

## Screening and Assessment of Coronary Heart Disease in HIV-Infected Patients

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Human immunodeficiency virus (HIV)-infected individuals are living longer in the era of antiretroviral therapy. As a result, they are increasingly prone to the development of concomitant chronic disease. Coronary heart disease (CHD) is the leading cause of death in the United States and Europe. Recent studies suggest that CHD rates may be increasing among HIV-infected patients (see Epidemiological Evidence for Cardiovascular Disease in HIV-Infected Patients and Relationship to Highly Active Antiretroviral Therapy, Working Group 2), and thus appropriate screening strategies for CHD in this population are needed. Recently, approaches to screening and assessment of cardiovascular disease (CVD) in HIV-infected individuals were discussed at a State of the Science Conference. Although insufficient evidence now exists to recommend a screening strategy for CHD in HIV that differs from that recommended in the non-HIV population, emerging risk factors and surrogate markers for atherosclerosis unique to the HIV population suggest specific strategies that may be useful in this population. Two broad screening categories are discussed here. The first screening strategy seeks to define the pretest likelihood of disease by identifying the presence of predisposing risk factors such as hypertension, elevated serum cholesterol, cigarette smoking, and physical inactivity. The second screening strategy aims at the detection of established CHD, even in its earliest stages.

### Screening for Cardiovascular Risk Factors

The currently available recommendations and guidelines for screening for the presence of cardiovascular risk factors in

the general, non-HIV-infected population are detailed in Table 1.<sup>1-7</sup>

The currently available recommendations and guidelines for screening for the presence of CVD risk factors in persons with HIV infection are detailed in Table 2. These recommendations take into account the evidence for dyslipidemia, insulin resistance, and changes in body fat distribution that have been shown to occur with highly active antiretroviral therapy (HAART) (see Contribution of Metabolic and Anthropometric Abnormalities to Cardiovascular Disease Risk Factors, Working Group 1).

### Screening for the Presence of Coronary Heart Disease

Routine evaluation of CHD in patients with HIV/AIDS should be guided by the established clinical practice guidelines and appropriateness criteria for test selection used in patients without HIV/AIDS.<sup>8,9</sup> However, referral for diagnostic testing should not be made if the underlying disease or any comorbidity is likely to limit life expectancy or to preclude coronary revascularization (American College of Cardiology [ACC]/American Heart Association [AHA] class III indication).<sup>8</sup> The decision to use invasive coronary arteriography or noninvasive stress tests should be preceded by the performance of a complete clinical history, physical examination, standard 12-lead ECG, and, importantly, an assessment of the pretest probability of CHD. Additionally, the assessment of global CHD risk can inform the selection of an appropriate initial diagnostic test.<sup>8,9</sup>

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**Table 1. Recommendations and Guidelines for Screening for Cardiovascular Risk Factors in the General Population**

Authority	Recommendation/Guideline
USPSTF	<p>Strongly recommends that clinicians routinely screen men <math>\geq 35</math> y of age and women <math>\geq 45</math> y of age for lipid disorders<sup>1</sup></p> <p>Clinicians should routinely screen younger adults (men 20 to 35 y of age and women 20 to 45 y of age) for lipid disorders if they have other risk factors for CAD<sup>1</sup></p> <p>Screening for lipid disorders should include measurement of total cholesterol and HDL-C<sup>1</sup></p> <p>Evidence is insufficient to recommend for or against triglyceride measurement as a part of routine screening for lipid disorders<sup>1</sup></p> <p>Evidence is insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose<sup>2</sup></p> <p>Adults with hypertension or hyperlipidemia should be screened for type 2 diabetes<sup>2</sup></p> <p>Strongly recommends that clinicians screen adults <math>\geq 18</math> y of age for high blood pressure<sup>3</sup></p> <p>Evidence is insufficient to recommend for or against routine screening for high blood pressure in children and adolescents to reduce the risk of CVD<sup>3</sup></p>
NCEP ATP III	In all adults $\geq 20$ y of age, a fasting lipoprotein profile (total cholesterol, LDL-C, HDL-C, and triglycerides) should be obtained once every 5 y <sup>4</sup>

USPSTF indicates US Preventive Services Task Force; CAD, coronary artery disease; and NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Reprinted from Berg AO, Allan JD. Introducing the third US Preventive Task Force. *Am J Prev Med.* 2001;20(3 suppl):3–4, copyright © 2001, with permission from Elsevier.

