

Perspective

Cardiovascular Risk and Risk Management in HIV-infected Patients

Patients with HIV infection are at risk of cardiovascular disease from the same factors posing risk in the general population—eg, smoking, dyslipidemia, hypertension, obesity, and diabetes. HIV infection itself and antiretroviral therapy pose additional risk, but available data indicate that the relative rate of myocardial infarction is low and declining in the HIV-infected population. Cardiovascular risk should be addressed before initiation of antiretroviral therapy and frequently during follow-up, and decisions to alter therapy on the basis of adverse changes in metabolic risk factors should be made on an individual basis. Virologic control is the primary goal for HIV-infected persons with cardiovascular risk, and is the primary consideration in determining when to start antiretroviral therapy and when to change regimens. This article summarizes a presentation on cardiovascular risk and risk management in HIV-infected persons made by Oluwatoyin Adeyemi, MD, at an International AIDS Society–USA Continuing Medical Education course in Chicago in May 2007. The original presentation is available as a Webcast at www.iasusa.org.

Cardiovascular Risk in HIV-infected Persons

Traditional risk factors for cardiovascular disease—eg, older age, male sex, previous or family history of cardiovascular disease, hypertension, diabetes, smoking, and lipid abnormalities—increase risk of cardiovascular events in both HIV-infected and uninfected individuals. HIV disease itself may confer additional cardiovascular risk, and antiretroviral therapy may contribute to increased risk, although the absolute increase associated with antiretroviral therapy appears to be low. The best prospective data show that the relative rate of myocardial infarction (MI) in the HIV-infected population is low and decreasing over time, and from a public health standpoint, MI and other cardiovascular events are a relatively small issue compared with overall HIV-related morbidity and mortality.

Cardiovascular risk must be considered in the overall care of adults with HIV infection. However, such risk should not influence the decision of when to initiate antiretroviral therapy, and the decision of which antiretroviral regimen to use should be made based on risk and benefit analysis that in-

cludes the clear survival benefit associated with maximal viral suppression.

It should be noted that recent data support better cardiovascular outcomes among HIV-infected persons in whom antiretroviral therapy is continued without interruption, than among those with CD4+ cell count–guided interruptions in treatment. An analysis from the Strategies for Management of Antiretroviral Therapy (SMART) trial showed statistically significant increases in relative hazards for the discontinuation strategy versus continuous treatment for: (1) the composite endpoint of clinical MI, silent MI, coronary artery disease requiring invasive procedure or surgery, or cardiovascular death (hazard ratio [HR], 1.57; $P = .05$); (2) this composite endpoint plus the composite endpoint of peripheral vascular disease, congestive heart failure, or coronary artery disease requiring medication (HR, 1.49; $P = .03$); and (3) both of the foregoing endpoints combined, plus unobserved death from unknown cause (HR, 1.58; $P = .009$; Phillips et al, 14th CROI, 2007). The total cholesterol to high-density lipoprotein (HDL) cholesterol ratio was markedly higher in patients in the discontinuation group, a risk factor that may have accounted for the marginally greater risk of cardiovascular disease in that group.

Assessment of cardiovascular risk in HIV-infected individuals without prior cardiovascular disease can be performed as it is in uninfected individuals, using modified Framingham risk scoring to determine 10-year risk in individuals with 2 or more cardiovascular risk factors. The risk score is derived from age, sex, total cholesterol, HDL cholesterol, systolic blood pressure or treatment for hypertension, and presence or absence of cigarette smoking. Diabetes is considered to pose risk for coronary events equivalent to risk posed by history of coronary disease. In addition to traditional risk factors for diabetes, HIV-associated risk factors possibly contributing to insulin resistance and diabetes may include peripheral lipotrophy, reduced adiponectin, increased liver and muscle fat, inflammatory cytokines, low testosterone levels, oxidant stress, hepatitis C virus infection, and protease inhibitor use. One analysis comparing diabetes risk in patients on antiretroviral therapy with that among matched HIV-uninfected controls found impaired glucose tolerance in 35% versus 5% of patients and a greater than 3-fold increased risk of progression to diabetes over 3 years in those receiving antiretroviral therapy (Grinspoon and Carr, *N Engl J Med*, 2005).

