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Management of Long-Term Complications of HIV Disease: Focus on Cardiovascular Disease.

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Perspective

Management of Long-Term Complications of HIV Disease: Focus on Cardiovascular Disease

HIV-infected individuals on effective antiretroviral therapy experience a number of non-AIDS noncommunicable diseases, such as cardiovascular disease, more frequently than uninfected individuals. Common pathways for such diseases are chronic immune activation and inflammation, including the prolonged inflammation associated with lower nadir CD4+ cell count. Prevention and treatment of non-AIDS conditions include treatment of traditional risk factors, lifestyle interventions, earlier initiation of antiretroviral therapy, and potentially therapies specifically targeting inflammation and immune activation (eg, statins). This article summarizes a presentation by Judith S. Currier, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, *held in New York, New York, in February 2017.*

Keywords: HIV, non-AIDS diseases, cardiovascular disease, CVD, heart failure, immune activation, inflammation, CD4+ cell count, interleukin-6, IL-6, statins

As HIV-infected individuals on effective antiretroviral therapy are living longer, a range of other health issues is emerging among these persons. A number of conditions, including cardiovascular disease (CVD), non–AIDS-related cancers, bone disease, diabetes, frailty, liver disease, lung disease, renal disease, and cognitive disorders, occur with more frequency in HIV-infected persons with viral suppression on antiretroviral therapy than in the general population. Efforts to determine how best to prevent and treat such conditions and whether they share underlying contributing causes are ongoing.

Survival and Comorbidities

Data from a study in the Netherlands indicate that the survival rate for treated HIV-infected individuals aged 50 years or older has steadily increased from the period from 1996 to 1999 to the period from 2006 to 2014 and is approaching the survival rate among uninfected individuals in this age group (Figure 1).[1] However, even when survival analysis is limited to HIV-infected persons who had no comorbidities before initiating antiretroviral therapy and who have maintained viral suppression throughout treatment, there remains a gap between the survival rates of such persons and the general population (Figure 1).[1]

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The prevalence of comorbidities is increasing as the population of individuals with HIV infection ages. Data from another study in the Netherlands indicate that the proportion of persons living with HIV infection aged 50 years or older will increase from 28%, as of 2010, to 73% by 2030.[2] Over this time, the proportion of HIV-infected persons with at least 1 noncommunicable disease from among CVD (including hypertension, hypercholesterolemia, myocardial infarction [MI], and stroke), diabetes, chronic kidney disease, osteoporosis, and non-AIDS malignancies is estimated to increase from 29% to 84%.[2] It is estimated that by 2030, 28% of HIV-infected individuals will have more than 3 noncommunicable diseases and that 54% will be on medications to treat these conditions.[2]

CVD in HIV Infection

A US study showed that between 1999 and 2013, the proportion of mortality attributable to circulatory CVD among HIV-infected individuals aged 25 years or older increased from 2.1% to 3.8% in women and from 1.9% to 4.9% in men.[3] These increases occurred during a period when mortality attributable to CVD decreased in the general population and among persons with other inflammatory diseases such as inflammatory polyarthropathies.

Some data indicate that the relative risk of CVD in HIV-infected individuals has decreased over time. In a cohort study from Kaiser Permanente Northern California, the adjusted MI rate ratio for HIV-infected versus uninfected persons decreased from 1.8 (95% confidence interval [CI], 1.3-2.6; incidence rate [IR], 276/100,000 vs 136/100,000 person-years) in the period from 1996 to 1999 to a nonsignificant 1.0 (95% CI, 0.7-1.4; IR, 195/100,000 vs 165/100,000 person-years) in the period from 2010 to 2011; rate ratios were 1.7, 1.3, and 1.3 for the periods from 2000 to 2003, 2004 to 2007, and 2008 to 2009, respectively.[4] This cohort likely reflects a population with well-managed HIV infection and access to preventive care, suggesting that such care may contribute to reducing CVD risk.

