

Perspective

Predicting and Preventing Cardiovascular Disease in HIV-Infected Patients

Cardiovascular disease (CVD) is the leading cause of non-HIV-related death in HIV-infected persons. The risk of CVD in HIV-infected persons appears to reflect the contribution of a number of factors, including non-HIV-related (traditional) cardiovascular risk factors, chronic inflammation associated with HIV infection, and metabolic adverse effects of antiretroviral therapy. Traditional CVD risk factors, however, are the major determinants of risk in HIV-infected patients and this population carries a high burden of such factors. HIV infection may also be an independent risk factor for CVD, but there is not yet sufficient evidence to consider HIV infection itself a coronary heart disease risk equivalent (eg, in the same manner as diabetes) or to change calculation of risk in the HIV-infected population. In the absence of specific randomized trials in the HIV-infected population, HIV-infected persons should be treated for cardiovascular risk factors according to current national guidelines for reducing risk, including those for aspirin use and for treatment of dyslipidemia, hypertension, and metabolic syndrome. This article summarizes a presentation by Wendy S. Post, MD, at the 14th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in Tampa, Florida, in June 2011. Dr Kerunne Ketlogetswe provided additional editing. The Clinical Conference is sponsored by the IAS-USA under the Health Resources and Services Administration (HRSA) contract number HSH250200900010C.

Cardiovascular disease (CVD) is the leading cause of non-HIV-related death in people with HIV infection. Risk in HIV-infected persons appears to reflect contributions of non-HIV-related cardiovascular risk factors, the chronic inflammatory response in HIV infection, as well as metabolic adverse effects of antiretroviral therapy (namely, insulin resistance, dyslipidemia, abnormal fat distribution, and hypertension).

Evidence of Cardiovascular Risk From Observational Studies

Observational studies suggest an increased risk for coronary heart disease (CHD) associated with HIV infection and antiretroviral therapy. However,

not all studies have yielded consistent results, with some studies finding an increased risk of CVD and others none, likely owing to limitations of study design among the different studies that prevent straightforward interpretation of the findings.

Compelling evidence that HIV infection itself increases the risk of CHD comes from recent data from the Strategies for Management of Antiretroviral Therapy (SMART) study. This study showed that interruption of antiretroviral treatment was associated with a statistically significant 80% increase in risk for mortality (hazard ratio [HR], 1.8; $P = .007$) compared with continuous treatment among more than 5000 patients with CD4+ cell counts above 350/ μ L.¹ Treatment interruption was also associated with a 70% increase in risk for major cardiovascular, renal, or hepatic disease (HR, 1.7; $P = .009$). For fatal or nonfatal CVD alone, the risk was increased by 60% (HR, 1.6; $P = .05$), suggesting that inadequately treated viral infection itself increased the risk of CVD. Inflammatory markers were strongly associated with mortal-

ity. At 1 month, increases in IL-6 and D-dimer occurred in 30% and 16% of patients, respectively, in the treatment interruption group versus 0% and 5%, respectively, in the continuous treatment group ($P < .0001$ for differences). Increases in IL-6 and D-dimer in the treatment interruption group were statistically significantly correlated with plasma HIV RNA levels ($P < .0001$).

In a case-control study in the SMART trial population, higher IL-6 and D-dimer levels were associated with dramatically increased risk of all-cause mortality, with the adjusted odds ratios (ORs) for the top quartile versus bottom quartile being 8.3 ($P < .0001$) for IL-6 and 12.4 ($P < .0001$) for D-dimer.² Elevated high-sensitivity C-reactive protein (hs-CRP) was also associated with increased risk of mortality (OR, 2.0; $P = .05$).

