State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living With HIV/AIDS: Executive Summary

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State of the Science Conference

Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living With HIV/AIDS

Executive Summary

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With successful antiretroviral therapy, patients infected with the human immunodeficiency virus (HIV) are living longer; however, recent reports suggest increased rates of coronary heart disease (CHD) among HIV-infected patients,[1] and cardiovascular disease has become an important cause of morbidity and mortality in this population.[2] Increased CHD rates in the HIV population may relate to traditional risk factors, including advancing age, higher smoking rates, dyslipidemia, insulin resistance, and impaired glucose tolerance. Cardiovascular disease may also be due to nontraditional factors, including changes in body composition with loss of subcutaneous fat and/or accumulation of visceral fat in some patients, inflammation, and direct effects of the virus on the vasculature, as well as to direct effects of specific antiretroviral drugs. Important questions remain as to the pathogenesis, detection, and treatment of cardiovascular disease and related risk factors in HIV-infected patients. These questions concern, among other things, the design of adequate trials to determine CHD incidence and the utility of existing CHD guidelines for screening, prevention, treatment, and risk stratification.

To ascertain the state of the science with respect to these and related questions, a multidisciplinary conference with interested HIV specialists, cardiologists, endocrinologists, primary care physicians, National Institutes of Health representatives, and patient advocates was convened June 28–30, 2007, in Chicago, Ill, and chaired by Drs Steven Grinspoon and Robert Eckel. The discussions focused on 6 areas of interest, each with its own working group, including the following: (1) the contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors (chaired by Drs Carl Grunfeld and Donald Kotler); (2) the epidemiological evidence for cardiovascular disease and its relationship to highly active antiretroviral therapy (HAART; chaired by Drs Judy Currier and Jens Lundgren); (3) the effects of HIV infection and antiretroviral therapy on the heart and vasculature (chaired by Drs Michael Dubé and Steve Lipshultz); (4) the screening and assessment of CHD in HIV-infected patients (chaired by Drs Priscilla Hsue and Kathleen Squires); (5) the development of appropriate CHD risk prediction models in HIV-infected patients (chaired by Drs Morris Schambelan, Kevin Yarasheski, and Peter Wilson); and (6) prevention strategies for CHD in HIV-infected patients (chaired by Drs James Stein and Colleen Hadigan).

For each area of interest, specific topics were covered in plenary lectures and in subsequent discussions with conference participants. Summaries for each working group were reported to the conference participants for discussion (indi-

Writing group reports are available online at http://circ.ahajournals.org (*Circulation*. 2008;118:e20–e28; e29–e35; e36–e40; e41–e47; e48–e53; and e54–e60).

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vidual working group summaries and a list of writing group members are available online with the present issue of *Circulation*). The proceedings were sponsored by an unrestricted educational grant from Bristol-Myers Squibb to the American Heart Association and by the American Academy of HIV Medicine. Per American Heart Association guidelines, the sponsor had no role in the planning of the meeting, choice of speakers, speaker content, or formulation of the scientific summary. In this executive summary, we summarize the major points of discussion and conclusions for each area of interest.

Contribution of Metabolic and Anthropometric Abnormalities to Cardiovascular Disease Risk Factors (Chairs: Carl Grunfeld, MD, PhD; Donald P. Kotler, MD)

HIV-infected patients manifest a number of metabolic and anthropometric abnormalities, including dyslipidemia and insulin resistance, as well as subcutaneous fat loss and relative visceral fat gain, which may contribute to increased cardiovascular disease risk.[3] The metabolic abnormalities may be due to HIV or its therapy and may be affected by environmental factors (eg, lifestyle, dietary intake, and weight changes associated with a restoration of health), as well as immunologic factors. In addition, the metabolic abnormalities may be interrelated (eg, dyslipidemia, insulin resistance, and central fat accumulation). The metabolic changes seen in HIV-infected patients are often heterogeneous and may relate to specific antiretroviral drugs within a class, as well as to the antiretroviral drug class, and they may differ by gender, race, ethnicity, and age. These changes may also present uniquely in HIV-infected children.

