

## Prevention Strategies for Cardiovascular Disease in HIV-Infected Patients

James H. Stein, MD, FAHA, Co-Chair; Colleen M. Hadigan, MD, MPH, Co-Chair; Todd T. Brown, MD, PhD; Ellen Chadwick, MD; Judith Feinberg, MD; Nina Friis-Møller, MD, PhD; Anuradha Ganesan, MD; Marshall J. Glesby, MD, PhD; David Hardy, MD; Robert C. Kaplan, PhD; Peter Kim, MD; Janet Lo, MD; Esteban Martinez, MD, PhD; James M. Sosman, MD; for Working Group 6

Effective antiretroviral therapy (ART) improves the survival of patients with human immunodeficiency virus (HIV) infection.<sup>1</sup> With increased life expectancy, HIV-infected patients increasingly are experiencing complications of illnesses that are not directly related to HIV infection.<sup>2</sup> Cardiovascular disease (CVD), the leading cause of death in the United States,<sup>3</sup> recently has been recognized as an important cause of morbidity and mortality among patients with HIV (see Working Group 2, Epidemiological Evidence for Cardiovascular Disease in HIV-Infected Patients and Relationship to Highly Active Antiretroviral Therapy).<sup>2,4-6</sup> Among these patients, traditional CVD risk factors predict CVD events; however, certain components of ART appear to be associated with increased CVD risk.<sup>5</sup> Much of the increased CVD risk observed in patients undergoing ART is related primarily to the effects of ART on traditional CVD risk factors; however, direct effects of ART on the vasculature and other inflammatory, immune, and viral factors associated with HIV infection may also contribute to increased CVD risk.<sup>5,7,8</sup>

A central tenet of preventing CVD is that the intensity of risk-reducing interventions should be based on the level of CVD risk.<sup>9</sup> Patients with established CVD are at the highest risk and qualify for the most aggressive risk factor management, with special focus on interventions that have been proven to prevent cardiovascular death, myocardial infarction, and stroke. For patients without established CVD, management is based on the presence of risk factors for developing complications of CVD, such as death, myocardial

infarction, and stroke<sup>9-12</sup> (see Working Group 4, Screening and Assessment of Coronary Heart Disease in HIV-Infected Patients). The intensity of CVD risk-reducing therapy, however, must be modified by the context of the patient's overall health. This is an especially important consideration in patients with HIV infection, who often have competing morbidities that may be as likely to lead to death or disability as CVD, such as complications of HIV, substance abuse, liver disease, or malignancy.<sup>2</sup> Also, to achieve the aggressive goals set forth in recent lipid and hypertension guidelines,<sup>10-12</sup> multidrug therapy frequently is necessary, which places many HIV-infected patients at risk for complications of polypharmacy. With these considerations, efforts to prevent CVD in patients with HIV should focus on improving modifiable risk factors such as cigarette smoking, hypertension, dyslipidemia, and disordered glucose metabolism. The initial choice of ART regimen and subsequent ART modifications also may be considered in planning CVD prevention strategies, with the recognition that maintenance of viral suppression is the primary concern, because the risks of inadequately treated HIV infection outweigh any increase in CVD risk that may be associated with ART, and with the understanding that uncontrolled viral infection may itself contribute to CVD risk.<sup>7,13,14</sup>

### Cigarette Smoking

Cigarette smoking is highly prevalent among patients with HIV (47% to 71%) and is more prevalent than in the general

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population.<sup>15,16</sup> Aside from having a history of CVD, current cigarette smoking is the most powerful predictor of CVD events among patients with HIV.<sup>5</sup> A reduction in CVD risk and total mortality associated with smoking cessation has been demonstrated in non-HIV-infected populations.<sup>17–20</sup> Furthermore, smokers with HIV have higher total mortality and are more likely to develop pneumonia, chronic obstructive pulmonary disease, cancers, and decreased quality of life than nonsmokers.<sup>21</sup>

Preventing individuals with HIV from starting smoking is critical, because stopping smoking remains a formidable challenge. Efforts directed at educating teenagers about the harmful effects of smoking and strategies to avoid use of cigarettes are important, because smokers frequently begin using cigarettes as teenagers or young adults.<sup>22</sup> A majority of current smokers with HIV desire to quit smoking<sup>23</sup>; however, physicians of patients with HIV are less likely than non-HIV healthcare providers to ascertain smoking status.<sup>21</sup> A minority of HIV care providers are confident that they can influence smoking cessation.<sup>21</sup> Challenges to achieving successful smoking cessation include lack of provider awareness, high rates of relapse due to nicotine addiction, lack of social network support, lack of access to proven smoking cessation strategies, drug interactions, and fatalism.