Risk Assessment

Data from the HIV Outpatient Study (HOPS) cohort show that traditional CVD risk factors predict risk for CVD in HIV-infected patients. Adjusted ORs for a CVD event were 3.3 for age greater than 40 years, 3.2 for diabetes, 1.9 for hyperlipidemia, and 1.7 for hypertension.³

The Framingham Risk Score (FRS), which incorporates traditional risk factors of age, total cholesterol, high-density lipoprotein (HDL) cholesterol (a negative risk factor), smoking status, and systolic blood pressure, is widely used to predict 10-year risk of myocardial infarction (MI) or CHD death. The FRS is valid and applicable in the HIV-infected population. There is increased interest in extending risk assessment beyond the 10-year interval. Particularly among younger individuals and women, in whom a cerebrovascular accident (CVA) is much more common as the initial presentation of CVD, the 10-year FRS can underestimate life-

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See page 167 for information on CME credit for this article.

time risk of CHD and preclude warranted intensive prevention strategies.⁴ As such, the American Heart Association (AHA) CVD Prevention Guidelines for women have been amended to define high risk as a 10%, 10-year risk for all CVD, not just CHD alone.

Coronary Calcification

Calcium is an integral component of arterial plaque, and increased coronary calcification is a risk factor for coronary events. Atherosclerosis begins early and most plaque ruptures occur at sites where there was previously less than 40% stenosis. Stress tests detect only bloodflow-limiting stenoses, whereas coronary calcium scans can detect more diffuse atherosclerosis that is not yet limiting flow. Coronary calcium scans may thus permit targeting of patients for aggressive primary prevention.

The MESA (Multi-Ethnic Study of Atherosclerosis) trial showed that coronary artery calcium score predicted CHD in each of 4 racial/ethnic groups and in men and women after accounting for traditional risk factors.⁵ The current AHA recommendations indicate that measurement of coronary artery calcium (CAC) is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10-year risk of 10%-20%; class IIa recommendation) and may be reasonable in persons at low to intermediate risk (10-year risk of 6%-10%; class IIb recommendation). Patients at low risk (10-year risk < 6%) should generally not undergo coronary calcium scanning. The cardiovascular substudy in the Multicenter AIDS Cohort Study (MACS) did not show increased CAC in HIV-infected individuals receiving antiretroviral therapy.⁶ Nonetheless, it may be considered in patients at intermediate risk to help guide the decision on how aggressively to treat such patients.

C-Reactive Protein (CRP)

In the general population, the inflammatory marker CRP has been strongly associated with risk for cardiovascular events in many, but not all, studies.

CRP is also associated with other cardiovascular risk factors, particularly metabolic syndrome. High CRP levels are predictive of total mortality in HIV-infected patients.¹ The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study examined whether treatment with rosuvastatin versus placebo could prevent cardiovascular events in more than 17,000 patients in the general population. Men aged 50 years or older and women aged 60 years or older with no prior CVD or diabetes, normal low-density lipoprotein (LDL) cholesterol level (< 130 mg/dL), and elevated high-sensitivity CRP (≥ 2 mg/L) were included.⁷ Rosuvastatin treatment was associated with a statistically significant 44% reduction in risk for the combined endpoint of MI, stroke, unstable angina, revascularization, or cardiovascular death (HR, 0.56; $P < .00001$). The number of patients needed to treat to prevent 1 event was 25. An unanswered question is whether statin therapy provides substantial preventive benefit even in patients without elevated CRP and LDL cholesterol level below 130 mg/dL.

Elements of Risk Management

The following are the ABCs of CVD risk management in both HIV-infected persons and uninfected persons:

- A:** Aspirin when indicated
- B:** Blood pressure control
- C:** Cholesterol management;
Cigarette smoking cessation
- D:** Diabetes and prediabetes management
- E:** Exercise

Aspirin

Data on the preventive effects of aspirin are conflicting. The Physician's Health Study, reported in 1989, showed that aspirin 325 mg every other day dramatically reduced the risk for a first MI compared with placebo among more than 20,000 men observed for 5 years; no reduction in risk for stroke was observed.⁸ However, the Women's Health Study, reported in 2005, found no benefit in preventing first major CVD event

with aspirin 100 mg every other day versus placebo among nearly 40,000 women observed for 10 years. A benefit was observed in women aged older than 65 years,⁹ however, and a subgroup analysis indicated a reduction in risk for stroke with aspirin treatment.