Lipid abnormalities occur early in HIV infection, with reduction in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and increases in triglycerides and very-low-density lipoprotein cholesterol. The net effect may be proatherogenic owing to the significant reduction in HDL cholesterol and increases in triglyceride levels, oxidized LDL, and small dense LDL. The mechanism of these changes is not completely understood, but increases in de novo lipogenesis and reduced very-low-density lipoprotein clearance have been reported[4] and may be related to immunologic status and cytokine levels.[5] The effects of these changes on plaque formation, macrophage recruitment, and foam cell formation have not been fully characterized. Although insulin resistance is associated with many of these processes, a reduction in insulin action was not uniformly seen among HIV-infected patients before the era of HAART and may be more prevalent with the increases in body mass index and fat distribution seen with restoration to health and improved virological suppression.

Before the widespread use of HAART, HIV infection was characterized by cachexia, increased resting energy expenditure, and sarcopenia.[6] Early studies suggest some relative central adiposity even among patients with low body mass index.[7] With the introduction of HAART, longitudinal studies of antiretroviral therapy initiation in antiretroviral therapy–naive patients found early increases in subcutaneous and visceral fat, with subsequent loss of subcutaneous fat and relative preservation of visceral fat with nucleoside reverse-transcriptase (NRTI) treatment.[8] Cross-sectional studies are in agreement with regard to the near-universal occurrence of peripheral and subcutaneous fat loss, particularly with NRTI treatment[9]; however, changes in abdominal fat are more heterogeneous. HIV-infected patients with lipoatrophy may actually have less absolute visceral fat than non–HIV-infected patients but relatively more visceral fat for a given body mass index across a range of body mass indexes, because lipoatrophy reduces body mass index.[10]

Significant gender differences may also be apparent, with accumulation of more gluteofemoral fat in women, but it remains unknown whether this is protective among HIV-infected women.[11] Among both women and men, accumulation of fat in the visceral and upper trunk depots is associated with hyperinsulinemia and dyslipidemia, including low HDL cholesterol and increased triglyceride levels, which suggests the potential utility of strategies to selectively reduce this fat compartment.[12] In addition, visceral fat accumulation may be associated with increased inflammation, which may link this depot to insulin resistance. Relative preservation or accumulation of dorsocervical fat (eg, the buffalo hump) and fat in the breasts may also occur in association with insulin resistance. Studies to date have shown that loss of peripheral fat is not linked to accumulation of central fat.[9] Morphological changes in different fat depots have not been well characterized in terms of adipocyte size and number.

Numerous effects of HAART, both class-specific and non–class-specific, have been reported with respect to lipids, glucose, and body composition. Among the protease inhibitors (PIs), ritonavir most significantly increases triglyceride.[13] Increased triglyceride levels may also occur with stavudine and efavirenz. LDL cholesterol increases modestly with initiation of most forms of HAART; this increase is not due to direct effects of specific antiretroviral drugs, but whether it relates to immune effects or restoration of health remains unclear.[14] Significant increases in LDL cholesterol among HIV-infected patients are more likely to be due to genetic and dietary causes. Although nonnucleoside reverse-transcriptase inhibitors (NNRTIs) increase HDL cholesterol, most other antiretroviral therapies do not, and low HDL cholesterol levels may contribute to CHD in HIV-infected patients.

Insulin resistance may be caused by specific drugs, including indinavir and other PIs,[15,16] but is less likely to occur with newer PIs. Similarly, NRTIs, in particular stavudine, may result in insulin resistance directly through inhibition of mitochondrial function in the muscle[17] or indirectly via effects to reduce peripheral fat.[18] Insulin resistance is also associated with changes in body composition, including increased visceral and upper trunk fat.

Finally, changes in renal function due to HIV may contribute to increased cardiovascular disease. Microalbuminuria is 5 times more common among HIV-infected patients than among non–HIV-infected subjects in the current era of HAART and is associated with black race and other cardiovascular disease risk factors.[19]

Important questions and priorities for future research were identified, including the need for better identification of HIV-related direct and indirect (eg, medication, body com-

position) effects on metabolic parameters, assessment of HIV- or antiretrovirus-induced proatherosclerotic changes in lipoprotein structure, determination of the contribution of dyslipidemia and insulin resistance to the development of cardiovascular disease, identification of the mechanisms and consequences of body composition changes for the development of cardiovascular disease, and identification of individual drug versus class effects on metabolic abnormalities in HIV-infected patients.