Current guidelines recommend the “5A” approach: ask about tobacco use, advise to quit, assess willingness to make a quit attempt, assist with the quit attempt, and arrange for follow-up.<sup>22</sup> Identification and successful treatment of smokers can be improved by systems-based management tools, such as incorporating smoking as a vital sign (so each patient is “asked”) and assigning the physician responsibility for advising the patient to quit smoking, for assessing their willingness, and for assisting with pharmacotherapy. Pharmacotherapy is the preferred approach to smoking cessation now that more effective medications are available, although their long-term safety and efficacy remain to be established.<sup>24–26</sup>

Specific research needs related to smoking cessation as a strategy to reduce CVD risk in patients with HIV infection include pharmacokinetic and pharmacodynamic studies to evaluate the effects of smoking cessation on ART and interactions between ART and smoking cessation pharmacotherapies, because smoking cessation affects hepatic enzymes involved in drug metabolism and may have other pharmacodynamic effects that have not yet been studied (Table 1). Further research also is needed on the costs and effectiveness of systems-based approaches to smoking cessation.<sup>27</sup>

### Hypertension

Hypertension is a powerful predictor of CVD events in the general population.<sup>11,28</sup> The prevalence of hypertension among patients with HIV infection has not been established with certainty, but in 2 US cohorts, it was 12% to 20% among individuals <40 years old and 35% to 41% for individuals ≥40 years old.<sup>29</sup> The best evidence suggests that ART may be associated with a modest increase in blood pressure and the prevalence of hypertension; however, these relationships may be confounded by increases in body mass index and other risk factors for the development of hypertension, so the effect of ART on hypertension is unclear.<sup>29–31</sup> The prevalence of

hypertension is expected to increase as the age of patients with HIV infection increases and the prevalence of HIV increases among patients in ethnic subgroups at increased risk of developing hypertension.<sup>29</sup> When hypertension is present, the magnitude of increased CVD risk associated with this risk factor probably is similar to that observed in the general population.<sup>11,28</sup> In the general population, dietary interventions are effective for reducing blood pressure.<sup>32,33</sup> In 1 study, patients with HIV who completed an intensive lifestyle intervention that included dietary and physical activity counseling, modeled after the Diabetes Prevention Program, experienced a significant reduction in blood pressure.<sup>34,35</sup> Pharmacotherapy for hypertension powerfully reduces CVD risk in non-HIV-infected patients.<sup>11,28</sup> Guidelines for the effective diagnosis and management of hypertension have been widely adopted and should be applied to patients with HIV until further data are available (Table 2).<sup>11,28</sup>

Specific research needs related to hypertension and CVD risk in patients with HIV infection begin with the need to obtain a better understanding of the prevalence of hypertension among patients undergoing ART, as well as the extent to which it influences risk of coronary artery disease, stroke, heart failure, and kidney disease. Pharmacokinetic and pharmacodynamic studies that evaluate interactions between commonly used antihypertensive therapies and ART are needed, given the overlap in metabolic pathways affected by ART and certain antihypertensive medications.<sup>36</sup>

### Dyslipidemia

Untreated HIV infection is associated with decreased total cholesterol and high-density lipoprotein cholesterol (HDL-C) and with increased triglycerides and the presence of small dense low-density lipoprotein (LDL) particles.<sup>37</sup> Atherogenic lipoprotein changes, including increases in total cholesterol, triglycerides, LDL cholesterol (LDL-C), small LDL, and apolipoprotein B-100, are seen in patients taking ART; however, HDL-C also increases with ART.<sup>12,38,39</sup> (See Working Group 1, Contribution of Metabolic and Anthropometric Abnormalities to Cardiovascular Disease Risk Factors.) In general, use of protease inhibitors is associated with more adverse lipid changes than use of nonnucleoside reverse-transcriptase inhibitors; however, the lipid effects of ART vary within classes, and there is notable interindividual variability in lipid responses to ART.<sup>40–47</sup> Lipids may worsen dramatically in some patients, and dyslipidemia in HIV-infected patients is associated with increased risk of CVD.<sup>5,48–50</sup> Severe hypertriglyceridemia (>1000 mg/dL) is a risk factor for pancreatitis, but the incidence of pancreatitis among patients with HIV infection is not known. The independent contribution of less severe degrees of hypertriglyceridemia to CVD risk in the HIV population is less clear, because it is associated with other metabolic abnormalities that also affect CVD risk, such as low HDL-C, hypertension, and insulin resistance.