### Calculation of the Pretest Probability of CHD and Global CHD Risk

Several electronic and paper-based tools for calculating the pretest probability have been published,<sup>10–12</sup> but they have not been validated specifically in the HIV population. Table 3 provides the details of 1 approach. In this model, patients with a pretest score of 0 to 8, 9 to 15, or  $>15$  points are assigned a pretest probability of low, intermediate, or high, respectively.<sup>10</sup> An intermediate pretest probability is the ideal scenario for selecting a noninvasive stress test in patients with a suspicion of CHD (ACC/AHA class I indication).<sup>8</sup> Patients with a high pretest probability have a high false-negative rate on noninvasive tests; therefore, they should be referred for invasive coronary arteriography. Similarly, patients with a low pretest probability have a high false-positive rate and thus are not ideal for a noninvasive stress test such as the exercise ECG. A stress test with nuclear perfusion imaging or wall motion imaging with echocardiography may be appropriate as an initial test in this patient group, however, especially if the short-term global CHD risk is intermediate or high.<sup>9</sup>

Several multivariate models are available for calculating global CHD risk.<sup>13–15</sup> The Framingham Risk Score,<sup>13</sup> the most commonly used model, incorporates age, sex, blood

**Table 2. Recommendations and Guidelines for Screening for Cardiovascular Risk Factors in HIV-Infected Individuals**

Authority	Recommendation/Guideline
IDS/HIVMA	<p>Fasting lipid levels should be monitored before and within 4–6 wk after starting HAART<sup>5</sup></p> <p>Fasting glucose levels should be measured before and during HAART; currently, routine monitoring of insulin levels and/or oral glucose tolerance testing are not recommended<sup>5</sup></p> <p>Routine measurements of body weight and patient self-report of body shape changes are sufficient for clinical practice<sup>5</sup></p>
New York State Department of Health AIDS Institute	<p>Obtain fasting lipid profile and fasting blood glucose before starting antiretrovirals, within 3 to 6 months of starting a new regimen, and annually thereafter<sup>6</sup></p> <p>For patients not receiving HAART, obtain fasting lipid profile and fasting blood glucose at baseline and annually<sup>6</sup></p> <p>Clinicians should screen all HIV-infected patients for use of illicit substances or tobacco at baseline and at least annually<sup>6</sup></p>
Australasian Society for HIV Medicine	<p>Measure fasting lipids (total cholesterol, HDL-C, LDL-C, and triglycerides) and glucose at baseline and regularly during HAART, at least yearly if normal or more frequently if abnormal<sup>7</sup></p> <p>Directly question patients about perceived changes in body shape on a regular basis<sup>7</sup></p> <p>Assess smoking status, blood pressure, and weight at each visit<sup>7</sup></p>

IDS/HIVMA indicates Infectious Diseases Society of America HIV Medicine Association.

pressure, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), diabetes, and smoking to calculate the 10-year CHD risk. Low, intermediate, and high risk are defined as 10-year risk of CHD of  $<10\%$ ,  $10\%$  to  $20\%$ , and  $>20\%$ , respectively. Patients with a low pretest probability who also have a low global CHD risk should not be referred for further diagnostic testing for CHD. However, asymptomatic patients or patients with a low pretest probability who have an intermediate CHD risk or have high-risk occupations (eg, airline pilots) are appropriate candidates for stress testing combined with nuclear or echocardiographic imaging as the initial diagnostic test.<sup>9</sup> For patients with HIV, risk prediction equations that incorporate protease inhibitor (PI) exposure and traditional risk factors have been proposed<sup>14,15</sup> and have been proved to be reasonably accurate in preliminary studies of HIV-infected men and women. The Framingham model, however, appears to underestimate CHD events in HIV patients who also smoke.<sup>14</sup> Further validation of the Framingham risk equation and development of more accurate HIV-specific equations for risk stratification are needed, but the existing equations may nonetheless be useful for providing a general estimate of risk (see Development of Appropriate Coronary Heart Disease Risk Prediction Models in HIV-Infected Patients, Working Group 5).

