal visceral adipose tissues; Chol, cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NS, not significant. Adapted with permission from Smith et al, XV Int AIDS Conf, 2004.

measures (increased LDL cholesterol and reduced HDL cholesterol levels) compared with exercise alone (Figure 2); however, the study groups were not well matched for lipid variables at baseline (Smith et al, XV Int AIDS Conf, 2004).

## Glucose Metabolism

Abnormalities of glucose homeostasis, primarily insulin resistance, are common in patients on antiretroviral therapy, with a greater frequency of abnormalities observed in patients receiving PIs. The mechanisms of these abnormalities remain largely undefined. Management includes encouraging weight loss for overweight individuals. Treatment with insulin-sensitizing agents may be beneficial; diabetes treatment guidelines should be followed in HIV-infected individuals.

Recent findings in this area include an association of hyperinsulinemia with the dorsocervical fat deposit termed “buffalo hump” in HIV-infected patients (Mallon et al, *J Acquir Immune Defic Syndr*, 2005). This finding indicates that patients with buffalo hump should be closely followed for insulin resistance and diabetes. It also suggests that caution should be exercised when using human growth hormone for treating buffalo hump, since growth hormone is associated with hyperinsulinemia.

Another recent study indicates that abnormal glucose metabolism may fuel cognitive dysfunction in HIV-infected patients (Valcour et al, *J Acquir Immune Defic Syndr*, 2005). The study indicated that diabetes is an independent risk factor for HIV-associated dementia, with the data hinting that subtle, prediabetic abnormalities in glucose regulation may also pose a risk for cognitive impairment. Among 203 adult patients aged 20 to 76 years (approximately 50% aged >50 years), older patients with diabetes were more likely to meet the research classification of HIV dementia. After adjustment for age, education, ethnicity, CD4+ cell count, duration of HIV infection, and PI-based therapy, diabetes was significantly associated with risk for HIV-associated dementia, with an odds ratio of 5.43, and the significant association remained after adjustment for coexisting vascular risk factors for dementia.

## Bone Disorders

Osteopenia, osteoporosis, and avascular necrosis have been reported in patients with HIV infection. An association of these disorders with PI-containing regimens with tenofovir has been reported in the past, but some recent small studies call this into question. Various risk factors may contribute to these abnor-

malities, including prior steroid treatment for avascular necrosis, cigarette smoking, and hormone therapy for osteoporosis. Clinicians need to be aware of the potential for bone disorders and should treat them early; however, routine screening is not recommended. Further study is needed to identify the etiology of decreased bone mineral density, risk factors, and appropriate prevention and treatment strategies. One recently reported study followed bone changes over 144 weeks in initially antiretroviral-naïve patients. Approximately 40% of patients had osteopenia at baseline, but, with treatment, there was no progression to osteoporosis over the course of follow-up. However, approximately 40% of patients were lost to follow-up, making it difficult to interpret the study findings.

## Mitochondrial Disorders

Mitochondrial toxicity of nRTIs may underlie or contribute to many of the metabolic abnormalities associated with these agents. Older nRTIs (eg, stavudine, didanosine, zidovudine, zalcitabine) are associated with a greater risk of toxicity than newer agents (eg, lamivudine, emtricitabine, abacavir, tenofovir). Mitochondrial toxicity has been implicated in neuromuscular toxicities such as polyneuropathy (zalcitabine, didanosine,

stavudine), myopathy (zidovudine, didanosine), and cardiomyopathy (zidovudine, zalcitabine, didanosine); pancreatitis (didanosine, stavudine); pancytopenias (zidovudine); hepatic microvesicular and macrovesicular steatosis (zidovudine, didanosine, stavudine, zalcitabine); peripheral fat wasting (stavudine); and hyperlactatemia and lactic acidosis. The role of HIV per se in mitochondrial toxicity is not clear.

There are data that indicate recovery in mitochondrial DNA following a switch to an nRTI-sparing regimen. In one study, mitochondrial DNA in both fat biopsies and peripheral blood mononuclear cells (PBMCs) increased in patients switched from nRTI therapy to an nRTI-sparing regimen (Boyd et al, XV Int AIDS Conf, 2004). The gain in fat mitochondrial DNA was significant only when the switch was from stavudine, not zidovudine, and the increase in DNA in PBMCs was significant only after switching from zidovudine, not stavudine (Figure 3; Boyd et al, XV Int AIDS Conf, 2004).

### Hyperlactatemia and Lactic Acidosis

As noted, hyperlactatemia and lactic acidosis appear to be due to nRTI mitochondrial toxicity, and greater risk is associated with older nRTIs, such as zalcitabine, didanosine, stavudine, zidovudine, lamivudine, and abacavir. The lactic acidosis observed is a "type B" lactic acidosis (dysfunction not due to lack of oxygen supply to tissue), for which mitochondrial dysfunction is a common pathophysiologic mechanism. Diagnosis

is difficult because symptoms are vague and nonspecific. Symptoms include nausea and vomiting, abdominal pain or gastric discomfort, unexplained fatigue, malaise, weight loss, and dyspnea. Symptoms may progress to severe, life-threatening metabolic acidosis. Although severe lactic acidosis is relatively rare, a high index of suspicion must be maintained for the disorder in any patient receiving nRTIs. Prompt discontinuation of the offending nRTI is associated with better prognosis. Onset of symptoms cannot be predicted by routine monitoring of lactate levels. Risk factors include older age, obesity, and female sex. Hepatic steatosis usually is present and may be a key part of the syndrome. A milder variant of the syndrome may exist in the form of hyperlactatemia without acidosis. Asymptomatic hyperlactatemia is, however, very rare.

