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HIV: A Chronic Condition

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By virtue of the success of anti-retroviral therapy (ART), human immunodeficiency virus (HIV) infection has evolved into a chronic disease in which the typical complications of acquired immune deficiency syndrome (AIDS) are no longer the dominant problem. Rather than dealing with acute and potentially life-threatening complications, clinicians are now confronted with managing a chronic disease that, in the absence of a cure, will persist for many decades.[1] This review will focus on the longer term sequelae and consequences of chronic HIV infection.

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The significant improvement in long-term survival of individuals with successfully treated and managed HIV infection has been described in detail in a prior article in this issue of *Journal of Insurance Medicine*. This article will focus upon HIV as a chronic condition and discuss the potential long-term consequences, ie, the impact on future mortality and morbidity, associated with HIV and aging. To emphasize the importance of this topic, the Administration on Aging (AoA) estimates that as of this year more than half of those living with HIV in the United States will be age 50 or older.[2]

Premature or Accelerated Aging

Normal aging is associated with chronic low-grade inflammation, which plays an important role in the initiation and/or progression of many age-related pathophysiologic processes and diseases. This inflammation, through various mechanisms, also contributes to immunosenescence, commonly defined as the functional decline of the adaptive immune system with age.[3] Immune activation and chronic inflammation are increased in HIV-infected individuals because of residual HIV infection, other viruses, such as cytomegalovirus reactivation, and increased bacterial product translocation in the gut due to altered mucosal integrity. Translocation is highly likely to result in a profound activation of the innate immune response.[4] Even with sustained suppression of HIV replication, many HIV-infected persons experience a syndrome characterized by increased T cell activation and evidence of heightened inflammation and coagulation, termed residual immune dysregulation syndrome or RIDS.[5] Thus, if immune activation and chronic inflammation are major factors in the aging process and these processes are more prevalent in HIV-infected individuals, even when the infection is well controlled, then these individuals will be more prone to develop, in advance, age-related diseases.[6]

Much published literature in recent years has focused on the concept of premature or accelerated aging as a consequence of chronic HIV infection, primarily mediated through immune activation and chronic inflammation.[6-8] While these terms are not always clearly defined,

three criteria should be required as part of their definitions: 1) HIV should affect conditions already known to be associated with aging in the general population, 2) HIV should increase the incidence of more than one age-related condition, and 3) the rate of these conditions should be greater than among uninfected patients of similar age. The numerical appearance of premature aging could be due to HIV acting as an accelerant of true biological aging or as an independent causal factor for one or more comorbid conditions.[9] It is also important to account for differential exposure to risk factors between HIV-infected and HIV-uninfected populations that are likely to result in residual confounding when assessing associations of HIV with increased risk of age-related illness.[8] Overall, in treated individuals who achieve durable suppression of HIV, natural aging, drug-specific toxicity, lifestyle factors, persistent inflammation, and possible residual immunodeficiency are causally associated with the premature development of many complications normally associated with aging. These include cardiovascular disease and cancer.[10] Other "non-AIDS" complications include neurocognitive decline, liver disease, kidney disease, bone disease, and a frailty phenotype.

The following sections will primarily address three of these complications related to chronic HIV infection: cardiovascular (and metabolic) risk and outcomes, cancer, and neurocognitive impairment.

CARDIOVASCULAR (CV) AND METABOLIC RISK AND OUTCOMES

As early as the late 1990s, changes in body fat distribution, termed lipodystrophy, began to appear in HIV-treated patients. It is likely that these changes are the net result of competing phenomena: the natural history of lipohypertrophy as a result of the direct impact of HIV and ART and physiological body fat changes observed in the aging population.[11] Friis-Moller and the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group demonstrated in 2003 that ART was independently associated with a 26% relative increase in the rate of myocardial infarction per year of exposure during the first 4 to 6 years of use.[12] The group subsequently published a paper in 2007 concluding that exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which was partly explained by dyslipidemia. There was no evidence of such an association for nonnucleoside reverse-transcriptase inhibitors (NNRTIs).[13] A more recent publication notes that NNRTIs are associated with lipid changes; however, newer agents exhibit more favorable impact on lipid profiles.[14]

Increased cardiovascular risk in HIV-infected individuals may be due to inflammatory lipid modulation not captured by traditional lipid profiles. Munger et al used advanced lipoprotein phenotyping inclusive of the HDL cholesterol efflux capacity (the measure by which HDL removes cholesterol from the vessel wall) and lipoprotein particle concentration and size to study a group of treated HIV-positive individuals who were on stable antiretroviral therapy and had relatively benign traditional lipid values: mean total cholesterol 178 mg/dL, LDL-C 108 mg/dL, HDL-C 44 mg/dL, and triglycerides of 122.5 mg/dL. Their findings demonstrated an atherogenic lipoprotein profile (elevated LDL particle counts, decreased LDL size, decreased protective large HDL levels, and reduced HDL cholesterol efflux capacity) in the study group with normal traditional lipid panels. While CV outcomes were not measured, the authors suggested further research is needed to determine the exact relationship of lipid sub-particle measurements and CV outcomes in HIV-infected individuals.[15]