HIV infection adversely affects cardiac function. Studies using cardiac magnetic resonance imaging (MRI) have shown a high burden of myocardial fibrosis and cardiac steatosis among asymptomatic HIV-infected individuals, decreased systolic function in HIV-infected individuals compared with controls, and increased pericardial fat among HIV-infected individuals with lipoaccumulation.[5-8]

Clinical studies have shown an increased risk of heart failure among HIV-infected persons.[9,10] In a study of 27,363 HIV-infected and 55,125 HIV-uninfected persons without CVD conducted between 2003 and 2012, HIV-infected persons had

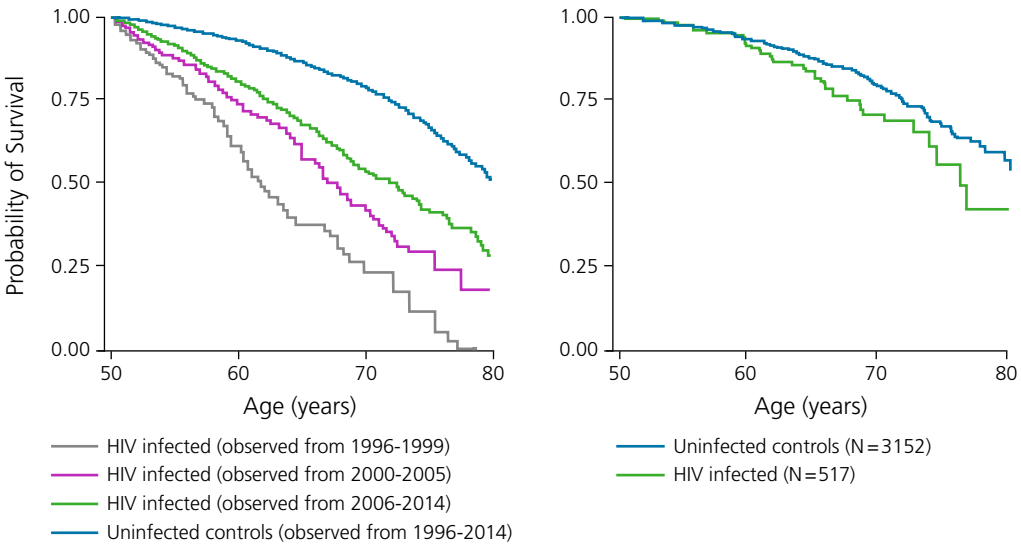

Figure 1. Long-term mortality in Dutch HIV-infected patients aged 50 years or older (left) and in a subset of those with well-controlled HIV infection and no prior comorbidities (right). Adapted from Legarth et al.[1]

a statistically significantly elevated risk of heart failure with preserved ejection fraction (EF) (EF, ≥40%; RR, 1.21; 95% CI, 1.05-1.40) and with reduced EF (EF, <40%; RR, 1.58; 95% CI, 1.36-1.89).[11]

Pathways for Non-AIDS Diseases in HIV

There may be common contributing factors for non-AIDS events in HIV infection, involving host genetics and lifestyle, HIV replication with resulting immune activation, and antiretroviral therapy. Measures of these risk factors include innate immune activation (eg, soluble CD14 [sCD14], sCD163, monocyte activation); history of low nadir CD4+ cell count—"area under the curve of chronic inflammation" or a low CD4 to CD8 ratio; copathogens (eg, cytomegalovirus [CMV] immune responses or CMV-specific T-cell responses); and abnormalities in coagulation (eg, tissue factor expression).

Single measurements of the coagulation marker D-dimer and the inflammation marker interleukin (IL)-6 were predictive of serious non-AIDS events or death in HIV-infected individuals over a period of 10 years (Figure 2).[12-14] In a biomarker analysis of the SMART (Strategies for Management of Antiretroviral Therapy) and ESPRIT (Evaluation of Subcutaneous Aldesleukin in a Randomized International Trial) trials that compared highest with lowest quartiles of IL-6, D-dimer, and the inflammatory marker high-sensitivity C reactive protein (hs-CRP), IL-6 was the strongest predictor for both non-AIDS malignancy and CVD among HIV-infected persons (Figure 3).[14] Similar associations have been found in cohort studies of immune activation. Higher levels of innate immune activation have been associated with all-cause mortality, CVD and thromboembolic disease,[15] non-AIDS cancers and lymphoma,[16] osteoporosis,[17] type 2 diabetes,[18] frailty,[19] chronic obstructive pulmonary disease,[20] bacterial pneumonia,[21] and neurocognitive dysfunction.[22] With regard to adaptive immune activation, T-cell activation predicted morbidity and mortality in a multinational case-cohort study,[23] and in a study among persons in Uganda.[24]

A high proportion of persons with HIV infection are coinfected with CMV. CMV infection may be responsible for some of the increased immunosenescence and increased proliferation of CD8+ T cells linked to comorbidities in the context of coinfection with HIV. Whether immunization or more effective therapy for CMV infection might reduce immune activation and immunosenescence in the context of HIV/CMV coinfection, thus reducing the risk of associated comorbidities, remains unknown.