Epidemiological Evidence for Cardiovascular Disease in HIV-Infected Patients and Relationship to HAART (Chairs: Judith S. Currier, MD; Jens D. Lundgren, MD, PhD)

The epidemiological evidence for an association between HIV and cardiovascular disease comes from a number of sources, including retrospective cohort studies, administrative and clinical databases, prospective HIV cohort studies, and randomized clinical trials of antiretroviral therapy. Taken together, these data suggest an increased risk of cardiovascular disease in HIV-infected patients (see *Circulation* online for the summary of Working Group 2). However, these studies also suggest that overall morbidity and mortality dropped steeply with the introduction of HAART.[20] Data from studies including non–HIV-infected control subjects, drawn largely from administrative data sets or retrospective cohort studies, suggest an approximate 1.5- to 2.0-fold increase in CHD in HIV-infected versus non–HIV-infected patients, with potentially larger differences seen among female HIV-infected patients relative to non–HIV-infected control subjects in gender-stratified analyses.[21–23] The choice of an appropriate control group with similar demographic background to that of an HIV-infected group (eg, young, racially diverse, and with similar lifestyle habits), is difficult, however, and may limit comparisons in such studies.

Although relative CHD rates appear to be increased, absolute rates remain low, which perhaps reflects the age and demographics of the HIV-infected population and the relatively short duration of risk factor exposure. In addition to ascertainment of relative risk, the relationship of traditional and nontraditional risk factors to the development of CHD in the HIV population has been determined in a number of prospective cohort studies. CHD rates have been associated with HAART, specifically with PI use compared with NNRTI use (eg, 1.16 per year of PI use [95% CI 1.1 to 1.23] versus 1.05 per year of NNRTI use [95% CI 0.98 to 1.13] over 5 to 6 years of exposure).[24] Furthermore, adjustment for dyslipidemia significantly (50%) attenuates this relationship, which suggests some role for dyslipidemia as a contributing factor to increased CHD rates.[25]

Importantly, smoking rates are higher in HIV-infected patients and also contribute significantly to increased risk.[24,26] Other traditional risk factors such as male sex and age, as well as diabetes mellitus and dyslipidemia, also contribute to CHD to a degree similar to that seen in non–HIV-infected patients (see *Circulation* online for summary of Working Group 2); however, rates of dyslipidemia and diabetes appear to be higher among HIV-infected patients.[23] Because HIV-infected patients live longer owing to the success of HAART, these factors may become even more important. Rates of nontraditional risk factors such as inflammation have not been well evaluated in terms of cardiovascular disease risk in the HIV-infected population.

Studies investigating the epidemiology of cardiovascular disease in HIV-infected patients must be careful to determine whether HIV infection is simply a marker for a population with increased rates of traditional risk factors. These studies must also determine whether HIV infection and antiretroviral therapy contribute independently to increased cardiovascular disease through effects on traditional or nontraditional risk factors. Importantly, randomized, controlled studies will be necessary to determine causality with respect to risk factors and HIV. For example, in a recent study, HIV-infected patients were randomized to continuous antiretroviral therapy for virological suppression or intermittent antiretroviral therapy on the basis of prespecified virological parameters.[27] The study was stopped prematurely because of increased deaths, progression to AIDS, and a marginal but unexpected increase in cardiovascular events in the intermittent-dosing arm. These data raise the question of whether there may also be beneficial effects of continuous antiretroviral therapy on certain traditional and nontraditional cardiovascular risk factors, including lipid levels and inflammation, that contribute to increased cardiovascular disease rates. Randomized trials with cardiovascular disease end points may be difficult to achieve and will take many years to complete in HIV-infected patients. Therefore, only limited data from such studies in HIV-infected patients will be available to inform decision making on cardiovascular disease in the near term.

Important questions and priorities for future research were identified, including the clinical significance of relative increases in CHD rates given the low absolute rates, the importance of appropriate control groups for comparison with non–HIV-infected patients, the relative impact of traditional and nontraditional risk factors on increased CHD rates, determination of the role of individual drugs as distinct from antiretroviral drug class effects, the implications of the epidemiological data for those patients beginning antiretroviral therapy in developing countries, and the risk profiles of new drugs being developed for the treatment of HIV disease. Determination of the true risk of CHD and its causes will become increasingly important in the long-term management of HIV-infected patients receiving antiretroviral therapy.