The clinical significance of low-level hyperlactatemia is unclear. Of concern is the role of the liver in the syndrome, with the findings being similar to what is observed in nonalcoholic steatohepatitis. Questions that remain to be answered include whether the condition poses potential for progression to cirrhosis and whether it is a confounding risk factor for liver failure in patients coinfecting with hepatitis B or C virus.

### Peripheral Neuropathy

nRTI-associated peripheral neuropathy is characterized by bilateral, symmetric, painful tingling sensations (dysesthesias) in the feet and toes, loss of tendon

reflexes (areflexia), and distal sensory loss. The disorder is primarily seen with didanosine and stavudine. It is variably reversible after stopping nRTI therapy. Nerve biopsies show damaged mitochondria. The condition is sometimes difficult to distinguish from neuropathy associated with HIV infection per se. Risk factors during nRTI treatment include low CD4+ cell count (<100/ $\mu$ L), prior history of an AIDS-defining illness or neoplasm, prior history of peripheral neuropathy, and use of other neurotoxic agents, including high alcohol consumption. Combination therapy with didanosine and stavudine increases risk of the disorder.

### Pancreatitis

Treatment with didanosine and stavudine is associated with a dose-dependent risk of pancreatitis, with the incidence probably ranging from 4% to 7% at currently recommended doses. Mitochondrial toxicity of nRTIs has been demonstrated in human pancreatic cell lines.

### Myopathy and Cardiomyopathy

Myopathy has been seen most commonly with zidovudine, although it is less frequent at current dosing levels. Mitochondrial DNA depletion and abnormal mitochondria have been described in skeletal and endomyocardial muscle from affected patients. Zidovudine-associated myopathy is difficult to distinguish from that caused by HIV infection per se. In the case of confirmed zidovudine-

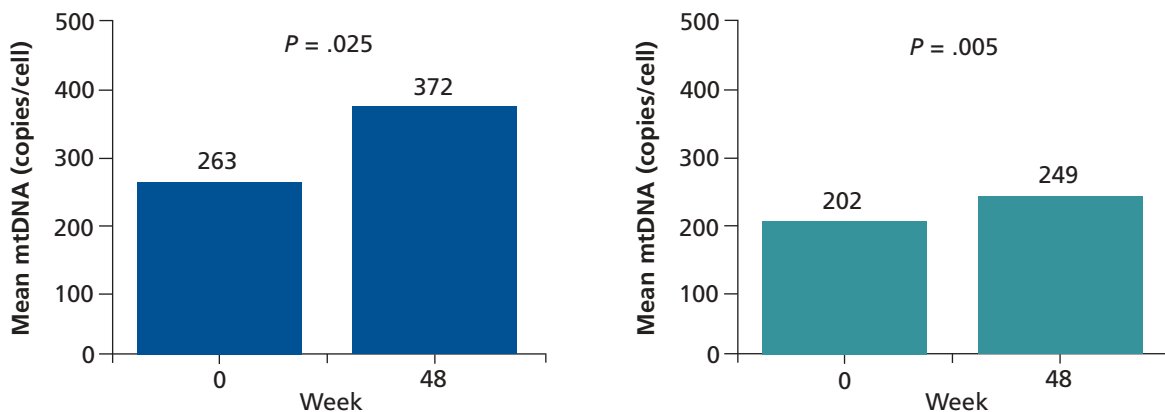


Figure 3. Changes in mitochondrial DNA (mtDNA) level in fat (left) and in peripheral blood mononuclear cells (PBMCs; right) over 48 weeks after switch to nRTI-sparing regimen. After stratification for prior nRTI, increase in fat mtDNA was significant only with switch from stavudine (not zidovudine) and increase in PBMC mtDNA was significant only with switch from zidovudine (not stavudine). Adapted with permission from Boyd et al, XV Int AIDS Conf, 2004.

**Table 1. Guidelines for Reducing Risk of Metabolic Complications**

- Think about the metabolic consequences of starting or switching antiretroviral therapy
- Assess the patient's risk factors and modify them when possible
- Lipodystrophy is easier to prevent than to reverse—avoid didanosine/stavudine
- Treat dyslipidemia, insulin resistance, and hypertension aggressively
- Think about lactate levels in patients with suggestive symptoms
- Be vigilant for bone disease—investigate symptoms, and treat such disease appropriately

associated myopathy and cardiomyopathy, clinical and histologic changes are reported to be reversible.

### Summary

Patients should be assessed for risk factors for metabolic complications of antiretroviral therapy prior to initiation of therapy and should be monitored for such complications every 3 to 6 months after starting treatment, at the time of switching therapy, and at least annually thereafter. Routine measurement of fasting glucose or glucose tolerance testing and routine monitoring of fasting lipids are recommended. Routine monitoring of anthropometric measurements, serum lactate levels, and bone density currently is not recommended.

Success of antiretroviral therapy does not depend solely on reducing plasma HIV-1 RNA levels to below 50 copies/mL. Metabolic complications of long-term therapy threaten the clinical benefits of such effective treatment. Table 1 provides basic guidelines for reducing the risk of metabolic complications.

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### Suggested Reading

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*Top HIV Med.* 2005;13(2):70-74.

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