### Choice of Noninvasive Stress Tests

The use of graded levels of stress to elicit myocardial ischemia forms the cornerstone of noninvasive testing for

**Table 3. Details for Calculating the Pretest Probability in Patients Suspected of Having Coronary Artery Disease**

Variable	Choose Response	Sum
Age (M/F), y		
<40/<50	3	
40–54/50–64	6	
≥55/≥65	9	
Estrogen status	Positive=–3	
Women only	Negative=3	
Angina history	Typical=5	
Diamond method	Atypical=3	
	Nonanginal=1	
Diabetes?	2	
Hyperlipidemia?	1	
Hypertension?	1	
Smoking (any)?	1	
Family history of CAD (first degree)?	1	
Obesity (BMI >27 kg/m <sup>2</sup> )?	1	
	<b>Total Score</b>	

CAD indicates coronary artery disease; BMI, body mass index. The pretest probability associated with a score of 0 to 8 points is low, 9 to 15 points is intermediate, and >15 points is high. The data in Table 3 were published in 2003 and do not reflect the more recent findings of estrogen replacement and cardiovascular risk. Cardiac risk may worsen with use of estrogen. Reproduced from Morise AP, Jalise F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. *J Am Coll Cardiol*. 2003;42:842–850. Used with permission from the American College of Cardiology Foundation.

CHD. Graded stress typically is applied in the form of physical exercise (using a treadmill or stationary bicycle) or pharmacological agents (using dipyridamole, dobutamine, or adenosine). Myocardial ischemia can be detected with standard 12-lead ECG, echocardiography, or nuclear imaging. The treadmill exercise ECG test, the most commonly used and least expensive stress test, has a mean sensitivity and specificity for detecting angiographically significant CHD of 68% and 77%, respectively. In patients with resting ST-segment abnormalities, left ventricular hypertrophy, left bundle-branch block, a ventricular paced rhythm, or the Wolff-Parkinson-White syndrome, an imaging study is preferred over exercise ECG. However, in a patient who is able to walk on a treadmill and has none of these ECG findings, current guidelines recommend the standard treadmill exercise ECG as the initial test of choice.<sup>8,9</sup>

The US Preventive Services Task Force recommends against the routine use of resting ECG, exercise treadmill test, or electron-beam computed tomography scanning for coronary calcium for screening for either the presence of severe coronary artery stenosis or the prediction of CHD events in adults at low risk for CHD events.<sup>16</sup> The US Preventive Services Task Force considers younger adults (ie, men <50 and women <60 years of age) who have no other risk factors for CHD (10-year risk of <5% to 10%) to be at low risk, whereas older adults or younger adults with ≥1 risk factors (10-year risk of >15% to 20%) are considered to be at

increased risk for CVD. In these adults considered to be at increased risk, the US Preventive Services Task Force found insufficient evidence to recommend for or against routine screening with ECG, exercise treadmill test, or electron-beam computed tomography scanning for coronary calcium. Until further data are obtained, these guidelines may be used similarly in the HIV population.

Pharmacological stress is recommended when patients are unable to perform adequate exercise. In patients with an intermediate pretest probability of CHD, the routinely used diagnostic tests (exercise ECG, planar thallium imaging, single-photon emission computed tomography perfusion imaging, stress echocardiography, and positron emission tomography) have sensitivities in the range of 68% to 91% and specificities of 73% to 88%.<sup>17</sup> In addition to their differences in sensitivity and specificity, these tests vary in the frequency of nondiagnostic test results, prognostic accuracy, relative cost, interobserver variability, and availability of local expertise to perform and interpret the tests.