Effects of HIV Infection and Antiretroviral Therapy on the Heart and Vasculature (Chairs: Michael P. Dubé, MD; Steven E. Lipshultz, MD)

Infection with HIV and its treatment with antiretroviral therapy may significantly affect the heart and vasculature. A number of potential mechanisms may contribute to these effects. HIV may exert direct effects on the myocardium and vascular endothelium, although data on direct cellular infection are limited.[28] Macrophages and other reservoir cells infected with HIV may affect vascular and myocardial function through paracrine and systemic release of inflammatory cytokines. In addition, alterations in lipid metabolism can affect plaque formation. Associated metabolic changes

(see *Circulation* online for the summary of Working Group 1), including insulin resistance and fat redistribution, may also affect endothelial and myocardial function.

Clinically, left ventricular dysfunction is common in HIV-infected patients and may go unrecognized or masked by concurrent illness and misdiagnosed as pulmonary or infectious in origin. Diagnosis is best performed by echocardiography, because ECG abnormalities may be seen in almost 60% of asymptomatic HIV-infected patients.[29] In patients undergoing ventricular biopsy for cardiomyopathy, myocarditis was seen in more than half of those studied in 1 series in the pre-HAART era.[30] HIV-related cardiomyopathy may carry a worse prognosis than other types of nonischemic cardiomyopathy. Nutritional deficiencies should also be considered.

Among children vertically infected with HIV, inadequate or reduced left ventricular wall thickness is a useful independent predictor of morbidity and increased risk of death within 24 months.[31] Even small decreases in fractional shortening can be associated with marked increases in 5-year mortality rates,[32] which may be associated with a low CD4 count and low weight, among other factors. However, causality is difficult to determine. Among children followed up in the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P2C2) longitudinal study of HIV-infected children, for example, cardiac mortality was high at 35%.[33] Studies suggest that immunomodulatory therapy with immunoglobulin may improve left ventricular function in this population.[34] Evidence for the effects of HIV on the heart and vasculature has come most often from studies performed before the current era of HAART, in which viremia was less adequately suppressed. The effects of HIV on the heart and vasculature in the current context of successful HAART have not been fully determined.

Endothelial dysfunction is present in antiretroviral therapy–naive HIV-infected patients but improves only somewhat with introduction of antiretroviral therapy. This may be because of the negative effects of specific individual antiretroviral drugs, viral protein–mediated endothelial activation,[35] or chemokine dysregulation, with activation of macrophages, smooth muscle cells, and enhanced atheroma formation. Data on direct infection of the vasculature are limited.[36]

Pulmonary hypertension is seen in 1 of 200 HIV-infected adults, with similar pathophysiology to that seen in non–HIV-infected patients.[37] Pulmonary hypertension carries a poor prognosis among HIV-infected adults.[38] In addition to ischemic cardiovascular disease, autonomic dysfunction and vasculitis are common among HIV-infected patients. The incidence of pericardial effusion has been reported to be up to 11% per year in HIV-infected adults.[39]

An increasing body of evidence suggests adverse effects of specific antiretroviral agents on the heart and vasculature, but these effects may not be class-specific. Toxicities may vary among drugs in a similar class and with respect both to cause and to whether exposure occurs in utero, in childhood, or during adult life. For example, zidovudine and stavudine may contribute to adverse effects on the myocardium through effects on myocardial function and depletion of mitochondrial DNA.[40]

Other potential mechanisms include disruption of normal glucose uptake into the myocardial cells with the use of specific PIs, including indinavir. Exposure to HAART in utero is associated with reductions in left ventricular wall mass and septal wall thickness in the first year after birth,[41] and these effects may resemble anthracycline cardiotoxicity. However, the overwhelming benefits of preventing mother-to-child transmission outweigh the potential negative long-term effects on cardiac function. Long-term follow-up of these children is important.