It is currently recommended that patients undergo metabolic assessment before beginning antiretroviral therapy, when switching regimens, at 3 and 6 months after starting or switching, and annually during stable therapy. In addition to blood glucose, measurements should include total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and triglycerides. Oral glucose tolerance testing may be considered in patients at high risk of developing diabetes—eg, those with family history of diabetes, obesity, or severe lipotrophy and lipoaccumulation.

Although Framingham risk scoring is widely used in routine practice and

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appears to be accurate in HIV-infected patients, it should be noted that there is at least preliminary evidence that an HIV-specific cardiovascular risk scoring system may prove to be more accurate in predicting outcomes. In the Copenhagen HIV Program Data Collection on Adverse Events of HIV Drugs (DAD) study, a DAD risk equation including traditional risk factors and duration of protease inhibitor exposure was compared with Framingham risk scoring. In the DAD cohort, there were 157 coronary events (more than 33,954 person-years of observation); the DAD risk equation predicted a total of 153 events, and the Framingham risk equation predicted 187 events (also a good correlation). The DAD risk equation is currently being assessed in a validation study in another DAD cohort.

Management of Cardiovascular Risk

Current guidelines support treating cardiovascular risk in HIV-infected patients in the same manner as recommended for the general population. Management may include diet and exercise intervention, smoking cessation, establishment of lipid goals and treatment of dyslipidemia, and institution of drug therapy (eg, statins, antihypertensives) in high-risk patients (eg, those with established coronary disease, diabetes, or moderate or high risk on risk scoring).

Switching of antiretroviral therapy may be considered if other methods of treating risk are not effective. Some of the decision points that arise in managing the at-risk HIV-infected patient can be appreciated through the following case history.

Case History

The patient is a 43-year-old African American man new to the practice. He smokes 1 to 2 packs of cigarettes per day, has a history of mild asthma, and his father died of an unspecified “heart problem” some time in his 50s. The patient was diagnosed with HIV infection 5 years ago. He recalls a CD4+ count of about 520 cells/ μ L and an HIV RNA level of approximately 20,000 copies/mL

from 6 months ago. His nadir CD4+ count was approximately 300 cells/ μ L 2 years ago. He had begun antiretroviral therapy 2 years before, apparently with zidovudine/lamivudine/efavirenz, but took the medication only intermittently for a few months because of adverse effects (nausea and sleep problems). He is approximately 10 lbs heavier than his ideal weight, but otherwise appears well. His blood pressure is 145/85 mmHg.

General cardiovascular risk management considerations are shown in Figure 1. Initial steps in management of the patient’s disease include: obtaining fasting lipid levels and setting lipid goals if necessary; discussing smoking cessation programs; discussing high blood pressure if verified or if there is an established history of hypertension; obtaining a comprehensive family history of cardiovascular disease (death from cardiovascular disease before 50 years of age in the father may count as a risk factor for the patient); and obtaining a risk score.

The patient is seen 3 weeks later. Laboratory work shows a CD4+ count of 375 cells/ μ L, HIV RNA level of 47,000

copies/mL, and normal complete blood cell count and chemistry. His blood pressure is 132/80 mmHg. His fasting lipid levels as of this visit are shown in Table 1; total and LDL cholesterol and triglyceride levels are elevated, and his HDL cholesterol is low. The patient is again counseled on smoking cessation and is offered additional resources to this end. He wishes to avoid using any medications at this time. It is agreed that the patient will focus on diet, exercise, and smoking cessation, and that he will return for repeat laboratory work in 3 months.