The harms of untreated HIV disease clearly outweigh any excess risk of CVD associated with antiretroviral therapy. Longer duration of treatment with older HIV protease

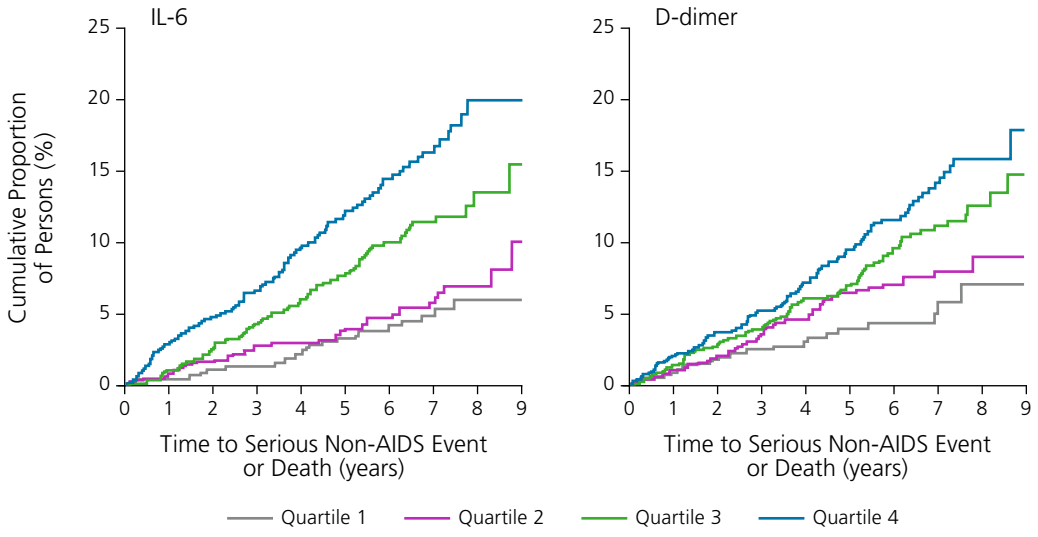

Figure 2. Association between single measurements of interleukin (IL)-6 and D-dimer and risk of serious non-AIDS events or death over 10 years. Adapted from Grund et al.[12]

inhibitors (eg, indinavir, ritonavir-boosted lopinavir) was associated with increased MI risk in observational studies.[25,26] However, no association between antiretroviral drugs and evidence of plaque on computed tomography (CT) angiography has been observed. Abacavir has been associated with increased relative risk of MI. The most consistent evidence of this association has been found among individuals with additional risk factors, and the mechanism of the association remains unclear. Recent evidence suggests a possible role for platelet reactivity as the underlying mechanism.[27-31]

AIDS Clinical Trials Group (ACTG) A5260s, a substudy of the ACTG A5257 study, examined the effects of newer antiretroviral regimens on CVD biomarkers and changes in carotid intima-media thickness (CIMT). Antiretroviral treatment–naive participants with no known CVD, diabetes, or use of lipid-lowering medications (n = 328) were randomly assigned to receive emtricitabine/tenofovir disoproxil fumarate (slash indicates coformulation) plus ritonavir-boosted atazanavir, raltegravir, or ritonavir-boosted darunavir. At 96 weeks, raltegravir was associated with a persistent decline in IL-6, whereas atazanavir and darunavir were not. A decline in D-dimer was observed with atazanavir or darunavir but not with raltegravir.[32] Measures of T-cell activation declined in each group, but changes in monocyte activation were inconsistent. Progression of CIMT was observed in each group over 144 weeks, although the rate of progression was lower in the atazanavir group than in the darunavir group, and the rate in the raltegravir group was intermediate. A bilirubin level of 0.6 mg/dL or higher at weeks 4 and 24 was associated with a reduced rate of progression of CIMT. Increases in bilirubin (which is an antioxidant) are characteristic of atazanavir.

The findings above raise the question of whether atazanavir may have a protective effect against CVD in the context of HIV infection. Higher bilirubin levels were associated with lower risk of type 1 MI and stroke but with higher risk of type 2 MI (resulting from oxygen supply/demand mismatch, such as during sepsis) in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort.[33] Atazanavir was associated with reduced risk (hazard ratio, 0.66) for MI but not for stroke in a US Veterans Affairs study.[34] Atazanavir is no longer considered a preferred drug because of the higher risk of discontinuation due to increases in bilirubin; however, it might be appropriate for individuals with high CVD risk.

