Perspective

Aging and HIV Infection: Focus on Cardiovascular Disease Risk

Effective antiretroviral therapy has extended life expectancy for individuals with HIV. Estimates from 2015 indicate that 47% of persons with HIV in the US were older than 50 years of age and 16% were older than 65 years. These older patients are at increased risk of age-related diseases and conditions. Further, there is substantial evidence that patients with HIV infection accumulate age-related conditions earlier than do those in the general population. There is risk for increased comorbidities and polypharmacy in the aging HIV-infected population. Specific measures for assessing and reducing the risk of cardiovascular disease and other age-related conditions in the aging HIV population are needed. This article summarizes a presentation by Judith A. Aberg, MD, at the International Antiviral Society-USA (IAS-USA) annual continuing education program held in Chicago, Illinois, in May 2019.

Keywords: HIV, aging, comorbidities, cardiovascular disease, diabetes, dyslipidemia, antiretroviral therapy

HIV infection, even when controlled with effective therapy, is associated with chronic immune activation that is superimposed on immunologic senescence in the older adult. Older persons with newly diagnosed HIV infection tend to have more advanced HIV disease at presentation, and there is a less robust immunologic response to antiretroviral therapy (ART) in this population. People with HIV (PWH) accumulate age-related diseases at a younger chronologic age and these conditions account for the majority of deaths in this population. Practitioners need guidance on how best to manage PWH who may develop or already have these comorbidities given the younger age at time of presentation, quicker progression, specific recommendations for PWH, and potential drug interactions.

Since the 1980s, the proportion of PWH older than 50 years has gradually increased. According to data from the Centers for Disease Control and Prevention, in 2015, approximately 47% of PWH in the US were older than 50 years and 16% were older than 65 years. In 2016, 17% of newly diagnosed cases of HIV were in adults aged 50 years or older, with 35% of these persons diagnosed with AIDS (down from 40% in 2015). African Americans accounted for 42% of cases, whites for 37% of cases, and Hispanics/Latinos for 18%. Men having sex with men is the most common mode of transmission in older men, and heterosexual contact is the most common mode in older women.

PWH on suppressive ART have an increased life expectancy compared with those not on ART, although life expectancy is still shorter than that in the general population, particularly among patients with low CD4+ cell counts and those who are on salvage ART regimens, most likely representing a more prolonged period of time with unsuppressed HIV. Issues in aging that need to be addressed include the impact of this increased life expectancy on prevalence and types of comorbidities. Considerations include the fact that older patients are more likely to be treatment experienced and to have had consequences of toxic effects of previous ART regimens (eg, metabolic derangements). A major issue for practitioners, given the likelihood of increased comorbidities with aging is the appropriateness of applying primary care practice guidelines for the general population to the population with HIV. To date, there is no systematic way to predict whether or what guidelines developed for the general population should apply to individuals with HIV, although the consensus appears to be that guidelines for PWH need to be more detailed and comprehensive. The 2013[1] Infectious Diseases Society of America HIV primary care guidelines are expected to be updated in 2020. The 2018 European AIDS Clinical Society guidelines are comprehensive and easy to use.[1] A revised version was released in November 2019 with expanded drug interaction tables including medications used to treat common comorbidities as well as specific recommendations for elderly PWH.[2]

The prevalence of cigarette smoking among PWH is much higher than in the general population irrespective of age, sex, race, ethnicity, education level, or income

Age-Associated Comorbidities

Health conditions prominent in aging patients include: cardiovascular disease (CVD); endocrine disorders; kidney disease; gastrointestinal and genitourinary malignancies; liver diseases; lung diseases, nervous system disorders; and psychosocial issues including depression and substance use.