In general, antiretroviral therapy improves endothelial function in HIV-infected patients, although data suggest that use of older PI regimens containing indinavir but not other PIs may worsen endothelial function. The potential mechanisms by which specific PI-based regimens can adversely affect endothelial function include reduction in nitric oxide production or release,[42] increases in reactive oxygen species,[43,44] impairment of cholesterol efflux from foam cells, and increased macrophage cholesterol ester accumulation through upregulation of the CD36 scavenger receptor.[45,46] Specific NRTIs, including stavudine and zidovudine, may also increase superoxide production in experimental models.[47]

Significant progress has been made in determining the mechanism and prevalence of HIV and antiretrovirus-related myocardial and vascular dysfunction, but important questions and priorities for future research were identified. These included the need to establish the specific effects of individual antiretroviral agents and identify the direct effects of HIV, as well as related indirect effects, establish biomarkers for vascular and myocardial dysfunction, and develop effective treatment strategies for these cardiovascular complications.

Screening and Assessment of CHD in HIV-Infected Patients (Chairs: Priscilla Y. Hsue, MD; Kathleen Squires, MD)

With an increase in CHD rates and aging of the HIV-infected population, screening for CHD assumes increasing importance. Insufficient data currently exist to recommend a screening strategy different from that for non–HIV-infected patients. However, specific cardiovascular risk factors that result from the complex metabolic effects of HIV infection and its therapy (eg, dyslipidemia, insulin resistance, and fat redistribution) suggest a number of useful approaches to screen for cardiovascular disease in HIV-infected patients.[48] As for the non–HIV-infected population, it is important to establish the pretest likelihood for CHD and then formulate a screening strategy to detect established disease based on the pretest likelihood of risk.

A number of tools exist to calculate the pretest probability of CHD, but these have not been fully validated in HIV-infected patients. The Framingham risk equation incorporates age, sex, blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus, and smoking to calculate a 10-year CHD risk. This equation has been investigated in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study and has been shown to perform reasonably well, although it somewhat underestimates CHD risk, particularly in smokers.[49] Further validation is required, and development of

optimal risk stratification models, perhaps including antiretroviral use and other specific HIV factors, is important (see also *Circulation* online for the summary of Working Group 5 on the development of cardiac risk prediction models in HIV-infected patients). Low, intermediate, and high risk are defined on the basis of 10-year risk of CHD <10%, 10% to 20%, and >20%, respectively.[50,51] According to the US Preventive Services Task Force,[52] patients with a low pretest probability and a low global CHD risk score (eg, <10%) should not be referred for further testing, whereas those with a high pretest probability (>20%) have a high false-positive rate on noninvasive tests, such as exercise ECG, and should be considered for invasive arteriography. Patients at intermediate risk are most suitable for noninvasive testing. These conclusions, however, are not derived from specific data on HIV-infected patients, in whom further research is needed. Furthermore, screening recommendations may be individualized to account for severity of individual risk factors, such as a significant family history of early cardiac disease.

The use of graded levels of stress is most commonly employed to detect myocardial ischemia. Stress may be physiological (eg, exercise) or pharmacological (eg, dipyridamole) and may be assessed with ECG, echocardiography, or nuclear imaging. The treadmill ECG has a sensitivity of 68% and specificity of 77% for detecting angiographically significant CHD, but these data have not been determined specifically for HIV-infected patients. In general, women have a higher false-positive rate of ST depression on exercise ECG, which makes it more difficult to formulate screening recommendations. It remains unknown whether higher false-positive rates are seen with ECG screening among HIV-infected women.

Newer inflammatory biomarkers, such as high-sensitivity C-reactive protein and adiponectin, may prove useful for identifying HIV-infected patients at risk for CHD; however, the specificity of such markers for the detection of CHD remains unclear in HIV-infected patients. Although the Centers for Disease Control and Prevention/American Heart Association guidelines recommend measuring high-sensitivity C-reactive protein in non–HIV-infected patients at intermediate risk for cardiovascular disease,[53] this strategy requires validation in HIV-infected patients, in whom high-sensitivity C-reactive protein levels are increased and have been shown to predict mortality in at least 1 cohort.[54] Adiponectin levels are decreased with increasing abdominal adiposity and lipoatrophy among HIV-infected patients and are increased with use of PIs among HIV-infected patients.[55] Long-term data on the clinical significance of reduced adiponectin in HIV-infected patients with fat redistribution are not available. In addition, apolipoprotein B100 may prove useful as a biomarker for CHD, especially in patients in whom LDL cholesterol levels are normal and triglyceride levels increased.[56]