A meta-analysis of more than 50,000 women and 44,000 men receiving aspirin at dosages of 100 mg every other day to 500 mg per day for 3.7 years to 10 years in primary prevention trials showed the following: (1) women, but not men, had a statistically significantly reduced risk for stroke; (2) men, but not women, had a statistically significantly reduced risk for MI; (3) both men and women had a statistically significantly reduced risk for a major cardiovascular event; and (4) neither men nor women had reduced risk for cardiovascular event plus all-cause mortality.¹⁰

In light of these data, what are the recommendations for aspirin use for primary prevention of CVD? The current AHA recommendations are that at-risk women aged 65 years or older receive 81 mg a day or 100 mg every other day, with the recommendation graded class IIa (benefit exceeds risk and cost). At-risk women younger than 65 years should receive aspirin for stroke prevention, with the recommendation graded class IIb (less robust evidence for benefit, but shown to be helpful in select patients). It is not recommended that optimal-risk women younger than 65 years receive aspirin therapy (class III; ie, not recommended for use, has no or limited evidence of benefit and may cause harm). For primary prevention of CVD in men, there is a class I recommendation (ie, benefits greatly outweigh the risks) for use of aspirin 75 mg to 162 mg daily in those at intermediate risk (10-year risk of CHD $\geq 10\%$).

Hypertension

Prehypertension, defined as systolic BP (SBP) 120 mmHg to 139 mmHg or diastolic BP (DBP) 80 mmHg to 89 mmHg, warrants intervention through lifestyle management. For patients with

stage 1 hypertension (SBP, 140-159 mmHg or DBP, 90-99 mmHg), initial therapy is thiazide-type diuretics for most. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, calcium channel blockers, or combinations of these may be considered, and are used more frequently now that they are available in generic formulations. Most patients with stage 2 hypertension (SBP \geq 160 mmHg or DBP \geq 100 mmHg) require 2-drug combinations. For both stage 1 and stage 2 hypertension, there are compelling indications for particular drug treatments.¹¹

LDL Cholesterol Reduction

Along with intensive lifestyle modification including diet and exercise, statin therapy has been the mainstay of reducing heart disease risk, and numerous studies over the years have shown a 30% to 40% reduction in risk for MI with statin therapy in primary prevention trials, and 20% to 30% in secondary prevention trials. The current National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines (Table 1) recommend an LDL cholesterol level goal of below 100 mg/dL (optional goal, < 70 mg/dL) in high-risk patients with CHD or CHD risk equivalents (10-year CHD risk > 20%). Moderately high-risk patients (2 or more risk factors; 10-year risk, 10%-20%) should aim for levels below

130 mg/dL (optional goal, < 100 mg/dL). Moderate-risk patients (2 or more risk factors; 10-year risk, < 10%) are recommended a goal level below 130 mg/dL, and low-risk patients (0-1 risk factor) should maintain an LDL cholesterol level below 160 mg/dL.¹² CHD risk equivalents include diabetes, peripheral vascular disease, carotid endarterectomy, and aortic aneurysm. There is evidence indicating that achieving the lower, optional LDL cholesterol level goal is associated with increased preventive benefit. Statin therapy should be monitored closely in patients receiving certain classes of antiretroviral drugs, which can potentiate the risk of myopathy.²¹

Triglyceride Reduction

Hypertriglyceridemia is common in individuals receiving antiretroviral therapy. Optimal fasting TG levels, defined as below 100 mg/dL, are a parameter of metabolic health in the recent AHA scientific statement on triglycerides and CVD.¹⁵ The statement also indicates that nonfasting TG levels can be used to screen individuals with high fasting levels, with normal nonfasting levels defined as below 200 mg/dL.

Desirable and high TG levels have been set at progressively lower levels in recommendations over the past 25 years. Currently, levels below 150 mg/dL are considered desirable, 150 mg/dL

to 199 mg/dL borderline, 200 mg/dL to 499 mg/dL high, and 500 mg/dL or above very high. In current lipid-lowering guidelines, lowering LDL cholesterol level is the primary goal, and lowering non-HDL cholesterol level is a secondary target once LDL cholesterol goals are met. The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than the goal for LDL cholesterol. This can be achieved either by intensifying statin therapy or adding nicotinic acid, a fibrate, or omega-3 fatty acids. If TG levels are greater than 500 mg/dL, lipid-lowering therapy is necessary to reduce the risk of pancreatitis. For lower TG levels, lifestyle modification is recommended, in part because studies of TG-lowering agents—niacin and fibrates—have yielded disappointing results.