It bears continual repeating that the prevalence of cigarette smoking among PWH is much higher than in the general population irrespective of age, sex, race, ethnicity, education level, or income. For example, smoking prevalence is 49% among PWH and 30% in the general population among individuals with less than a high school education and 32% and 15% among those with more than a high school education, respectively.[3] Much progress

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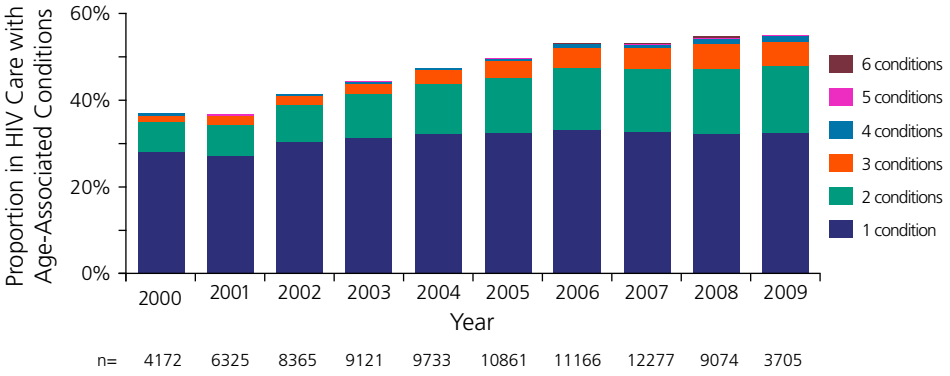

Figure 1. Increase in proportion of people with HIV-infection with age-associated comorbidities from 2000 to 2009 as reported by the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design). Adapted from Wong et al.[4]

could be made in reducing and preventing comorbidities in PWH with interventions and programs focusing on smoking cessation.

Figure 1 shows the increase in proportion of patients with age-associated comorbidities during the early 2000s as reported by the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design); an update is expected in the near future.[4] As can be seen, this includes an increase in the numbers of patients with numerous comorbidities. These data showed that, as in the general population, hyperlipidemia and hypertension are the most common conditions. Data from an Italian cohort indicate that additional chronic comorbidities accrue in PWH a decade earlier than in the general population, such that PWH in the 41- to 50-year age range have similar comorbidity profiles as individuals in the general population aged 51 to 60 years (Figure 2).[5]

As a risk enhancer, the presence of HIV infection can lower the risk-based threshold for initiating statin therapy

Data from the New York City HIV Surveillance Registry for 2001 to 2012 showed that the proportion of CVD deaths among all deaths increased in the HIV population from 6% to 15%, and decreased in the general population.[6] The risk of CVD death was significantly higher among those with HIV than those in the general population for every 10-year age group from 25 years to 64 years, whereas no significant difference was observed in the 65 to 74 year age group. It was also found that risk of CVD death was significantly lower among PWH who had viral suppression than among those without full suppression.

In the Italian cohort mentioned above, analysis of patients aged 65 years or older showed increasing prevalence of a number of health conditions by duration of HIV infection. However, there was no significant difference in overall prevalence in the PWH population compared with the general population for CVD or hypertension, whereas significantly higher rates were found among the HIV population for dyslipidemia, chronic kidney disease, and type 2 diabetes.[7] Data from this cohort also showed that number of comorbidities and number of medications in addition to ART increased with increasing duration of HIV infection emphasizing the issue of polypharmacy in this older population. The association of CVD with duration of HIV infection may reflect a longer period of time of viremia especially during the era when ART was not recommended until the CD4+ count was below 200 cells/μL or below 350 cells/μL and more toxic ART with metabolic adverse effects were prescribed.

Assessment and Management of CVD Risk in HIV Infection

Despite evidence of the earlier onset of CVD in the PWH population, it still has proven difficult to determine to what degree HIV infection increases risk of CVD or to determine to what degree risk assessment instruments for the general population apply to the PWH.[8-10] As noted above, smoking remains one of the largest contributors to development of CVD and the incremental increase in risk associated with HIV infection other traditional risk factors has been difficult to calculate. A step toward quantifying additional risk posed by HIV infection has been taken in the 2018 American Heart Association multispecialty guideline on management of blood cholesterol for primary prevention of atherosclerotic CVD.