Surrogate markers for CHD, including carotid intimal-medial thickness and computed tomographic angiography, have been investigated but not validated as independent predictors of CHD outcomes in HIV-infected patients. Among HIV-infected patients, some studies have reported increased carotid intimal-medial thickness in association with traditional risk factors and PI use. In a longitudinal study, traditional risk factors were also associated with more rapid progression of carotid intimal-medial thickness in HIV-infected versus non–HIV-infected subjects.[57] Similarly, coronary artery calcium scores have been reported in several studies of HIV-infected patients and have been associated with the presence of traditional risk factors[58] and PI use[59] in some studies. A limitation in this regard is that the coronary artery calcium score may not detect early plaque lesions, especially in young adults, women, and ethnic minorities. In contrast, endothelial dysfunction, as assessed by flow-mediated dilation or other techniques, may be an early manifestation of atherosclerosis. Studies have demonstrated endothelial dysfunction in association with the PI indinavir,[60] but this effect may not occur with other PIs. The long-term clinical significance of these effects on endothelial function is not known.

Important questions and priorities for future research were identified, including the need to determine the optimal screening strategy and risk stratification algorithm, define the sensitivity and specificity of diagnostic tests for CHD, and determine the clinical utility of inflammatory and surrogate markers of CHD in HIV-infected patients.

Development of Appropriate CHD Risk Prediction Models in HIV-Infected Patients (Chairs: Morris Schambelan, MD; Peter W.F. Wilson, MD; Kevin E. Yarasheski, PhD)

Validation of CHD risk prediction models is important for the development of prevention strategies in HIV-infected patients (see also *Circulation* online for the summary of Working Group 6 on prevention strategies for CHD in HIV-infected patients). An important question in the development of risk prediction models is whether existing risk stratification equations, such as the Framingham equation, are valid in HIV-infected patients and whether HIV-specific equations need to be developed. In this regard, it is important to determine whether traditional risk factors captured in existing equations relate similarly to risk among HIV-infected patients and whether HIV-specific variables, such as antiretroviral use and duration of HIV, should be included to improve the accuracy of risk stratification models.

Current risk stratification equations were generally developed on the basis of long-term (>10 years) prospective observations of homogeneous populations of middle-aged patients with chronic exposure to risk. In contrast, HIV-infected patients are diverse in terms of both demographics (eg, younger and more racially diverse) and intensity and duration of risk exposures. In addition, existing equations do not take into account important factors relating to substance abuse, immune function, lifestyle choices, and the unique risks of specific antiretroviral drugs. An important related question is the degree to which CHD risk is increased with newer antiretroviral agents.

Although estimates of risk are generally similar in HIV-infected and non–HIV-infected patients,[24,61] potential differences with respect to both traditional and nontraditional risk factors suggest the need to determine the value of HIV-specific equations. Indeed, preliminary data using existing

models may overpredict[49] or underpredict[62] cardiovascular risk depending on whether the end point is myocardial infarction or a broader composite end point and whether patients are smokers or nonsmokers. New models will need to account for the dynamic and changing nature of antiretroviral therapy and will likely need to be developed and validated separately for diverse geographic regions and for subpopulations such as adolescents. Longitudinal studies of sufficient duration that capture critical end points (eg, myocardial infarction versus composite end points that include stroke or cardiac procedure) and risk factors are necessary to develop accurate CHD risk stratification models for HIV-infected patients.

Several key indices are utilized in the development of CHD-prediction models. It is important to know the relative risk associated with a given risk factor and to determine discrimination, the probability that a model assigns a higher risk to those who develop the factor (eg, diabetes mellitus) than those who do not. Calibration of a model determines how closely the predicted outcomes agree with actual outcome. Risk-stratification models can be recalibrated if relative risk is ranked appropriately but is consistently overestimated or underestimated.