The patient does not return for follow-up for 5 months. He has gained 5 lbs and is still smoking “due to stress of a new job.” His blood pressure is 132/80 mmHg. His fasting lipid levels have increased, as shown in Table 1. The patient’s Framingham risk score indicates 19% risk of a coronary event over the next 10 years, placing him in the high-risk category. His CD4+ count is 300 cells/ μ L and HIV RNA level is 78,000 copies/mL. It is decided to restart antiretroviral therapy with lopinavir/ritonavir plus tenofovir/emtricitabine. As an alternative, a ritonavir/atazanavir-

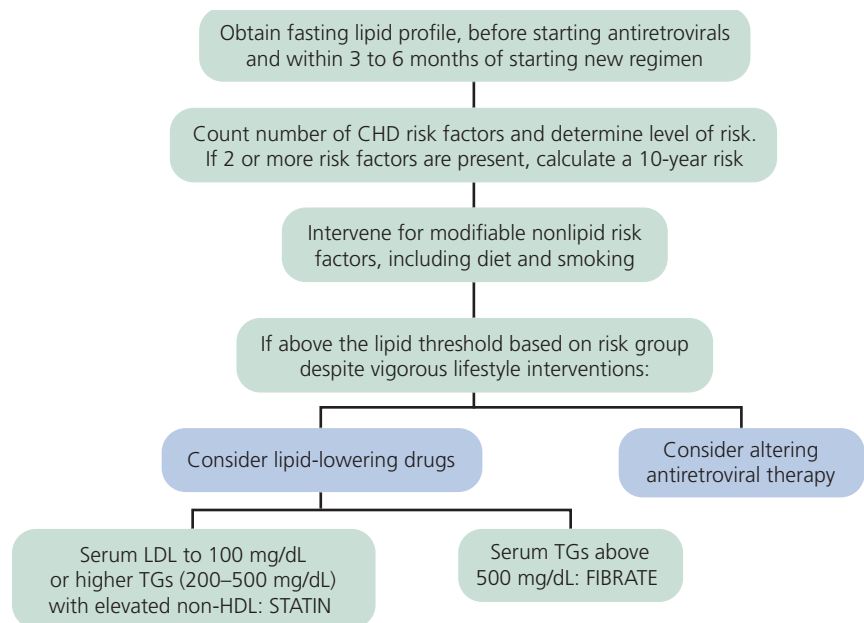


Figure 1. Guidelines for managing dyslipidemia and cardiovascular risk in HIV-infected patients receiving antiretroviral therapy. CHD indicates coronary heart disease; LDL, low-density lipoprotein cholesterol; Non-HDL, non-high-density lipoprotein cholesterol; and TGs, triglycerides. Adapted from Dubé et al, *Clin Infect Dis*, 2003.

Table 1. Patient Risk Factor Summary

Date	Fasting Lipids (mg/dL)*	Smoker?	Blood Pressure (mmHg)	Lipid-lowering Treatment	10-year Risk of Coronary Event by Framingham Risk Source
2/1	TC:220 TG:240 HDL:32 LDL:140	Yes	132/80	--	--
7/1	TC:240 TG:260 HDL:32 LDL:156	Yes	132/80	--	19%
10/1	TC:256 TG:310 HDL:36 LDL:158	Yes	132/80	--	20%
11/1	TC:215 TG:240 HDL:42 LDL:125	Yes	132/80	Pravastatin	11%
12/1	TC:190 TG:180 HDL:44 LDL:110	Yes	132/80	Pravastatin, ezetimibe, omega-3 fatty acid supplement	8%

*On current National Cholesterol Education Program guidelines, total cholesterol (TC) value below 200 mg/dL is normal, low-density lipoprotein (LDL) cholesterol level below 70 mg/dL is optimal, triglyceride level below 150 mg/dL is normal, and (for men) high-density lipoprotein (HDL) cholesterol level greater than or equal to 60 mg/dL is protective (and improves risk score).

based regimen would provide a better lipid effect and allow once-a-day dosing. The patient is advised that lipid-lowering therapy should be instituted next if the profile is not improved at the next visit. The patient's antiretroviral therapy is well tolerated, and after 12 weeks on treatment, his CD4+ count has increased to 390 cells/ μ L and his HIV RNA level is below 50 copies/mL. His blood pressure remains unchanged. He is still smoking. Total cholesterol and triglyceride levels have increased again, with HDL cholesterol increasing somewhat (see date 10/1 in Table 1). His 10-year risk of coronary disease is now 20%. The patient is started on 20 mg of pravastatin, which he tolerates well.

