

## Perspectives

# Metabolic Complications of Antiretroviral Therapy: Coronary Artery Disease Risks

*Coronary artery disease (CAD) risk factors have been increasingly observed in HIV-infected patients receiving potent antiretroviral therapy, although such risk factors were also detected in patients prior to use of potent combination regimens. Risk factor profiles, epidemiologic data on risk of CAD clinical events, and risk assessment and management were discussed by Marshall J. Glesby, MD, PhD, at the San Francisco course in April.*

In 1998, Henry and colleagues (*Lancet*) reported 2 cases of myocardial infarction in young men with HIV disease receiving protease inhibitor-including antiretroviral therapy. The report of these cases was followed by more than a dozen additional case reports, generating considerable concern about accelerated atherosclerosis in HIV-infected patients receiving potent antiretroviral therapy. Coronary artery disease (CAD) risk has thus recently emerged as an important clinical concern; Dr Glesby noted, however, that cardiac involvement is relatively common in advanced HIV infection (including pericardial effusion, endocarditis, and cardiomyopathy), and that CAD risk factors and atherosclerosis were described in HIV-infected patients in the early years of the epidemic.

Reports of risk factors prior to the era of potent antiretroviral therapy include observation of hypertriglyceridemia and decreased high-density lipoprotein (HDL) cholesterol levels (Grinfeld et al, *Am J Med*, 1989); increased plasma levels of endothelial cell products (eg, von Willebrand factor, tissue plasminogen activator; Lafeuillade et al, *J Acquir Immune Defic Syndr*, 1992); and vascular endothelial damage and significant coronary artery stenoses in autopsy series in children and young adults (Joshi et al, *Pediatr Pathol*, 1987; Paton et

al, *Res Virol*, 1993). Despite mounting evidence, however, there are no definitive data indicating that CAD is accelerated in the setting of treated or untreated HIV infection (compared to a matched HIV-seronegative adult population).

### CAD Risk Factors in HIV-Infected Patients

Antiretroviral therapy has been associated with a number of metabolic abnormalities known to increase cardiovascular risk in the general population. Among these are increased total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels. Of note, the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz has been associated with an increase in total cholesterol level that includes a sizable increase in HDL cholesterol; increased HDL cholesterol is protective against CAD. Similarly, recent data from the Atlantic study (Van der Valk et al, 8th CROI, 2001) indicate that patients receiving nevirapine/didanosine/lamivudine exhibited a 33% increase in HDL cholesterol level, an increase of a mag-

nitude rivaling the best increases observed with lipid-modifying treatment with niacin. Insulin resistance is observed with protease inhibitor therapy, although frank diabetes is uncommon. Truncal/visceral adiposity has been epidemiologically associated with protease inhibitor-based therapy.

A recent report has indicated an association of protease inhibitor therapy with hypertension. In a retrospective review of patients presented by Hewitt and colleagues (mean age, 37 to 40 years, approximately 40% being African-American) who had no history of hypertension and had received no prior protease inhibitor therapy with the exception of hard-gel capsule saquinavir, new-onset hypertension was detected in 22% of 178 patients beginning indinavir treatment, 9% of 164 beginning nelfinavir treatment, and 7% of 104 receiving non-protease inhibitor-containing therapy (8th CROI, 2001). Kaplan-Meier analysis, correcting for time on therapy, indicated that more than 50% of indinavir recipients would develop hypertension over 600 days of exposure, compared with approximately 35% of nelfinavir recipients and 35% of

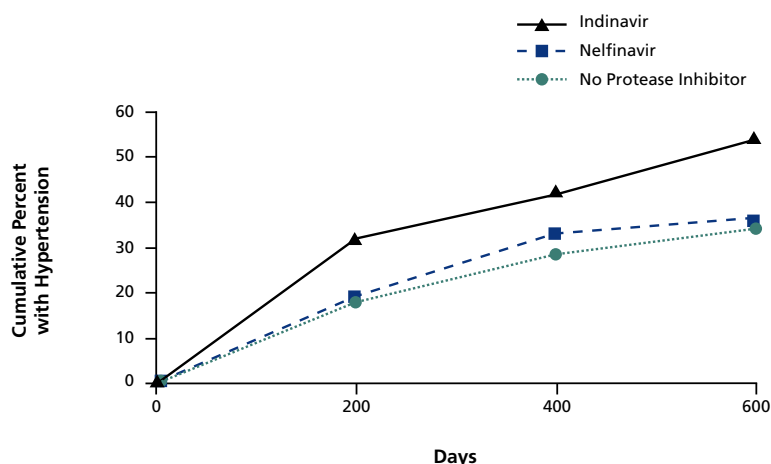


Figure 1. Kaplan-Meier plot of cumulative incidence of new-onset hypertension after start of treatment with indinavir, nelfinavir, or a non-protease inhibitor-containing regimen. Adapted with permission from Hewitt et al, 8th CROI, 2001.