HIV-specific models for CHD risk prediction have been proposed. For example, the DAD study assessed a model that incorporated PI exposure along with traditional risk factors to predict myocardial infarction. The HIV-specific equation predicted 153 events over 33 594 person-years compared with 157 actual events and 183 events predicted by the Framingham study.[49] The receiver operating characteristic discrimination statistic was good at 0.78. However, the Framingham risk prediction equation has yet to be validated among a general population of patients living with HIV. Other risk prediction models such as PROCAM (Prospective Cardiovascular Munster Study) have not been tested in HIV-infected patients. Moreover, it is not known whether surrogate end points, such as carotid intimal-medial thickness, will perform as well as or better than clinical end points in these models. It is important to recognize that equations such as the Framingham equation were developed for risk stratification and that individual patients may have a myocardial infarction even if characterized as being at low risk. Prevention may be undertaken in patients at lower risk, but strategies for such patients must balance risk and benefit.

Important questions and priorities for future research were identified, including the design of appropriate prospective studies, choice of end points and risk factors resulting in optimal sensitivity and specificity, and rigorous validation of newly derived models. In this regard, a multicenter, multinational prospective study will be necessary to develop an accurate risk prediction model for use in HIV-infected patients, but this will take many years and require careful planning for the capture of relevant risk factors and end points. In the interim, the use of preliminary HIV-specific and existing non–HIV-specific equations, such as Framingham, may help clinicians identify patients who are most appropriate for risk factor reduction. Finally, it will be useful to recalibrate existing models that appear to predict events reasonably well but systematically overestimate or underestimate risk.

Prevention Strategies for Cardiovascular Disease in HIV-Infected Patients (Chairs: James H. Stein, MD; Colleen M. Hadigan, MD, MPH)

As with non–HIV-infected patients, an important principle for HIV-infected patients is that risk-reducing interventions should be based on the level of CHD risk and whether the presence of cardiovascular disease has been established. In this regard, the focus of the Chicago conference was on the prevention of cardiovascular disease among patients without established disease and strategies to reduce modifiable risks in this large population of HIV-infected patients. Unique considerations among the HIV-infected patients include other comorbid conditions and potential drug interactions with antiretroviral medications. Cigarette smoking is highly prevalent in patients with HIV, with estimates of >50% prevalence in some studies,[26] and smoking is a significant risk factor for CHD in HIV-infected patients. Smoking prevention and cessation strategies are important but have not been fully evaluated or implemented among HIV-infected patients. Evaluation of efficacy and the potential for drug interactions with smoking cessation pharmacotherapies is also critical.

Traditional risk factors for cardiovascular disease, including diabetes mellitus and dyslipidemia, are more prevalent among HIV-infected patients than among the general population.[23] Evidence to date also shows a modest increase in the prevalence of hypertension, and this risk may further increase with aging of the HIV-infected population. Preliminary studies suggest a relatively modest relationship of hypertension to CHD among patients with HIV compared with non–HIV-infected patients[61] and a beneficial effect of lifestyle intervention on blood pressure in this population.[63] Until further data are available on the mechanisms of hypertension and the potential for drug interaction with antiretroviral agents, existing guidelines for the prevention and treatment of hypertension in non–HIV-infected patients should be used.

Dyslipidemia, with decreased total and HDL cholesterol and increased triglyceride, is seen in untreated HIV infection. Additional atherogenic changes, including increases in total and small dense LDL, triglycerides, and apolipoprotein B100, occur in patients receiving antiretroviral therapy, but these effects vary by drug within class and between classes.[60] Furthermore, these effects can be influenced by concomitant insulin resistance, changes in fat distribution (including subcutaneous fat loss and accumulation of visceral or upper trunk fat[12]), and increased saturated fat intake among HIV-infected patients.[64]

Few data are available on the effects of lipid-lowering therapy for primary or secondary prevention of CHD outcomes, although small studies have shown improvement in lipid levels and endothelial function in HIV-infected patients.[65] In addition, strategies to improve visceral adiposity may improve dyslipidemia,[66] although lifestyle modification programs have had only limited effects on serum lipids in HIV-infected patients.[63] Specific guidelines for the approach to lipid management in HIV-infected patients have been published that outline the potential interactions with antiretroviral therapy and unique considerations for therapy in this population.[67] These guidelines focus on the impor-

tance of reducing LDL and non-HDL cholesterol levels given the proven cardiovascular disease risk reduction that is observed when these lipid markers are reduced in patients without HIV.[67]