A recent example of such studies is the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) study.¹⁴ The AIM-HIGH study compared treatment with simvastatin versus simvastatin plus extended-release niacin in more than 3000 men and women with vascular disease, low HDL cholesterol level (< 40 mg/dL in men, < 50 mg/dL in women), high TG levels (150-400 mg/dL), and LDL cholesterol level 180 mg/dL or below. The primary endpoint was the composite endpoint of CHD death, MI, CVA, or high-risk acute coronary syndrome hospitalization.

The mean age at study entry was 64 years. A majority of patients had CHD (92%), metabolic syndrome (81%), and hypertension (71%), and many had diabetes (34%). Nearly all (94%) were on statin therapy at study entry. At baseline, mean LDL cholesterol level was 71 mg/dL, mean HDL cholesterol level was 34.9 mg/dL, and median TG level was 161 mg/dL.¹⁵

The study was stopped early after an interim analysis at 32 months showed no difference in the primary endpoint (HR, 1.05; for simvastatin plus niacin versus simvastatin; *P* value not significant) despite reductions in TG and increases in HDL cholesterol in the niacin

Table 1. National Cholesterol Education Program Adult Treatment Panel Guidelines on Low-Density Lipoprotein Cholesterol Goals

Patient Category	Low-Density Lipoprotein Cholesterol Goal
High Risk Coronary heart disease (CHD) or CHD risk equivalents (10-year CHD risk > 20%)	< 100 mg/dL (optional goal < 70 mg/dL)
Moderately High Risk 2 or more risk factors for CHD (10-year CHD risk, 10%-20%)	< 130 mg/dL (optional goal < 100 mg/dL)
Moderate Risk 2 or more risk factors for CHD (10-year CHD risk < 10%)	< 130 mg/dL
Low Risk 0 or 1 risk factor for CHD	< 160 mg/dL

Adapted from Grundy et al.¹²

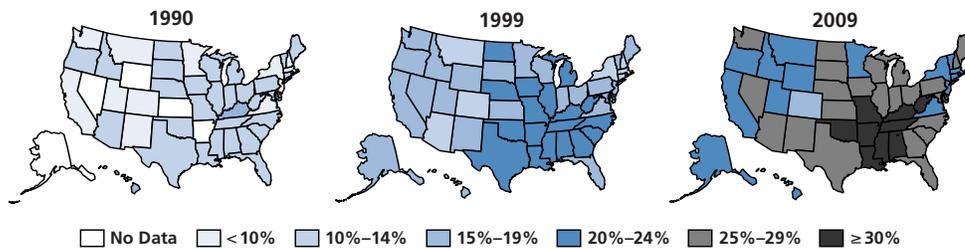


Figure 1. Obesity rates among adults in the United States during 1990, 1999, and 2009. Obesity is defined as a body mass index greater than or equal to 30 kg/m², or about 30 pounds overweight for a 5-foot, 4-inch person. Adapted from Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System.¹⁸

group. A greater occurrence of stroke was observed in the simvastatin/niacin group versus the simvastatin-only group (1.6% vs 0.7%, respectively), although this may be a chance finding. Although the addition of niacin in this study provided no preventive benefit, these results should not be extrapolated to other populations given the well-controlled LDL cholesterol level at baseline in the study patients. It is likely that results of this study will not lead to recommendations to stop niacin in patients already receiving and tolerating the drug. However, physicians may be less likely to start niacin treatment in patients with well-controlled LDL cholesterol levels.