The selection of the most appropriate initial noninvasive diagnostic test for CHD in women is an important challenge. The lower prevalence of CHD in women compared with men of the same age and a higher rate of false-positive ST-segment depression on exercise ECG contribute to this challenge.<sup>18</sup> As a result, selection of an imaging stress test may be preferable to the standard stress ECG as the initial test in women with an intermediate pretest probability of CHD.<sup>18</sup>

The sensitivity of exercise treadmill test, pharmacological stress imaging, and stress echocardiography in the HIV-infected population remains unknown. In a study of 99 asymptomatic HIV-infected individuals without known CHD, 11% were shown to have a positive stress test result, with 1 patient requiring coronary artery bypass graft surgery.<sup>19</sup>

### Emerging Risk Factors for CHD

In the general population, the inflammatory response plays a critical role in all stages of atherogenesis from its inception to plaque rupture.<sup>20,21</sup> Many factors suggest that HIV-infected individuals are at greater risk for CVD as a result of the HIV infection itself and/or synergistic interactions between side effects of some antiretroviral agents and predisposing traditional cardiovascular risk factors.<sup>22</sup> Currently, the underlying mechanisms associated with CVD and HIV are not clearly understood<sup>23</sup> (see also Contribution of Metabolic and Anthropometric Abnormalities to Cardiovascular Disease Risk Factors [Working Group 1] and Effects of HIV Infection and Antiretroviral Therapy on the Heart and Vasculature [Working Group 3]). However, several noninvasive surrogate biological markers (biomarkers) have been demonstrated to monitor the inflammatory process and lipid metabolism. Inflammatory biomarkers include proinflammatory cytokines, chemokines, products of hepatic circulation, and immunoglobulin molecules.<sup>24–27</sup> Lipid biomarkers include the traditional lipid profile, other lipoproteins, LDL fractions, and HDL subfractions.

Of the inflammatory biomarkers, only high-sensitivity C-reactive protein (hsCRP) has been recommended for use in clinical practice by the Centers for Disease Control and Prevention (CDC) and the AHA.<sup>24</sup> Epidemiological data have

shown that hsCRP has had the strongest association with prognosis for new cardiovascular events in patients with unstable angina and myocardial infarction.<sup>28,29</sup> On the basis of the available evidence, the CDC/AHA suggest that patients with moderate risk (10% to 20% risk of CVD over 10 years) may benefit from measurement of hsCRP to identify individuals who should be considered for medical therapy (ie, lipid-lowering, antiplatelet, or other cardioprotective drugs). In a cohort of HIV-infected women, CRP level was an independent predictor of mortality ( $P < 0.01$ ) after adjustment for age, body mass index, serum albumin, CD4 lymphocytes, and HIV-1 RNA.<sup>30</sup> Data from the Multicenter AIDS Cohort Study showed that levels of CRP were associated with HIV disease progression independently of CD4 count and HIV RNA levels.<sup>31</sup> Early studies suggest that increased CRP is a function of changes in fat distribution independently of viral load or CD4 count in HIV-infected women.<sup>32</sup> For patients with HIV, the role of hsCRP in clinical practice is less clear because results could be confounded by comorbid health conditions,<sup>33</sup> and studies investigating the relationship between CRP and CHD, controlling for traditional risk factors, are needed in the HIV population. Other biomarkers include adiponectin, serum amyloid A, vascular cell adhesion molecule-1, intracellular adhesion molecule-1, lipoprotein-associated phospholipase A<sub>2</sub>, and monocyte chemoattractant protein-1. Adiponectin is reduced in HIV-infected patients with fat redistribution and may contribute to insulin resistance.<sup>34</sup> Although epidemiological studies suggest that these inflammatory biomarkers are unrelated to each other, *in vitro* and *in vivo* studies indicate that these markers are involved at different stages of atherosclerotic lesion formation.<sup>26</sup> There are no data yet to suggest that use of these biomarkers adds to that of traditional risk factors in the evaluation of CHD risk among HIV-infected patients in clinical practice. In addition, HIV-infected patients may have impaired fibrinolysis<sup>35</sup> and thus may be at higher risk for thrombosis compared with uninfected patients.