Adverse dietary habits are common in patients with HIV and contribute to dyslipidemia<sup>51</sup>; therefore, a trial of dietary modification may be appropriate before initiation of drug therapy.<sup>12</sup> In patients with HIV, the only prospective cardiovascular outcomes data showing the benefits of lipid-

lowering therapy are studies showing that treatment with statins improves endothelial function<sup>52,53</sup>; however, an observational study reported that among HIV-infected patients with dyslipidemia, use of lipid-lowering therapy was associated with reduced CVD rates.<sup>50</sup> Pharmacotherapy for dyslipidemia powerfully reduces CVD risk in non-HIV-infected patients.<sup>9,10</sup> Guidelines for the effective diagnosis and management of dyslipidemia have been widely adopted<sup>9,10</sup> and are the basis of the general approach to the patient with HIV; however, current pharmacological strategies for treating dyslipidemia in patients undergoing ART are limited by drug interactions, relative lack of efficacy, and, potentially, pill burden, as well as consideration of comorbidities (Table 2).<sup>12,54–58</sup> Therefore, separate guidelines for the management of dyslipidemia in patients with HIV have been developed.<sup>12</sup> These guidelines focus on the importance of reducing LDL-C and non-HDL-C levels, given the proven CVD risk reduction that is observed when these lipid markers are reduced in patients without HIV.<sup>9,10,12</sup>

There are several research needs related to dyslipidemia and CVD risk in patients with HIV infection (Table 1). Given the reduced efficacy and safety issues with lipid-lowering therapy in patients undergoing ART, confirmation of the cardiovascular benefits of standard lipid-lowering strategies in patients with HIV who are undergoing ART would be ideal; however, cost and logistics may be prohibitive. Prospective studies on progression of a surrogate marker, such as carotid intima-media thickness or other markers of vascular injury, would be useful. Current guidelines focus on LDL-C and non-HDL-C; however, the additional predictive value of apolipoprotein B-100 and other lipoprotein markers is not known in patients with HIV. This is a matter of special interest for patients with HIV, because many patients undergoing ART have combined dyslipidemia or hypertriglyceridemia, and some patients with increased triglycerides who have achieved LDL-C and non-HDL-C targets may still have an excess of atherogenic particles. More guidance is needed regarding strategies for safely and effectively treating combined dyslipidemia in patients with HIV. Finally, pharmacokinetic and pharmacodynamic studies to evaluate interactions between lipid-lowering therapies and newer ART agents are needed. These studies also need to be performed with new and selected older ART agents in children and teenagers.

### Disordered Glucose Metabolism

Use of ART is associated with increased visceral adiposity, insulin resistance, and disordered glucose metabolism, which increases future risk of type 2 diabetes mellitus and CVD.<sup>43,59,60</sup> The prevalence of type 2 diabetes mellitus among patients with HIV ranges from 6% to 18%, and for men, it appears to be increased relative to noninfected controls.<sup>61</sup> Impaired fasting glucose (defined as fasting blood glucose >100 mg/dL) or impaired glucose tolerance (defined as a 2-hour glucose >140 mg/dL after a 75-g glucose load) is increased in patients with HIV<sup>60</sup> and is associated with ART exposure.<sup>60,62–66</sup> In addition to ART exposure, risk factors for insulin resistance and type 2 diabetes mellitus in patients with HIV include male sex, increasing age, increasing body weight, and increasing waist circumference, as well as eth-