Dr Glesby is Assistant Professor of Medicine at Weill Medical College of Cornell University, New York, New York.

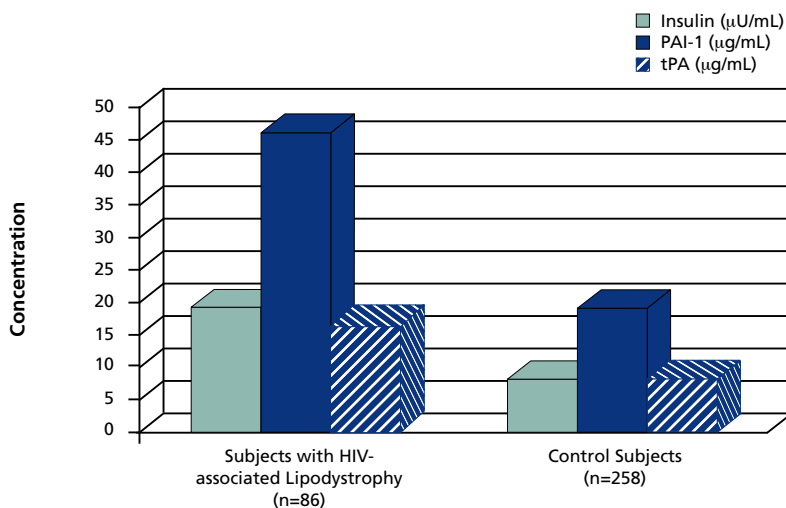


Figure 2. Comparison of insulin, plasminogen activator inhibitor-1 (PAI-1), and tissue plasminogen activator (tPA) concentrations in patients with HIV-associated lipodystrophy and control subjects without HIV infection. Adapted with permission from Hadigan et al, *J Clin Endocrinol Metab*, 2001.

recipients of non-protease inhibitor regimens (Figure 1). Although generalization from these data should be tempered by recognition that accurate blood pressure data are difficult to obtain and that the 2 groups of protease inhibitor recipients had lower CD4+ cell counts and higher viral loads at the start of treatment, the high frequency of hypertension observed in the indinavir recipients is a cause for concern.

Another recent report has indicated abnormal levels of regulators of fibrinolysis in patients with lipodystrophy. As shown in Figure 2, 86 patients with self-reported HIV-associated lipodystrophy exhibited increased levels of fasting insulin, tissue plasminogen activator, and plasminogen activator inhibitor-1 compared with 258 individuals from the Framingham Offspring Cohort matched for body mass index, age ( $\pm 5$  years), and gender (Hadigan et al, *J Clin Endocrinol Metab*, 2001). The association between insulin resistance and levels of these fibrinolysis markers in the general population is well-described, and epidemiologic data suggest that elevations in these markers are associated with increased cardiac event rates in patients with documented CAD.

It should be noted that there is the potential for other risk factors not directly associated with HIV disease or antiretroviral therapy to have a high

prevalence in HIV-infected individuals. For example, Bowers and colleagues (3rd Int Conf Nutr HIV Infect, 1999) found that 70% of 102 patients assessed at a Veterans Administration HIV clinic were cigarette smokers, a proportion that is markedly greater than that in the general population. Of interest with regard to other risk factors is a recent report from Thiebaut and colleagues (8th CROI, 2001) suggesting absence of association between cytomegalovirus

serologic or disease status and carotid intimal-medial thickness as a marker for coronary atherosclerosis.