Diabetes mellitus occurs in 6% to 18% of patients with HIV[68] and may be related to antiretroviral therapy, HIV infection, or changes in body composition. Furthermore, insulin resistance and impaired glucose tolerance are seen in almost 50% of HIV-infected patients with body composition changes[69] and are also associated with antiretroviral exposure. No data are available as to the optimal regimens for the treatment of diabetes mellitus in HIV-infected patients, nor is it known whether the use of lifestyle modification or insulin-sensitizing agents prevents the development of diabetes mellitus in HIV-infected patients with impaired glucose tolerance. The clinical significance of impaired glucose tolerance remains unknown in this population, but preliminary studies of lifestyle modification in HIV-infected patients modeled after the Diabetes Prevention Program do suggest reductions in hemoglobin A1c over 6 months.[63] Insulin-sensitizing agents may be useful to reduce insulin resistance and may also help to reduce central fat accumulation[70] or induce small increases in subcutaneous fat in some lipoatrophic insulin-resistant patients,[71] but they should not be used for the sole purpose of improving body composition. Moreover, the risk profile of these drugs may be great, with the potential for interaction with antiretroviral therapy. Measurement of fasting glucose and lipids at least yearly in HIV-infected patients and with changes in antiretroviral therapy is critical.

Antiretroviral therapy, particularly the use of PIs, may be associated with CHD, as suggested by the DAD study,[24] but limited data on the effects of specific agents are available. However, continuous use of antiretroviral therapy for viral suppression is associated with reduced mortality and less cardiovascular disease than intermittent antiretroviral therapy, which suggests that these agents may also be protective by unknown mechanisms potentially related to reduced inflammation or effects on lipids if used continuously.[27] Nonetheless, it is important to consider the known metabolic effects of individual drugs in choosing an antiretroviral regimen, particularly in those patients with preexisting CHD risk factors.

Important questions and priorities for future research were identified, including the reasons for increased smoking rates and the optimal prevention and cessation strategies for smoking, determination of the clinical significance of impaired glucose tolerance and dyslipidemia on CHD outcomes, the optimal treatment strategies and targets for management of dyslipidemia, the role of lifestyle intervention for metabolic abnormalities, and the optimal choice, sequencing, and duration of antiretroviral therapy with respect to primary and secondary prevention of CHD in HIV-infected patients.

Conclusions

HIV-infected patients are living longer owing to the success of antiretroviral therapy, but a number of recent studies suggest increased cardiovascular disease in this population, and cardiovascular disease now ranks as a major cause of death in this population. Dyslipidemia, insulin resistance, inflammation, and changes in body composition are all likely to contribute to this, and these abnormalities may be interrelated and due to HIV infection, related inflammation, or toxicities associated with specific antiretroviral agents. Development of optimized screening, prediction, and treatment algorithms for cardiovascular disease in HIV-infected patients is of utmost importance. A critical need exists for more research in this area.

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Disclosures

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Esteban Martinez	University of Barcelona	Abbott; BMS; Gilead; GSK	Abbott; BMS; Boehringer-Ingelheim; Gilead; GSK	None	None	Abbott; BMS; Gilead; GSK
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James H. Stein	University of Wisconsin	NIH; BMS; Kos; LipoScience; PreMD; Sanofi-Aventis; Siemens; Sonosite	Abbott; LipoScience; Merck (all relationships terminated); Schering-Plough	None	Pfizer; Takeda (all honoraria donated directly to charity)	Intellectual property licensed to Wisconsin Alumni Research Foundation related to the use of ultrasound for cardiovascular risk prediction
Zelalem Temesgen	Mayo Clinic College of Medicine	Abbott; Gilead; Merck; BMS; Tibotec	Abbott; Tibotec	None	None	None
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KEY WORDS: AHA Conference Proceedings ■ AIDS ■ HIV ■ cardiovascular diseases ■ myocardial infarction ■ antiretroviral therapy, highly active ■ protease inhibitors

Correction

In the AHA Conference Proceedings by Grinspoon et al, "State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living With HIV/AIDS: Executive Summary," which published ahead of print June 19, 2008, and appeared in the July 8, 2008, issue of the journal (*Circulation*. 2008;118:198–210), the following correction is needed:

In the list of authors, the middle initial for Dr Lundgren should be "D." It has been updated to read, "Jens D. Lundgren."

This correction has been made to the print and current online versions of the article.

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