Interventions to Reduce Non-AIDS Events in HIV

Interventions that may reduce non-AIDS events in persons with HIV infection include lifestyle changes, earlier initiation of antiretroviral therapy, and treatments for inflammation and immune activation. Lifestyle interventions include smoking cessation, as smoking may synergize with HIV to increase mortality; screening for and treating hypertension and diabetes; diet and exercise; use of aspirin; and use of statins and other lipid-lowering treatments. It is notable that deaths related to smoking may outnumber those due to HIV-related diseases [35]

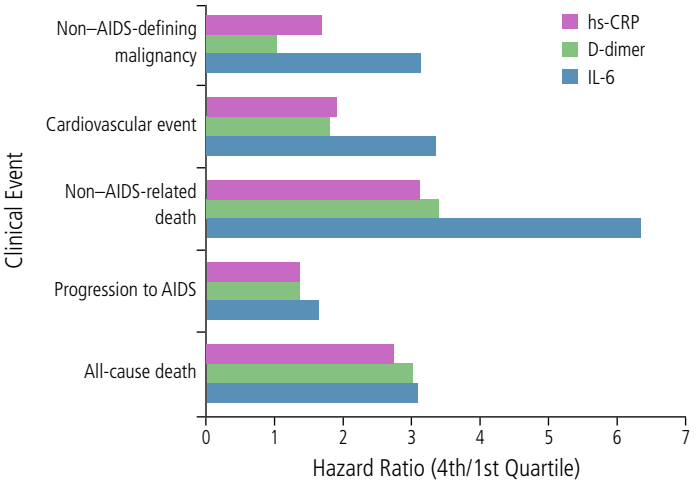

Figure 3. Hazard ratios for clinical events in 1st and 4th quartiles for plasma levels of the biomarkers interleukin (IL)-6, D-dimer, and high-sensitivity C-reactive protein (hs-CRP) in the SMART (Strategies for Management of Antiretroviral Therapy) and ESPRIT (Evaluation of Subcutaneous Aldesleukin in a Randomized International Trial) study populations. Adapted from Borges et al.[14]

Data from the START (Strategic Timing of Anti-Retroviral Treatment) trial, which examined initiating treatment at a CD4+ cell count above 500/µL or waiting until it dropped below 350/µL, showed benefits in reducing non-AIDS endpoints, not including differences in risk of CVD, in neurocognitive performance, or in risk of chronic obstructive pulmonary disease. The population of this trial was relatively young, and the 3-year follow-up period may have been too short to capture differences in some outcomes. However, some of the non-AIDS conditions may be linked to immunologic changes associated with immunodeficiency, including exposure to lower CD4+ cell count nadirs and greater levels of inflammation.[36] Opportunistic infections (OIs) and CVD events increased with lower nadir CD4+ cell count among individuals whose antiretroviral treatment was interrupted in the SMART trial, which compared continuous treatment with interrupting treatment when CD4+ cell count was above 350/µL and restarting it when CD4+ cell count fell below 250/µL (Figure 4).[36] In the START trial, nadir CD4+ cell count was much higher among participants whose antiretroviral treatment was delayed than in those who treatment was interrupted in the SMART trial, and there were fewer OIs and CVD events.[36] However, there still appears to be a benefit associated with the higher nadir CD4+ cell count among those who initiate antiretroviral treatment immediately compared with those whose treatment is delayed. Thus, although CVD is not generally thought to be linked to immune deficiency, nadir CD4+ cell count and history of long-term immune activation may contribute to CVD risk. There is also evidence of impaired vascular function and increased arterial inflammation even in early HIV infection, suggesting that there may be a continuum of CVD risk in this setting.

Other strategies for targeting immune and inflammatory mechanisms include CC chemokine receptor 5 (CCR5)