A primary concern regarding the CAD risk factors observed in HIV-infected patients is the resemblance of the complex of findings in some, particularly those with lipodystrophy, to the metabolic or insulin resistance syndrome associated with high risk for diabetes and CAD in the general population. The metabolic syndrome is characterized by dyslipidemia (increased triglyceride levels, small, dense LDL, and decreased HDL levels), insulin resistance, obesity (body mass index  $>25$  kg/m<sup>2</sup>, waist:hip ratio  $>0.85$ , or waist circumference  $>100$  cm), and hypertension. Definitions of the metabolic syndrome frequently include the presence of a procoagulant state.

### Incidence of Ischemic Cardiovascular Events

A number of studies have sought to determine whether rates of CAD clinical events are increased in HIV-infected patients. In an analysis of data from phase 3 clinical trials of indinavir, nelfinavir, ritonavir, and saquinavir, the rate of myocardial infarction over a mean of 1 year of follow-up among 7668 patients randomized to protease inhibitor plus nucleoside reverse transcriptase

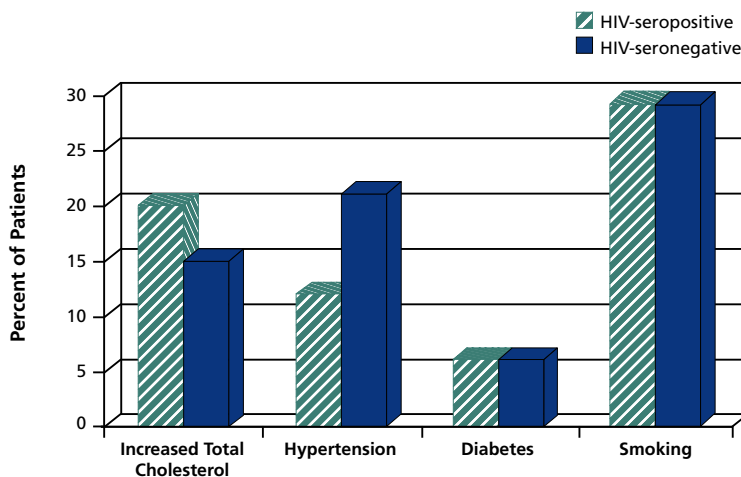


Figure 3. Proportion of 264 HIV-infected patients and 264 noninfected control subjects with increased total cholesterol, hypertension, or diabetes, or who smoked cigarettes (smoking). Adapted with permission from Klein et al, 8th CROI, 2001.

inhibitor (nRTI) therapy was found not to differ significantly from the rate among 3318 patients randomized to dual nRTIs alone (mean age of patients, 37 years), with rates being similar to those in population-based epidemiologic studies (Coplan et al, 7th CROI, 2000).

Klein and colleagues (8th CROI, 2001) recently updated findings from the Kaiser Permanente data set on hospitalization rates for coronary heart disease among HIV-infected patients stratified by protease inhibitor use and age- and gender-matched patients not known to be HIV-infected. The analysis included data only on men, since no cardiovascular events had occurred in women. Among 4541 HIV-infected men with a median follow-up time of 4.3 years (total, 14,703 patient-years), 53 hospitalizations for coronary heart disease events had occurred, yielding an age-adjusted event rate of 5.5 per 1000 population that was 60% greater than the 3.4 per 1000 population rate observed in patients without HIV infection. No difference in event rate was observed between protease inhibitor and non-protease inhibitor patient groups.

To determine the potential influence of known risk factors on this difference in event rate, risk factor data provided by a survey in the Kaiser Permanente population were compared between 264 HIV-infected patients and 264 patients without HIV infection. As shown in Figure 3, the frequency of increased cholesterol level was slightly higher in the HIV-infected patients, whereas the frequency of hypertension was somewhat lower and the frequencies of both diabetes and cigarette smoking were equivalent. These findings suggested that the increase in coronary heart disease hospitalizations among the HIV-infected patients was not due to the presence of such traditional risk factors.

In a smaller retrospective review among 951 patients receiving antiretroviral therapy without protease inhibitors between 1990 and 1998 and 383 receiving protease inhibitor-including therapy between 1995 and 1998, 5 cases of myocardial infarction occurred in the protease inhibitor group over an average of 1.5 years of follow-up and 3 occurred in the non-protease inhibitor group over 1.2 years of follow-up (Jutte et al, AIDS, 1999). Although the number of total

events was thus quite small, the risk of myocardial infarction was calculated to be increased by 5-fold in the protease inhibitor group. The incidence of 1.06 per 100 patient-years of observation (95% confidence interval [CI], 0.42-2.24) in the protease inhibitor group was significantly greater than the incidence of 0.21 per 100-patient-years (95% CI, 0.06-0.54) in the non-protease inhibitor group ( $P = .025$ ).