**Table 1. Controversial Issues, Gaps in Knowledge, and Future Research Priorities**

Smoking
<ol style="list-style-type: none"> <li>1. Why are smoking rates higher in HIV-infected patients?</li> <li>2. What are the optimal strategies for smoking cessation in HIV-infected patients?</li> <li>3. Do smoking cessation and the use of smoking cessation medications affect the efficacy and safety of ART?</li> </ol>
Hypertension
<ol style="list-style-type: none"> <li>1. What is the prevalence of hypertension in HIV-infected patients?</li> <li>2. What is the magnitude of increased CVD risk conveyed by hypertension among patients with HIV?</li> <li>3. Are there specific interactions between antihypertensive agents and ART that should inform the sequence and dosing of antihypertensive therapy in HIV-infected patients?</li> </ol>
Dyslipidemia
<ol style="list-style-type: none"> <li>1. How much does the hypertriglyceridemia observed in patients undergoing ART contribute to CVD risk?</li> <li>2. Are the cardiovascular benefits of lipid-lowering therapy in patients with HIV similar to those observed in the non-HIV-infected population?</li> <li>3. What is the optimal sequence of lifestyle interventions and pharmacological therapy in HIV-infected patients?</li> <li>4. Are LDL-C and non-HDL-C the best targets of lipid therapy in patients with HIV?</li> <li>5. What is the utility of apolipoprotein B-100 and other lipoprotein markers for CVD risk prediction in patients with HIV?</li> <li>6. Given the potential for interaction between specific lipid-lowering medications and ART, what are the optimal lifestyle and pharmacological treatment strategies for managing dyslipidemia in patients with HIV?</li> </ol>
Disordered glucose metabolism
<ol style="list-style-type: none"> <li>1. What are the mechanisms of insulin resistance in patients with HIV? What is the role of viral infection, body composition, and ART?</li> <li>2. What is the clinical significance of impaired glucose tolerance in the patients with HIV? Should it be treated, and how?</li> <li>3. What is the optimal treatment for diabetes mellitus? What are the roles of lifestyle modification, insulin-sensitizing agents, and insulin?</li> </ol>
Antiretroviral therapy (see also Working Group 2 on Epidemiological Evidence for CVD)
<ol style="list-style-type: none"> <li>1. How should the presence of metabolic abnormalities and potential for treatment interactions affect the choice and sequence of ART initiation and switching?</li> <li>2. How does a strategy of switching ART compare with managing CVD risk factors in patients with ART-associated metabolic abnormalities?</li> <li>3. What are the direct and indirect effects of ART on the vasculature?</li> <li>4. Do the effects of ART on immune and inflammatory markers affect CVD risk, and if so, how do these effects compare with traditional CVD risk factors?</li> </ol>

nicity and hepatitis C coinfection.<sup>29,63,67</sup> Impaired fasting glucose and impaired glucose tolerance are best treated nonpharmacologically with lifestyle interventions such as dietary changes and exercise, although medications can be considered (Table 2).<sup>35,68,69</sup> In patients with HIV, regular exercise and an intensive lifestyle intervention that includes dietary and exercise counseling has salutary metabolic effects and tends to reduce insulin resistance.<sup>34,70</sup> Metformin and thiazolidinediones tend to improve insulin resistance in pa-

**Table 2. Summary of Interventions to Reduce CVD Risk in Patients With HIV Infection**

Risk Condition	Treatment/Interventions	Major Findings	Limitations
Cigarette smoking	Interpersonal counseling	Increased quit rates	No studies of pharmacotherapy in patients with HIV
Hypertension	Dietary and physical activity counseling* CCBs Other antihypertensive agents	Reduced blood pressure Drug interactions between CCBs and PIs	Limited data from controlled studies regarding safety and efficacy of pharmacotherapy
Dyslipidemia	Dietary and physical activity counseling* Statins, fibrates, fish oil, niacin	Modest improvement in lipids Statins improve endothelial function Multiple drug interactions with ART	Short duration; long-term efficacy for CVD reduction not known Effectiveness of newer lipid-lowering agents not known Interactions with newer ART regimens need to be clarified
Disordered glucose metabolism	Dietary and physical activity counseling* Metformin and TZDs	Improvement in glycemia Metformin reduces insulin resistance and VAT TZDs may improve SAT	Lactic acidosis with metformin CVD risks with TZDs not clear Safety and efficacy of sulfonylureas not established Interactions with ART regimens need to be clarified
Use of ART	Modification of initial ART based on metabolic profile and CVD risk Switching of ART to reduce metabolic side effects	Modest effects on lipids and insulin resistance Statins and fibrates may be more effective	Small studies, often uncontrolled or used older ART regimens Effects on CVD risk not known Risk of viral relapse and resistance Inadequately suppressed HIV increases total and possibly CVD mortality

CCBs indicates calcium channel blockers; PI, protease inhibitor; TZDs, thiazolidinediones; VAT, visceral adipose tissue; and SAT, subcutaneous adipose tissue.

\*Components and duration of lifestyle modification program in patients with HIV are not known.

tients with HIV; however, the long-term effectiveness of these agents for the prevention and treatment of diabetes mellitus in patients with HIV is not known.<sup>71–73</sup> Some studies also suggest insulin resistance is increased among children undergoing ART.<sup>74,75</sup> Patients initiating ART should be screened for impaired fasting glucose and diabetes mellitus by measurement of fasting glucose levels at baseline, annually, and after changes are made to ART regimens. Measurements of insulin and hemoglobin A<sub>1c</sub> as screening tests are not recommended by current guidelines.<sup>76</sup> Oral glucose tolerance testing may help to identify and distinguish between patients with impaired glucose tolerance and those with diabetes mellitus.