The new guideline includes measurement of CVD risk in younger age groups than previous guidelines (including 0-19- and 20-39-year age groups) and includes HIV infection as a risk enhancer. As a risk enhancer, the presence

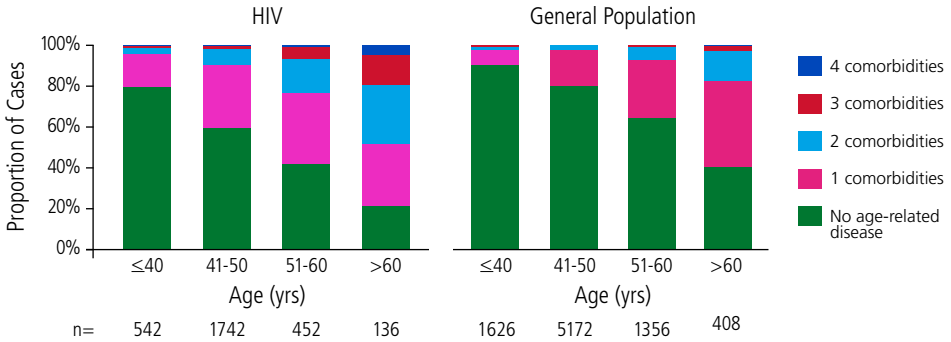

Figure 2. Data from an Italian cohort from 2002 to 2009 showing accrual of additional chronic comorbidities in patients with HIV infection a decade earlier than in the general population. Adapted from Guaraldi et al.[5]

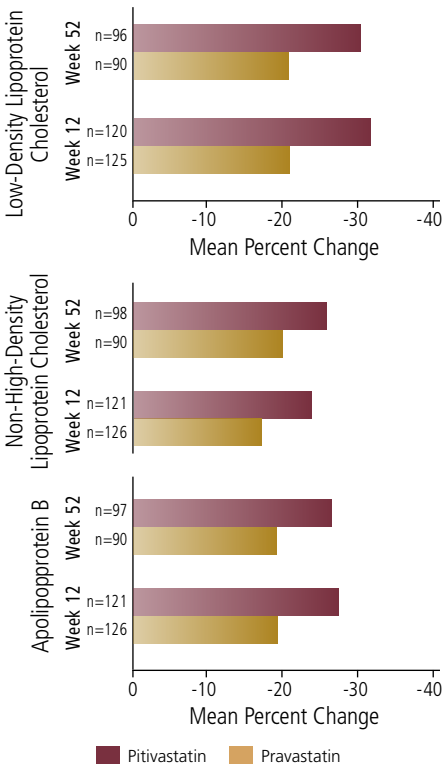

Figure 3. Results of the INTREPID (Pitavastatin versus Pravastatin in Adults with HIV-1 Infection and Dyslipidaemia) trial showing the superiority of pitavastatin in reducing low-density lipoprotein cholesterol (LDL-C, top) and non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (bottom) at 12 and 52 weeks. The reductions in atherogenic lipids are equal to what is observed in persons without HIV infection. Adapted from Aberg et al.[11]

of HIV infection can lower the risk-based threshold for initiating statin therapy. Thus, for example, in adults aged 40 to 75 years without diabetes and an intermediate 10-year risk of a CVD event (7.5%-19.9%), the presence of HIV infection (or other risk enhancers) favors the initiation of statin therapy. Further, the guidelines encourage discussion of starting statin therapy in patients at borderline risk (10-year risk of 5.0%-7.5%) if HIV infection or another risk enhancer is present. In individuals at intermediate risk who are uncertain about starting statin therapy, coronary artery calcium imaging may be recommended, with a score of 1 to 99 favoring statin therapy and higher scores warranting statin therapy. At this time, imaging for non-calcified plaque remains investigational.

Among statins, rosuvastatin, atorvastatin, and pitavastatin are the best choices for persons with HIV. Simvastatin and lovastatin should not be used in patients receiving an HIV protease inhibitor or cobicistat due to drug-drug interactions, and pravastatin has a drug interaction with boosted darunavir. From a drug interaction perspective, pitavastatin may be the safest although it is more expensive than rosuvastatin or atorvastatin and may not be available on payor formularies. Lipid levels

Pitavastatin was superior in reducing LDL-C, non-HDL-C, and apolipoprotein B at 12 and 52 weeks; these reductions in atherogenic lipids were essentially the same as what is observed in the general population

should be measured at the time of HIV diagnosis, at the start of ART, with any change in ART, to assess response to statin therapy, and every 12 months during statin treatment.

It has been proposed that statins may not work as well in persons with vs without HIV, but this does not appear to be the case. Figure 3 shows results of the INTREPID (Pitavastatin versus Pravastatin in Adults with HIV-1 Infection and Dyslipidemia) trial comparing pitavastatin with pravastatin in PWH with dyslipidemia.[11] Results showed that pitavastatin was superior in reducing low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B at 12 and 52 weeks; these reductions in atherogenic lipids were essentially the same as what is observed in the general population studies.