In an analysis of the incidence of myocardial infarction by duration of protease inhibitor use in multiple hospitals in France through 1999, Mary-Krause and colleagues identified 54 cases of myocardial infarction in 36,907 patient-years of follow-up (8th CROI, 2001). The myocardial infarction rates increased with increasing duration of protease inhibitor exposure; although the rate decreased after 36 months, this decrease presumably is an artifact of the small sample size with exposure of such duration. Use of an age-adjusted standardized morbidity ratio showed that the rate of myocardial infarction in the patients with longer duration of protease inhibitor use was significantly greater than the rate of myocardial infarction in the general population as derived from epidemiologic data.

Although these analyses on balance indicate increased risk for cardiovascular events among patients receiving antiretroviral therapy, they are limited in important respects, including the generally short duration of follow-up and the small numbers of events observed in the studies. In addition, there is potential for biased ascertainment in the studies, with events in protease inhibitor-receiving patients being more frequently reported due to heightened awareness of the potential association of such treatment with CAD risk. Moreover, these studies generally have included no adjustments for CAD risk factors or stage of HIV disease. Since some patients included in these analyses may have been more likely to have been prescribed protease inhibitor treatment by virtue of having advanced HIV disease, the current data could mask an effect of HIV disease stage on CAD risk. It is worth noting that studies utilizing such noninvasive measures of atherosclerosis as electron beam computed tomography, carotid intimal-

medial thickness, and brachial artery reactivity have yielded conflicting results with regard to relative risk of disease in HIV-infected individuals, with some data indicating that smoking is a better predictor of abnormalities than protease inhibitor use or HIV infection status.

## CAD Risk Assessment and Risk Management

With some caveats, it appears to be appropriate to assess HIV-infected individuals for CAD risk and to manage those with risk factors in a manner similar to that employed with individuals from the general population. The potential presence of risk factors should be taken into account in history taking and physical examination. In terms of specific laboratory tests, routine measurement of fasting lipid profiles can be recommended. Although there has been some advocacy for assessment of insulin levels or performance of oral glucose tolerance tests, in Dr Glesby's opinion, adoption of such testing on a routine basis may be premature given the absence of knowledge regarding how best to manage abnormalities in HIV-infected patients in order to reduce CAD risk.

With regard to overall risk assessment, American Heart Association guidelines (Grundy et al, *Circulation*, 1999) assign risk based on standard risk factors derived from the Framingham cohort study, recommending encouragement of a healthy lifestyle in individuals at low risk of coronary heart disease, aggressive risk reduction in those at high risk, and consideration of further risk stratification (eg, through noninvasive assessment of myocardial ischemia or coronary atherosclerotic burden) in those at intermediate risk. The recent guidelines of the National Cholesterol Education Program Adult Treatment Panel III (JAMA, 2001) use a similar approach of risk stratification using data derived from the Framingham study for patients in certain risk categories.

Henry and colleagues (8th CROI, 2001) performed risk assessment in a group of 100 patients randomly selected from the population of the AIDS Clinical Trials Group (ACTG) 372 study who had

achieved viral suppression on zidovudine/lamivudine/indinavir with or without abacavir and had a median duration of indinavir treatment of 42 months. Dyslipidemia and insulin resistance were common in the population, with 39% having total cholesterol levels above 200 mg/dL, 24% having LDL cholesterol levels above 160 mg/dL, 12% having triglyceride levels above 400 mg/dL, and 56% having insulin resistance by homeostatic model assessment. With use of a Framingham risk estimate instrument (see Grundy et al, *Circulation*, 1999) that determines absolute 10-year risk for coronary heart disease events based on risk points assigned for age, gender, total cholesterol level, HDL cholesterol level, systolic blood pressure, and presence or absence of diabetes or smoking, the group had an average score (4.33) that indicated moderately increased risk compared with individuals of the same age without any of the risk factors.