Guaraldi et al studied 400 HIV-infected patients by performing cardiac computed tomography imaging to identify coronary artery calcium (CAC). Vascular age was estimated on the basis of the extent of CAC. Increased vascular age was observed in 162 patients (40.5%), with an average increase of 15 years (range, 1-43 years) over the chronological age. Univariate analysis indicated

that multiple traditional risk factors for vascular disease were associated with increased vascular age. In multivariate analysis, an elevated, current CD4+ cell count was the only predictor of increased vascular age. The authors noted that this was a counterintuitive finding and in contrast to other studies which demonstrated that low CD4+ cell counts were associated with CV risk and incident CV disease. However, it was hypothesized that the discrepancy might be explained by a U-shaped curve effect with both ends of the spectrum leading to increased CV risk and outcomes based on different pathophysiologic mechanisms.[16]

Another more recent study published in 2014 by Post et al also assessed CAC in men who have sex with men who were HIV-infected and compared them with non-HIV-infected controls. Both groups were aged 40-70 years, weighed less than 200 pounds, and had no history of coronary revascularization. After adjustment for age, race, CT scanning center, and cohort, the prevalence ratio (PR) of CAC in HIV-infected men was 1.2 (95% CI, 1.08-1.35). However, after adjustment for CAD risk factors, the association became borderline with PR of 1.12 (95% CI, 0.99-1.26). Another significant finding was that more HIV-infected than non-infected men had a higher PR of non-calcified plaque, 1.25 (CI, 1.10-1.43), which persisted after adjustment for age, race, CT scanning center, cohort, and additional CAD risk factors. The authors also found that the prevalence of non-calcified plaque increased with advancing age in HIV-infected men (PR per 5-year increase in age, 1.17 [CI, 1.11-1.23]) but not for uninfected men (PR per 5-year increase in age, 1.03 [CI, 0.966-1.11]). They noted non-calcified plaque may be more prone to rupture, leading to acute coronary syndromes.[17]

Hsue et al assessed another CV risk factor, namely that of carotid intimal medial thickness (IMT), in groups of treated HIV-infected patients, HIV-infected patients who were untreated but had undetectable viral loads and preserved CD4+ cell counts (HIV controllers), and HIV-negative controls. HIV-positive participants had much higher median IMT results than HIV-negative participants (0.91 mm vs 0.72mm, $p<0.001$) even after adjusting for traditional CV risk factors. HIV controllers also had a higher median IMT than HIV-negative subjects even when restricting the analysis to those with CD4+ counts >500 cells/mm^3. The authors note that the carotid IMT was higher among all groups of HIV subjects, irrespective of antiretroviral treatment or the level of viremia. The unexpected finding of a high IMT in HIV controllers suggests that other factors contribute to the pathogenesis of HIV-associated atherosclerosis. They argued for a possible role of persistent HIV-associated inflammation as a potential cause for the accelerated observed atherosclerosis in HIV disease.[18]

A large recent study of the US veteran population assessed the association of acute myocardial infarction (AMI) and HIV infection. Freiburg et al studied a cohort of over 80,000 participants (33% HIV positive, >97% male) and excluded those with baseline cardiovascular disease. After adjustment for traditional Framingham risk factors and substance abuse, they determined that AMI events were consistently and significantly higher for HIV-infected individuals across three age categories (40-49, 50-59, and 60-69 years) by an overall hazard ratio of 1.48 (95% CI, 1.27-1.72). Moreover, even those achieving HIV-1 RNA levels less than 500 copies/mL demonstrated a hazard ratio of 1.39 (95% CI, 1.17-1.66). It was suggested that the Framingham risk score may underestimate AMI risk among HIV-infected people. An editorial pointed out that this study, compared to previous studies, was able to control for a variety of potential confounders and provided a better estimate of the effect of HIV infection itself on AMI rates.[19]

While the previous study primarily included men, another study, published in 2014, specifically analyzed the risk of cardiovascular events in HIV-infected women. The cohort consisted of 2187 women in the Veterans Aging Cohort

Study of whom 32% were infected with HIV and all were free of cardiovascular disease (CVD) at baseline. Primary outcomes observed included acute myocardial infarction, unstable angina, ischemic stroke, and heart failure. After adjusting for multiple traditional CV risk factors plus diabetes, renal disease, and substance abuse, HIV-infected women experienced an increased risk of total CVD events by a hazard ratio of 2.8 (95% CI, 1.7-4.6). The authors noted that few studies have focused on women and even fewer included CVD events and that their results were consistent with earlier studies that linked HIV infection to an increased risk of CHD, ischemic stroke, and subclinical atherosclerosis in women. It remained to be established as to whether or not HIV-infected women are at greater risk for CVD than HIV-infected men.[20]