Of the lipid biomarkers, apolipoprotein (apo) B has been discussed as a potential substitute for LDL-C and non-HDL-C in the screening and treatment of CVD.<sup>36,37</sup> Some studies suggest that apoB is a stronger predictor of CVD than LDL-C,<sup>36,38</sup> and the combined ratio measurement of apoB and apoA-I is superior to any of the conventional cholesterol ratios (LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C) in predicting the risk for CVD.<sup>39</sup> The Insulin Resistance Atherosclerosis Study<sup>40</sup> found that 10% of subjects had an apoB >120 mg/dL but did not have an elevated LDL-C or non-HDL-C, implying that current lipid guidelines may miss these individuals.<sup>41</sup> However, the results of other large-scale prospective studies have not been consistent with regard to apoB and apoA-I. In the Atherosclerosis Risk in Communities Study,<sup>42</sup> apoB and apoA-I were strongly predictive of CVD when considered alone but did not contribute when considered together with LDL-C, HDL-C, and triglycerides. The Goettingen Risk, Incidence and Prevalence Study found that LDL-C was a stronger predictor of myocardial infarction than the ratio of apoB to apoA-I or apo B.<sup>43</sup> In light of these observations, the addition of the ratio of apoB to apoA-I to clinical measures should be considered a tool to fine-tune the

risk assessment and targets of therapy. Among HIV-infected patients, use of PIs is associated with an atherogenic lipid profile<sup>44,45</sup> and increased apoB<sup>46,47</sup>; thus, evaluation of apoB may prove useful to further define risk when LDL-C is normal and triglyceride levels are increased. In HIV-infected patients, treatment with lipid-lowering therapy has been shown to improve atherogenic lipid profiles (see also Prevention Strategies for Cardiovascular Disease in HIV-Infected Patients, Working Group 6).<sup>44,48</sup>

Plasma levels of the amino terminal fragment of prohormone brain-type natriuretic peptide (NT-proBNP) are predictive of cardiovascular morbidity and mortality and can identify patients who are at risk for events in the future.<sup>49</sup> A study of 495 HIV-infected individuals who were treated with HAART showed that these individuals had higher NT-proBNP levels compared with age-matched blood donors.<sup>50</sup> Like hsCRP, the ability of NT-proBNP to predict cardiovascular events in HIV-infected individuals remains unclear and requires further studies.

### Surrogate Marker Studies of Atherosclerosis

Surrogate markers for CVD serve as reasonable alternatives to defined cardiovascular end points in clinical studies, although each marker has limitations.<sup>51</sup> Whether these markers are as useful for documenting CVD in the individual patient is less clear. The validated surrogate markers that predict cardiovascular outcomes include measurement of carotid intimal wall thickness (cIMT) and coronary calcium scores (CCS). Three large studies have demonstrated that cIMT was an independent predictor of coronary artery disease.<sup>52–54</sup> Precise standardization of protocols for obtaining cIMT images and methods to ensure precise positioning are necessary for these measures to be valid in the assessment of atherosclerosis and in determining progression. In addition, the value of a single cIMT measurement is unclear, and it may be that the rate of progression over time is more valuable in determining CVD risk than a measure at a single point in time. Computed tomography can accurately and reproducibly quantify the presence of coronary calcium.<sup>51,55,56</sup> Although the CCS correlates well with total atherosclerotic plaque burden, it reflects advanced (calcified) lesions. As such, it may be less useful as an indicator of clinical risk at early stages when risk-reduction interventions may be more successful.

Both of these surrogate markers have been studied in HIV-infected populations, typically to identify factors associated with CVD. In cross-sectional studies of cIMT, older age, male sex, smoking, and increased body mass index frequently were associated with increased cIMT.<sup>57–65</sup> One AIDS Clinical Trials Group study was uniquely designed with triads of patients enrolled simultaneously: HIV-infected patients with a history of PI use; HIV-infected patients with no PI exposure; and age-, sex-, ethnicity-, smoking history-, blood pressure-, and menopausal status-matched, HIV-negative control subjects.<sup>61,66</sup> There was no correlation between PI use or HIV infection and cIMT, but traditional risk factors of age, HDL, and body mass index were associated. The sample size was small in all of these studies, and follow-up was limited in duration. In 1 longitudinal study,

148 HIV-infected patients and 68 HIV-negative control subjects were studied over 1 year.<sup>67</sup> Age, LDL, smoking, Latino ethnicity, hypertension, and HIV infection were associated with increased cIMT.<sup>67</sup> One-year progression of cIMT in HIV-infected patients was more accelerated than in HIV-negative controls: 0.074 versus 0.006 mm/y. Age, Latino ethnicity, and CD4 nadir were all associated with progression of cIMT. Of note, each of these studies used different methodologies for evaluating IMT and different patient populations.