With regard to the use of such an instrument for risk assessment, however, it needs to be remembered that absolute risk in the Framingham population, which largely includes whites of European descent, may differ from that in other populations for any given set of risk factors. Further, the level of risk reflected in the algorithm is averaged risk, and much variability exists with regard to individual risk. In addition, the duration of dyslipidemia may be important to coronary heart disease risk, with risk in a patient who has had elevated lipid levels for many years potentially differing from that in an individual who had normal lipid levels until recently beginning potent antiretroviral therapy. It is also the case that risk might be modified in HIV-infected individuals by the presence of such potential risk factors as visceral fat, coagulability/fibrinolysis abnormalities, and insulin resistance.

As in the general population, the foundation of risk management in HIV-infected patients includes diet and exercise, smoking cessation, and treatment of hypertension. With regard to the latter, there are studies in development to evaluate potential pharmacokinetic interactions between specific antiretroviral drugs and antihypertensive agents, with there having been some concern

**Table 1.** National Cholesterol Education Program Adult Treatment Panel III Guidelines for Intervention Based on Low-Density Lipoprotein Cholesterol

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes† (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents* (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)
2+ risk factors† (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 risk factor	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

\*Diabetes is considered a CHD risk equivalent.

†Risk factors: (1) cigarette smoking, (2) hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication), (3) low HDL cholesterol (<40 mg/dL), (4) family history of premature CHD (ie, CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), and (5) age (men ≥45 years; women ≥55 years). Subtract 1 risk factor if HDL cholesterol ≥60 mg/dL.

‡Therapeutic lifestyle changes refer to a risk reduction approach involving (1) reduced intakes of saturated fats and cholesterol, (2) options for enhancing LDL reduction such as plant stanols/sterols and increased soluble fiber, (3) weight reduction, and (4) increased physical activity.

CHD indicates coronary heart disease; LDL indicates low-density lipoprotein; HDL indicates high-density lipoprotein. Adapted from National Cholesterol Education Program, *JAMA*, 2001.

over interactions between protease inhibitors and calcium channel blockers. Treatment of dyslipidemia can be performed according to National Cholesterol Education Program guidelines or the ACTG Cardiovascular Disease Focus Group guidelines (Dubé et al, *Clin Infect Dis*, 2000). Studies are ongoing to determine the effects of treatment with thiazolidinediones and metformin on insulin resistance. Studies are also ongoing to identify treatments for lipodystrophy, including studies with recombinant human growth hormone. However, the effects of even such standard treatment as lipid-lowering therapy on risk in HIV-infected patients remains unclear, since risk in these patients has not been adequately defined.

With regard to treatment of dyslipidemia, the National Cholesterol Education Program Adult Treatment Panel guidelines identify LDL cholesterol levels at which drug treatment should be initiated and target LDL

cholesterol levels according to degree of risk in primary and secondary prevention populations (Table 1). In the latest version of these guidelines, subjects whose 10-year risk of a coronary event exceeds 20% are managed the same way as those with known coronary disease. People with diabetes automatically fall into this high-risk category; for nondiabetic subjects with 2 or more risk factors, 10-year risk should be calculated using the Framingham instrument to guide management.

A small number of uncontrolled studies in small groups of HIV-infected patients with dyslipidemia have shown the expected effects in cholesterol and triglyceride level reductions from lipid-lowering treatment with atorvastatin, gemfibrozil, and pravastatin (Henry et al, *Lancet*, 1998; Hewitt et al, *AIDS*, 1999; Baldini et al, *AIDS*, 2000).

Thus far, reports of randomized, controlled studies are limited to one study of 31 subjects showing a greater



decrease in total cholesterol level and increase in HDL cholesterol level with pravastatin compared with dietary advice (Moyle et al, 40th ICAAC, 2000) and one study demonstrating a mean decrease in triglyceride level of 116 mg/dL with gemfibrozil treatment in a 16-week placebo-controlled trial in 37 patients (Miller et al, 8th CROI, 2001). Although the decrease with gemfibrozil in the latter study was statistically significant compared with placebo, triglyceride levels in gemfibrozil patients were not brought to normal levels. ACTG study A5087 currently is comparing open-label treatment with micronized fenofibrate (200 mg qd) and pravastatin (40 mg qd) for up to 48 weeks in patients with fasting LDL cholesterol level at or above 130 mg/dL and triglyceride value of 200 mg/dL or greater despite diet and exercise, with combined therapy being instituted at week 16 for inadequate lipid-lowering response at week 12. The monotherapy arms were recently closed because of failure to meet predefined criteria for successful therapy. Dual therapy is still being evaluated.