Specific research needs related to disordered glucose metabolism and CVD risks include assessment of how well recognition and management of diabetes mellitus are achieved in patients with HIV (Table 1). Preliminary data indicate that fewer than half of HIV-infected patients with diabetes mellitus achieve hemoglobin A<sub>1c</sub> targets.<sup>77</sup> The optimal treatment strategies for diabetes mellitus in patients with HIV have not been determined. In this regard, potential drug interactions and unique mechanisms of diabetes mellitus need to be considered. In addition, further research to characterize the CVD risk conveyed by disordered glucose metabolism in patients with HIV infection relative to the non-HIV population is needed, including research on the extent to which disordered glucose metabolism and its associated increase in CVD risk are reversed when ART is modified.

### Antiretroviral Drug Use and CVD Risk

Although control of HIV infection remains the overriding priority when choosing an initial ART strategy or making subsequent changes in ART, preexisting CVD and CVD risk may also be given consideration. Observational studies have suggested that increasing years of exposure to ART are associated with increased CVD risk.<sup>5,43</sup> Several studies have demonstrated improvements in CVD risk factors, particularly improvements in lipid profile, through modification or selection of ART.<sup>41,42,78,79</sup> On the other hand, there are compelling data to support an increase in total mortality and possibly CVD risk when HIV is inadequately suppressed or ART is withdrawn (see Working Group 2).<sup>13</sup> Indeed, 1 study demonstrated that use of ART was associated with short-term decreases in CVD risk and overall mortality.<sup>80</sup> Initiation of ART currently is driven primarily by risk of HIV disease progression and loss of immune function; however, the metabolic profiles of drugs should be considered, especially in patients with CVD or those who are at high or moderately high cardiovascular risk (>10% risk of myocardial infarction or coronary death over 10 years).<sup>10</sup>

Whether a strategy of switching ART is superior to managing CVD risk factors in patients with ART-associated metabolic abnormalities is not clear, and this decision must be individualized on a per-patient basis. Treatment of HIV may improve some CVD risk factors, while exacerbating others (Table 1). Some of the excess CVD risk related to ART may be attributed to alterations in lipids and disordered glucose metabolism<sup>5</sup>; however, options for subsequent ART regimens

may be constrained by HIV resistance, medication toxicity, and tolerability. Newer drugs and emerging classes of ART may provide better options with regard to CVD risk factors.

Specific research needs related to ART and CVD risk in patients with HIV infection remain (Table 1). A better understanding of how initiation, choice, and duration of ART exposure affects CVD risk should be attained by prospectively studying the effects of ART on traditional CVD risk factors, emerging risk factors, vascular structure and function, and well-validated CVD events such as cardiac death, myocardial infarction, and stroke. In addition, a clearer understanding of the effects of ART on immune and inflammatory markers that may play a role in CVD risk is needed. Studies evaluating the time course and extent of the reversal of adverse metabolic effects and excess CVD risk of ART when ART is changed are needed. Finally, for children, research is needed to more fully appreciate the influences of initiation, selection, and duration of ART on cumulative CVD risk and disease burden.

### Conclusions

CVD risk assessment and risk reduction are essential components of preventive medical care that are increasingly important for patients with HIV infection. As the population of HIV-infected patients ages and accumulates CVD risk that is, at least in part, related to ART, efforts to appropriately recognize and manage CVD risk will be necessary. Lifestyle modification, including smoking cessation, increased physical activity, weight reduction for those who are overweight or obese, and education on healthy dietary practices are the cornerstones of CVD risk reduction. These strategies, combined with appropriate management of dyslipidemia, disordered glucose metabolism, and hypertension, will help maximize the long-term health of persons living with HIV. Research is needed to identify the lifestyle modifications that are most effective for reducing CVD risk in patients with HIV, whether they differ by age, sex, ethnicity, and socioeconomic status, and what barriers exist to their implementation. It is especially important to develop simple and clear messages to educate patients and HIV care providers about the importance of CVD prevention in HIV patients, the importance of identifying and treating CVD risk factors in individuals at moderately high or high CVD risk, and how smoking, adverse dietary habits, and physical inactivity increase CVD risk.

### Note Added in Proof

Recent data<sup>81</sup> suggest that use of a growth hormone–releasing factor significantly reduces visceral fat in HIV-infected patients on HAART with visceral fat accumulation. In addition, this strategy improved lipids without aggravating glucose. These data raise the important question as to whether strategies aimed at reducing visceral fat, a known cardiovascular risk factor in non-HIV patients, may improve CVD risk in HIV patients.

### 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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## Prevention Strategies for Cardiovascular Disease in HIV-Infected Patients

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