CCSs have been reported in 7 cross-sectional studies in HIV-infected individuals. In 1 study, 17 HIV-infected individuals were compared with HIV-negative control subjects; CCS appeared to be higher in HIV-infected individuals.<sup>68</sup> Other studies have demonstrated a correlation with the use of the PI nelfinavir alone or with PI use in general.<sup>69–71</sup> Another study, however, showed no association with HIV or with PI use when HIV-infected individuals were compared with HIV-negative individuals. In univariate analysis of a cohort of 327 HIV-infected individuals, an abnormal CCS was predicted by age, triglycerides, and remnant lipoprotein C in both men and women.<sup>64</sup> There was a trend for duration of HIV infection to be associated with an increased risk for abnormal CCS in both men and women. In studies that reported CCS in cocaine users, cocaine was associated with increased CCS.<sup>69,70</sup> The sample size in all of these studies was small (17 to 98 participants), and populations were biased (entirely black and/or cocaine users).

Flow-mediated vasodilation of the brachial artery is a method to assess endothelial function. Endothelial dysfunction may be an early manifestation of atherosclerosis<sup>72</sup> and is important in the pathogenesis of CVD.<sup>73</sup> Endothelial function of the brachial arteries and endothelial function of the coronary arteries are strongly correlated.<sup>74</sup> Most important, endothelial function is independently predictive of both short- and long-term cardiovascular events.<sup>75,76</sup> In a cross-sectional study of 37 HIV-infected adults who were receiving antiretroviral therapy, PI therapy was associated with endothelial dysfunction.<sup>45</sup> A recent substudy of a large antiretroviral clinical trial found that all 3 HAART regimens studied improved endothelial function as early as 4 weeks after treatment was started, suggesting that regardless of the type of antiretroviral agent, treatment of HIV disease may contribute to improved endothelial function (see also Effects of HIV Infection and Antiretroviral Therapy on the Heart and Vasculature, Working Group 3).<sup>77</sup>

Improvements in imaging technology may expand the utility of these diagnostic strategies. The questions that remain about the specific risks of CVD among HIV-infected populations may be addressed with well-conducted surrogate marker studies. The usefulness of these surrogate markers in evaluating an individual's risk is not as clear.

### Controversial Issues, Gaps in Knowledge, and Future Research Priorities

The extent to which HIV infection or its treatment alters the underlying pathophysiology and progression of atherosclerosis remains unresolved. Preclinical screening strategies that rely on the pretest likelihood of disease are still largely extrapolations from conventional risk factor profiles, and

screening modalities may not perform as expected in this population. Furthermore, atypical symptoms of myocardial ischemia can delay diagnosis and affect outcomes, and it remains unknown whether ischemic symptomatology is atypical in HIV-infected patients or whether such patients have high rates of silent ischemia, as is seen in patients with diabetes mellitus. Several key areas for future research were identified:

- Define the sensitivity and specificity of diagnostic tests for coronary disease such as exercise or pharmacological stress testing, nuclear imaging, and stress echocardiography in HIV-infected patients.
- Determine the clinical utility of surrogate markers such as hsCRP, cIMT, coronary calcium, and flow-mediated vasodilatation of the brachial artery in the early detection of CHD in HIV-infected patients.
- Compare the spectrum of clinical presentations of angina and ischemia in patients with and without HIV to determine presentation patterns and silent ischemia rates in the HIV population. In this regard, determining the effects of age, gender, and race on ischemic symptomatology among HIV-infected patients is critical.
- Determine the long-term outcomes of HIV patients after coronary events and develop appropriate risk reduction and treatment strategies (eg, medical versus interventional) based on these data.

In the absence of HIV-specific studies, recommendations for both the screening and diagnosis of coronary artery disease in the HIV-infected individual do not differ generally from the strategies that have been proven effective in uninfected populations. The gaps in our knowledge base regarding best screening and treatment practices need careful ongoing clinical and basic study in large populations with long follow-up if we are to refine our approach to the detection and amelioration of CHD and other CVDs in the HIV-infected population.

### Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary, which is available online at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189622>.

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