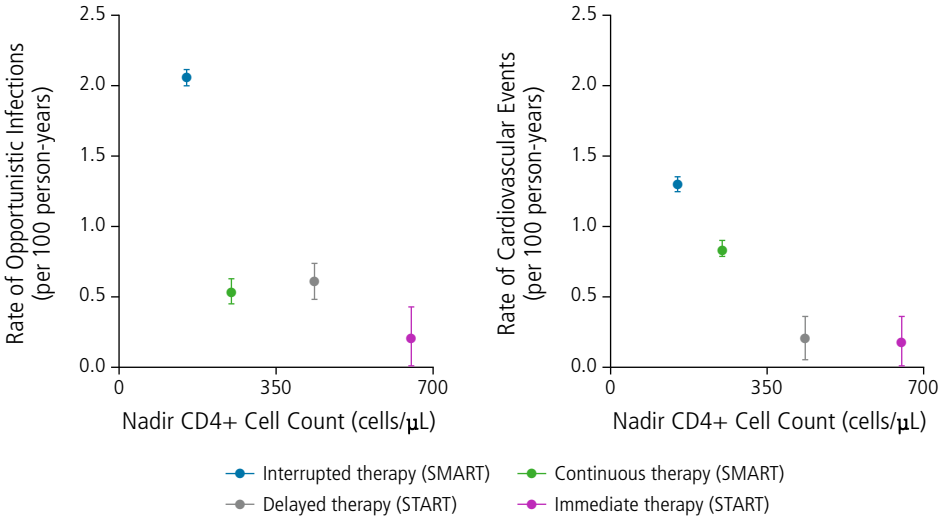

Figure 4. CD4+ cell count nadir and risk for opportunistic infections (left) and cardiovascular events (right) with interrupted versus continuous antiretroviral therapy in the SMART (Strategies for Management of Antiretroviral Therapy) study and delayed versus immediate antiretroviral therapy in the START (Strategic Timing of Anti-Retroviral Treatment) study. Adapted from Hunt et al.[36]

antagonists, IL antagonists, methotrexate (which can lower IL-6), and statins. CCR5 antagonists and the investigational CCR2 antagonist cenicriviroc (which also targets CCR5) are currently being evaluated for potential cardiovascular benefits in clinical trials. IL-1β inhibition with the monoclonal antibody canakinumab, which was recently shown to reduce CVD events in 10,061 patients without HIV infection who had a prior episode of myocardial infarction and an elevated high sensitivity C-reactive protein level.[37] A pilot study in 10 individuals showed a reduction in arterial inflammation after a single infusion of canakinumab, and a reduction in IL-6 but no change in T-cell activation.[38]

Some studies have suggested that current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines[39] for statin use may underestimate risk for cardiovascular events in HIV-infected individuals. In one study, only 25% of participants with coronary plaque with 1 or 2 high-risk morphologic features on CT angiography met the 2013 guideline eligibility criteria for statin therapy.[39] In another study which analyzed the ability of the Framingham Risk Score, ACC/AHA Pooled Cohort Equation, Systematic Coronary Risk Evaluation (SCORE), and the HIV-specific D:A:D (Data Collection on Adverse Effects of Anti-HIV Drugs) study equation to predict CVD events in the HIV Outpatient Study population, Framingham Risk Score performed best but still underestimated the incidence of CVD events.[40] A larger study in the CNICS cohort found that the ACC/AHA Pooled Cohort Equation accurately predicted MI risk among white men but underpredicted events among black men and women.[3] White women had too few events to assess predictive accuracy.

Statin therapy improves traditional and immune-related risk factors in HIV-infected individuals. Lowering of low-density lipoprotein (LDL) cholesterol level with statin therapy is similar in persons with or without HIV infection. Statin therapy has also been shown to dampen immune activation. In one study, rosuvastatin treatment substantially reduced monocyte activation over 48 weeks compared with placebo, as indicated by decreases in circulating levels of sCD14 and the macrophage-derived lipoprotein-associated phospholipase A2 (Lp-PLA2), as well as improved CIMT.[41-43]

Safety of statins continues to be of concern in long-term use, particularly with regard to their effect on glucose control and potential interactions with HIV protease inhibitors. Recent data on pitavastatin indicate no adverse effects on blood glucose levels and no interactions with protease inhibitors, suggesting that this drug might be appropriate for HIV-infected individuals. The effects of pitavastatin on CVD events is currently being evaluated in the large-scale REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial.[44] In REPRIEVE, a target population of 6500 HIV-infected participants who do not meet criteria for statin therapy are randomly assigned to receive pitavastatin or placebo. Substudies are examining the effects of pitavastatin on CT angiography outcomes, differences in outcome by sex, renal outcomes, and effects on muscle function.

Summary

Non-AIDs events are a growing cause of morbidity and mortality among persons with treated HIV infection. Inflammation and immune activation may be contributing to the prevalence of non-AIDS events among HIV-infected persons, and measurement of biomarkers of inflammation and immune activation may have utility in predicting risk and informing interventions. Traditional CVD risk factors remain important and should be the focus of interventions. Optimal methods for predicting CVD risk are undefined at present. Novel interventions to reduce inflammation for persons on antiretroviral therapy remain an important area of investigation.

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