Smoking Cessation

There is a high prevalence of smoking in HIV-infected patients. Efforts to encourage smoking cessation, including behavioral support and pharmacotherapy with nicotine replacement, bupropion, or varenicline in appropriate patients, should be used.¹⁶

Metabolic Syndrome

Americans spend more money on fast food than on higher education.¹⁷ As shown in Figure 1, the prevalence of obesity, defined as body mass index (BMI) greater than or equal to 30 kg/m², has increased dramatically in the United States over the past 2 decades.¹⁸ This epidemic of obesity is accompanied by epidemics of metabolic syndrome and diabetes, both of which are associated with dramatically increased risk of CVD. For example, the

risk of MI in patients with diabetes is equivalent to the risk of recurrent MI in nondiabetic patients with prior MI; the risk is increased 2-fold compared with either of these groups in patients with both diabetes and prior MI.

Metabolic syndrome is defined as the presence of any 3 of the following 5 criteria: (1) fasting glucose level 100 mg/dL or higher, (2) TG level 150 mg/dL or higher, (3) blood pressure (BP) 130/85 mmHg or higher, (4) HDL cholesterol level less than 50 mg/dL in men or less than 40 mg/dL in women, and (5) central obesity, defined as abdominal waist circumference greater than 35 inches in women and greater than 40 inches in men.

In addition to controlling other specific risk factors, management of metabolic syndrome emphasizes weight reduction through lifestyle modification. It is highly beneficial for patients with metabolic syndrome, and especially those with diabetes, to meet with a nutritionist or nurse practitioner who can spend time reinforcing lifestyle modification strategies. Goals for weight reduction are BMI of 18.5 kg/m² to 24.9 kg/m² or waist circumference of less than 35 inches for women and less than 40 inches for men, with a 10% weight reduction during the first year of treatment.¹⁹

Diet and Exercise

The basic approach to weight reduction is to initiate caloric restriction and increase caloric expenditure. The AHA dietary committee recommendations for CVD risk reduction are shown in Table 2.²⁰ For most people, changes involve eating more fruits and vegeta-

bles (a good method is to ensure that at least half the dinner plate contains vegetables), more whole-grain, high-fiber foods, and more fish, while reducing saturated fat intake and consumption of food or drinks with added sugar. Food should be prepared with little or no salt, particularly for patients with hypertension.

Exercise goals are a minimum of 30 to 60 minutes of exercise 5 times per week, with an optimal level of 30 to 60 minutes 7 times per week.¹⁹ Aerobic activity (walking, jogging, cycling) should be encouraged and supplemented with an increase in daily activities (eg, walking breaks at work, gardening, household work). Medically supervised programs (eg, cardiac rehabilitation) should be encouraged for high-risk patients such as those with recent acute coronary syndrome or revascularization and those with heart failure. Patients should also be encouraged to perform resistance training (eg, with weight machines or free weights) twice a week.

Table 2. American Heart Association Nutrition Committee Dietary Recommendations for Cardiovascular Disease Risk Reduction

- Balance calorie intake and physical activity to achieve or maintain a healthy body weight
- Consume a diet rich in fruits and vegetables
- Consume whole-grain, high-fiber foods
- Consume fish, especially oily fish, at least twice a week
- Limit intake of saturated fat to less than 7% of energy, trans fat to less than 1% of energy, and cholesterol to less than 300 mg/day by:
 - Choosing lean meat and vegetable alternatives
 - Choosing fat-free (skim), 1% fat, and low-fat dairy products
 - Minimizing intake of partially hydrogenated fats
- Minimize intake of beverages and foods with added sugar
- Choose and prepare foods with little or no salt
- If alcohol is consumed, do so in moderation

Adapted from American Heart Association Nutrition Committee.²⁰

Summary and Recommendations

HIV-infected persons carry a high burden of traditional CVD risk factors, and these factors are the major determinants of risk in the HIV-infected population. HIV infection may be an independent risk factor for CVD—although there is not yet sufficient evidence to consider it a CHD risk equivalent. Inflammatory and coagulation markers are associated with increased mortality, and possibly CVD, in HIV infection. There is a potential role for antiretroviral therapy to decrease CVD risk, as the beneficial effects of antiretroviral therapy on immune dysfunction and inflammation appear to outweigh the proatherogenic effects of antiretroviral agents.