After 4 weeks on pravastatin, good reductions in total and LDL cholesterol and triglyceride levels are observed, and although levels are still above normal, there is improvement in HDL cholesterol (see date 11/1 in Table 1). He is still smoking and has not lost weight. The improvement in his lipid profile has reduced 10-year coronary risk to 11%, although he is still in the high-risk category. It is decided to add ezetimibe and an omega-3 fatty acid supplement to the lipid-lowering therapy. After 4 weeks (see date 12/1 in Table 1), there is further improvement in his lipid pro-

file, resulting in reduction of 10-year risk to 8% and placing him in the moderate-risk category.

If the patient were to stop smoking at this point, his 10-year risk would drop to 2%, placing him in the low-risk category. Had he stopped smoking after his first risk assessment, his 10-year risk would have decreased from 19% to 5% (borderline low/moderate risk) on the basis of smoking cessation alone.

The large effect of smoking cessation on coronary risk is of particular import for HIV-infected patients since there appears to be a high prevalence of smoking in HIV-infected persons—as high as 70% in some clinics. At Dr Adeyemi's center, approximately 60% to 65% of HIV-infected patients are current smokers, and the prevalence is 70% among a subpopulation aged 50 years or older with numerous other cardiovascular

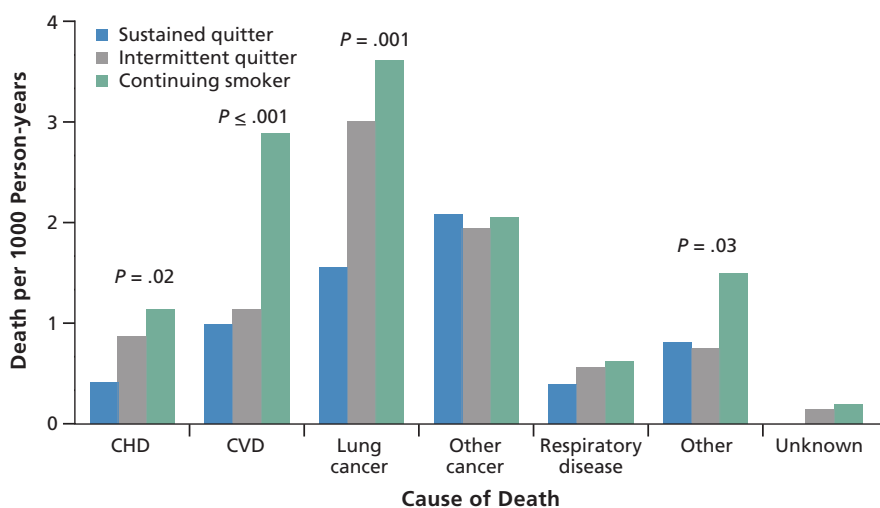


Figure 2. Mortality over 14.5 years in a general population after a 10-week smoking intervention program among "sustained quitters," "intermittent quitters," and "continuing smokers." CHD indicates coronary heart disease; CVD, cardiovascular disease. Adapted from Anthonisen et al, *Ann Intern Med*, 2005.

risk factors. The effect on survival of continuous or intermittent quitting with a 10-week smoking cessation program in the general population is shown in Figure 2; there is no reason to suspect that smoking cessation would not similarly benefit HIV-infected persons.

Summary

As in the general population, individual cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and smoking have an additive or synergistic impact on overall risk and should be addressed at initiation of antiretroviral therapy and frequently during follow-up. Lifestyle modification should be the first management approach, including smoking cessation, diet modification, and increased exercise. In managing hyperlipidemia, the decision to use lipid-lowering therapy or to switch antiretroviral therapy regimens should be individualized. The impact of smoking

cessation is greater than the impact of any other intervention in reducing overall risk, and although cardiovascular risk should be considered when starting or changing antiretroviral therapy, virologic control should be the overriding consideration.

Presented by Dr Adeyemi in May 2007. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Adeyemi in September 2007.

Dr Adeyemi was on the Speakers' Bureaus of Abbott and Tibotec.

Suggested Reading

Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med.* 2005;142:233-239.

Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of

dyslipidemia in HIV-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis.* 2005;37:613-627.

Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med.* 2005;352:48-62.

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