CANCER

In the pre-ART era, it was clear that HIV-infected individuals were at increased risk for AIDS-defining cancers, namely non-Hodgkin lymphoma (NHL), Kaposi sarcoma (KS), and invasive cervical cancer. With the advent of ART, data indicate that the incidence of NHL and KS dramatically decreased, although not to levels present in the general population. Invasive cervical cancer rates remained stable throughout the period. The incidence of many non-AIDS defining cancers were also elevated relative to the general population in the pre-ART era, but were overshadowed by the overwhelming presence of the AIDS-defining cancers. Data in the ART era indicate that non-AIDS defining cancer rates have increased significantly for anal, colorectal, liver, lung, oropharyngeal, renal, and vaginal cancer, Hodgkin lymphoma, and melanoma. Prostate cancer rates also increased but remain paradoxically lower than general population throughout the pre- and ART eras.[21] The types of cancers in HIV-infected individuals are similar to those who have undergone organ transplantation, thus immune dysfunction may be the underlying mechanism for the excess risk. Many of these cancers are associated with an infectious cause and it has been suggested that infection-related cancer will probably become an increasingly important complication of long-term HIV infection.[22]

Cancer incidence from the Swiss HIV Cohort Study was reported relative to three time periods: pre-ART era (1985-1996), early ART era (1997-2001), and late ART era (2002-2006). NHL and KS declined over all three periods. While there was individual variation among the types of non-AIDS defining cancers, the overall rate of non-AIDS defining cancers was similar in all periods and approximately double that in the general population. The authors noted that their results did not support claims that ART per se had an adverse influence on cancer risk.[23]

Screening for non-AIDS defining cancers in the HIV-infected population should take into account the risk of a particular type of cancer, life expectancy, and benefits and harms that may result from screening. Sigel et al suggest that screening for anal, liver, and lung cancer may require adaptation for those with HIV infection because of increased risk, as well as behaviors and conditions common among those with HIV. The group also noted that screening recommendations for cervical, breast, and colon cancer should be similar for the general population and those infected with HIV.[24]

NEUROCOGNITIVE IMPAIRMENT

Neurological manifestation of HIV infection is commonly represented by cognitive impairment. Severe and progressive impairment is now rare in the ART era, yet a majority of HIV patients perform below expectations on formal neurocognitive tests.[25] One explanation for the on-going presence of abnormalities, despite treatment, is that low level viremia in the CNS may continue, driving neurodegeneration either by toxic inflammatory activation and/or toxic viral products.[26] Variability in the penetration of antiretroviral drugs across the blood brain barrier exists. However, there is no current evidence that there are significant differences between high and low CNS

penetrating antitretrovirals and neuropsychometric performance.[25]

The neurocognitive disturbances in brain function are referred to as HIV-associated neurocognitive disorder (HAND). This disorder is further divided into three levels of severity: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).[27]

Heaton et al conducted a comprehensive study on 1555 HIV-infected individuals by performing detailed neuromedical, psychiatric, and neuropsychological examination during the ART era. They concluded that while ART has had a major impact on the course and long-term prognosis of HIV, all but the most severe CNS manifestations of infection remain very common. Their results showed that 2% of participants met criteria for HAD, down significantly compared with the pre-ART era. However, 44% met criteria for milder forms of cognitive impairment, which is similar to the pre-ART era. The lowest risk of measurable impairment occurred in the subgroup with suppressed plasma viral loads and nadir CD4 $\geqslant$200 cell/mm^3 (30% vs 47%). They suggest further studies should clarify whether early disease events (eg, profound CD4 decline) trigger chronic CNS changes and what impact early treatment with ART may have to prevent or reverse changes.[28] Another study, published in 2011, reached similar conclusions. The authors questioned if some of the newer antiretrovirals may have toxic effects on the CNS, although they noted this could not be ruled out based on the results of their study.[29]

Not all studies have reached the same conclusion regarding cognitive impairment. McDonnell reported results in 2014 on a smaller study of 248 HIV-positive men who have sex with men (MSM) compared with 45 HIV-negative MSM. The groups were assessed with neuropsychological tests and questionnaires of depression, anxiety, and activities of daily living. Prevalence of HAND was 21.0% in the HIV-positive group (13.7% ANI, 6.5% MCD, 0.8% HAD). The results were not significantly different than the HIV-negative group. The authors suggested that neurocognitive impairment may be overestimated in the HIV-positive MSM group.[30]

CONCLUSION

The improvements in mortality during the ART era are well described and a tribute to the success of medical therapy. It is becoming more apparent now, however, that individuals, even under optimal treatment for HIV, are at significant risk for long-term health consequences that may threaten the sustainability and permanence of mortality improvements. Undoubtedly, clinicians will become more aware of these risks and begin to address and seek interventions to reduce this risk. The impact of these conditions will need to be assessed carefully as on-going consideration is given and analysis is performed to determine eligibility for life and living benefits coverage for these individuals.

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