The ongoing REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) is examining the effect of pitavastatin in PWH with 10-year CVD risk of 15% or lower in the prevention of major adverse cardiovascular events. A mechanistic study within the trial is examining the effect of statin therapy on coronary plaque, vascular inflammation, and immune activation.

HIV infection has been recognized as a prothrombotic condition in which a hypercoagulable state places patients at increased risk for deep vein thrombosis or other clotting that increases risk for ischemic CVD events. Activated platelets have been implicated in thrombotic CVD events because of their proinflammatory and thrombogenic effects. PWH have increased circulating platelet-monocyte complexes and their platelets express high levels of P-selectin. Aspirin is a low-risk and low-cost platelet inhibitor that has immunomodulatory properties. It has been shown to decrease risk of mortality and CVD events in individuals with known CVD however aspirin's role in CVD and cancer primary prevention in those at risk remains controversial.

Although it may appear that aspirin should be broadly used in PWH, with regard to primary preventive daily aspirin therapy, the PWH who may be most likely to benefit are those aged 40 years or older who have diabetes. The reason for this is that although aspirin has proven benefit in secondary prevention of CVD events, recent data indicate that use of aspirin in primary prevention in individuals at moderate risk of CVD was not associated with pre ventive benefit and resulted in an increased risk of gastrointestinal bleeds. In the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial, more than 12,000 patients were randomly assigned to receive 100 mg aspirin daily or placebo over 5 years.[12] No significant differences between groups in rates of death, heart attack, or stroke were observed, whereas the aspirin group had a significantly higher rate of gastrointestinal bleeds. However, the primary prevention ASCEND trial in more than 15,000 patients with diabetes randomly assigned to aspirin or placebo for 7.4 years showed a significant reduction in serious vascular events in the aspirin group compared with the placebo group (8.5% vs 9.6% respectively; rate ratio, 0.88; $P = .01$)[13]; risk of major bleeding events was also significantly higher in the aspirin group

than in the placebo group (4.1% vs 3.2% respectively; rate ratio, 1.29; *P*= .003). Thus, risks and benefits of aspirin therapy must be weighed even among patients with diabetes in the primary prevention setting.

The new American Diabetes Association definition of diabetes is: HbA1c

PWH who may be most likely to benefit from preventative daily aspirin therapy are those aged 40 years or older who have diabetes, but risks and benefits must be weighed

of 6.5% or higher; fasting plasma level of 126 mg/dL or higher confirmed by repeat testing; plasma glucose level 2 hours after 75 g oral glucose tolerance test of 200 mg/dL or higher; or random plasma glucose level of 200 mg/dL or higher with polyuria and polydipsia. Numerous studies have now shown that HbA1c is not an accurate measure of blood glucose in PWH. Depending on ART being taken, it may underestimate or overestimate blood glucose level. Thus, the new guidelines stipulate that in conditions associated with an altered relationship between HbA1c and glycemia, such as HIV infection and sickle cell disease, only plasma blood glucose criteria should be used to make a diagnosis of diabetes.

Summary

There is excess CVD risk in the population with HIV. Risk in persons aging with HIV may be different than that in individuals newly diagnosed with HIV infection. The greatest modifiable risk factor for comorbid conditions is smoking. The etiology of CVD associated with HIV infection is multifactorial, including chronic inflammation, direct viral effects, effects of ART drugs and other medications, and other factors. There remains a need for improved risk assessments for CVD in the PWH population. Fasting blood glucose (or other plasma blood glucose criteria) rather than HbA1c should be used to diagnose diabetes in PWH on ART. The 2018 American Heart Association (AHA) multispecialty guidelines provide more guidance on manangement of blood cholesterol level among PWH than in prior publications. Following the recommendations of the American Diabetic Association (ADA) and AHA provides additional guidance for the primary prevention of CVD in PWH. For example, those aged 40 years or older with diabetes and LDL-C greater than 70 mg/dL should be on a statin and aspirin if no contraindications are present. Measures to improve incorporating primary care prevention during routine HIV monitoring visits are needed.

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