In the absence of specific randomized trials in the HIV-infected population, HIV-infected persons should be treated for CVD risk factors according to current national guidelines for the general population. Further studies are needed to assess the efficacy of specific interventions to prevent CHD in HIV-infected patients. For now, there are not enough data to support the use of inflammatory and coagulation markers or subclinical imaging for routine risk prediction in clinical care for HIV-infected patients. There are no data yet to support routine use of aspirin or statin treatment in all HIV-infected patients beyond use as specified in national guidelines.

Lecture presented by Dr Post in June 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Post and Dr Ketlogetswe in December 2011.

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Topics in Antiviral Medicine™

Continuing Medical Education

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Instructions

This journal-based continuing medical education (CME) activity provides a review of cardiovascular disease and HIV infection. To complete the activity, the learner is instructed to:

- Read the article (see pages 169-173)
- Review a selection of the references
- Reflect on how the information might be applied to clinical practice
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On completion of this activity, learners will be able to describe evidence from observational studies regarding HIV infection and cardiovascular disease (CVD), and describe risk assessment and risk management for CVD.

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This activity is intended for physicians involved in the care of patients infected with HIV or other viruses. It is also relevant to nurse practitioners, physician assistants, nurses, and other health professionals who provide care for people with viral diseases.

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Dr Post and Dr Ketlogetswe have no relevant financial affiliations to disclose.

Dr Richman has been a consultant to Biota, Bristol-Myers Squibb, CHIMERx, Gen-Probe Inc, Gilead Sciences, Inc, Idenix Pharmaceuticals, Inc, Johnson & Johnson, Merck & Co, Inc, and Monogram Biosciences, Inc. He has been the recipient of research grants or contracts from Merck & Co, Inc. Dr Richman has been a stock options holder of CHIMERx and Idenix Pharmaceuticals, Inc.

Dr Benson has no relevant financial affiliations to disclose.

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This CME activity is offered from **January 30, 2012, to January 30, 2013**. Physicians (MDs, DOs, and international equivalents) who receive a passing score on the posttest and submit the registration and evaluation forms are eligible to receive CME credit. Nonphysician health care practitioners will receive a certificate of attendance.

Posttest Questions

Check the box next to the best answer to each of the questions below. To earn CME credit, you must receive a passing score of 80% or more correct.

1. What is the major determinant of risk for cardiovascular disease in HIV-infected patients?
 - A. Chronic inflammation and accelerated aging associated with HIV infection
 - B. Adverse effects of antiretroviral therapy on metabolism
 - C. Traditional cardiovascular disease risk factors such as diabetes, smoking, hypocholesterolemia, and hypertension
2. Which statement about the Framingham Risk Score (FRS) is **correct**?
 - A. The FRS can be used to predict 10-year risk of cerebrovascular accident
 - B. The FRS can underestimate lifetime risk of coronary heart disease in women
 - C. The FRS is not valid for use in the HIV-infected population
3. According to current American Heart Association/American College of Cardiology recommendations, which group has the **strongest recommendation** (Class I) for aspirin use (daily or every other day) for the primary prevention of cardiovascular disease (CVD)?
 - A. Men with 10-year risk of coronary heart disease of 10% or higher
 - B. Women aged 65 years and older who are at risk for CVD
 - C. Women younger than 65 years who are at risk for CVD
4. In the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) study, simvastatin was compared with simvastatin plus extended-release niacin. Which statement about the AIM-HIGH study findings is **correct**?
 - A. Increases in triglyceride level occurred in the simvastatin/niacin group
 - B. No statistically significant difference in primary endpoint was observed between the 2 treatment groups
 - C. A greater occurrence of stroke was observed in the simvastatin-only group than in the simvastatin/niacin group
5. Evidence from the SMART (Strategies for Management of Antiretroviral Therapy) study of antiretroviral treatment interruption suggests that HIV infection itself increases the risk of coronary heart disease. Which statement about the SMART study findings is **correct**?
 - A. Treatment interruption was not associated with an increase in risk for mortality or cardiovascular disease
 - B. Treatment interruption was associated with an increase in risk for mortality, but was not associated with increase in risk for cardiovascular disease
 - C. Increases in IL-6 (interleukin 6) and D-dimer in the treatment interruption group were statistically significantly correlated with plasma HIV RNA levels

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2. _____
3. _____

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