Preliminary treatment guidelines of the ACTG Cardiovascular Disease Focus Group recommend statin treatment as first choice and fibrate treatment as second choice in patients with isolated elevation in LDL cholesterol level; a fibrate or statin as first choice and combination fibrate/statin treatment as second-line therapy in combined hyperlipidemia; and fibrate treatment as first choice and statin treatment as second choice in patients with isolated hypertriglyceridemia. Although pharmacokinetic interactions between antiretroviral agents and lipid-lowering drugs have yet to be fully investigated, there is clear potential for interactions with statin drugs, since many of these are metabolized via the cytochrome P450 system. ACTG study A5047 in healthy volunteers has demonstrated interactions between ritonavir/saquinavir and statins. In this study, atorvastatin acid levels were increased by 343% and total active atorvastatin levels were increased by 74%, simvastatin acid levels were increased by 2676%, and pravastatin levels were decreased by 47%, in the presence of ritonavir/saquinavir (Fichtenbaum et al, 7th CROI, 2000). It was thus suggested that atorvastatin could be used starting

at a low dose (eg, 10 mg daily), that simvastatin should be avoided, and that pravastatin is probably safe for use. Rhabdomyolysis has been reported in a few patients receiving statins while on protease inhibitor-containing regimens.

A number of studies have assessed the effects of switching from protease inhibitors to other agents on lipid levels and insulin resistance (Table 2). In general, data from these studies indicate that lipid profiles are improved by switching from a protease inhibitor to an NNRTI or abacavir. With regard to potential treatments for other risk factors, a small placebo-controlled study has shown that metformin treatment produces a significant reduction in markers of impaired fibrinolysis in HIV-infected patients (Hadigan et al, *J Clin Endocrinol Metab*, 2001). After 12 weeks of treatment, plasminogen activator inhibitor-1 levels had been reduced from baseline by a mean of 16% ( $P = .02$ ) and tissue plasminogen activator levels had been reduced by a mean of 11% ( $P = .03$ ) in metformin recipients, with levels of both increasing somewhat in the placebo patients.

Less attention has been paid to lifestyle modifications, such as smoking cessation. For many patients, smoking undoubtedly confers greater risk than lipid abnormalities. Unfortunately, no data exist on smoking cessation in this patient population (Niaura et al, *Clin Infect Dis*, 2001).

## Summary

The metabolic derangements observed in HIV-infected patients, whether they are associated with antiretroviral treatment or not, likely place many at increased long-term risk of accelerated atherosclerosis. This risk may be particularly enhanced in patients who have body fat distribution abnormalities. Although definitive data on risk of CAD in the HIV-infected population are lacking, the preliminary data on prevalence of CAD and incidence of clinical ischemic events do provide cause for concern. Thus, risk stratification and reduction of modifiable risk factors are indicated for HIV-infected patients.

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**Table 2.** General Results of Selected Antiretroviral “Switch” Studies

Initial Drug	Replacement Drug	Total Cholesterol	Triglyceride Levels	Insulin Resistance
Protease inhibitor (Gharakharian 2000, Lafon 2000, Martinez 2000, Viciano 2000)	Efavirenz	Little or no change	Variable effects	Decrease or no change
Protease inhibitor (Barreiro 2000, Negredo 2000, Raffi 2000, Ruiz 2000, Tebas 2000)	Nevirapine	Decrease or no change	Decrease or no change	Reversal or no change
Protease inhibitor (Opravil 2000, Walli 2001)	Abacavir	Decrease	Decrease	Reversal
Stavudine (Saint-Marc 1999)	Zidovudine	No change	Decrease	No change or decrease in protease inhibitor-experienced patients

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## Guidelines for the Assessment and Management of Metabolic Complications

The International AIDS Society–USA has convened a panel of 12 experts to develop guidelines for the assessment and management of metabolic complications in HIV infection and antiretroviral therapy, including glucose abnormalities and insulin resis-

tance, lipid abnormalities, body fat distribution changes, lactic acidemia, and bone disease. Chaired by Morris Schambelan, MD, and Constance A. Benson, MD, the panel will submit its report for publication shortly.

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