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Aging with Complex Chronic Disease: The Wrinkled Face of AIDS

By Amy C. Justice, MD, PhD

Introduction

People living with HIV taking combination Antiretroviral Therapy (treatment) are living long enough to experience a diverse array of aging related conditions such as osteoporosis, cardiovascular disease, chronic obstructive pulmonary disease (COPD), renal disease, liver cirrhosis, and cancer. Nevertheless, the spectrum of disease experienced by people aging with HIV is not identical to that experienced by aging HIV-negative individuals. Instead, diseases among those living with HIV are jointly determined by HIV disease progression, treatment toxicity, and the behaviors, conditions, and demographics associated with HIV infection. Further, these conditions are occurring at younger ages among HIV-positive individuals than among people of similar racial and ethnic backgrounds who are HIV-negative.

Living with HIV is likely to directly contribute to the risk of many of these conditions through a cascade of mechanisms including, but not limited to, microbial translocation (so-called "leaky gut"), chronic immune activation ("inflammation"), and increased thrombosis and hypercoagulability (increased blood clot formation).[1, 2] Treatment toxicity, both from HIV and non-HIV treatments, likely also increases the risk of some conditions. However, HIV and its treatment is typically not as strong a risk factor as those risk factors previously established among those without HIV infection.

Thus, among those in treatment, HIV has become a complex chronic disease in which there is no single cause of injury and resulting morbidity, or functional decline of the immune system, bone marrow, brain, lungs, liver, and kidneys, as well as mortality. Instead, they reflect cumulative loss of body functions from multiple interacting causes leading to organ system failure, decline in quality of life, decline in physical ability, repeated hospitalizations, and, eventually, death. The good news is that this process can likely be delayed through improved health behaviors and comprehensive, integrated, medical care.

As a result, HIV-positive persons, their health care providers, and policy makers need to ask, "how can we maximize the quality and quantity of life for people living with HIV receiving antiretroviral treatment?" Of course, early antiretroviral treatment with excellent adherence remains a central part of any effective approach. Nevertheless, viral load and CD4 cell counts do not tell us all we need to know about the overall health of a person living with HIV. Now that people on treatment with HIV are having sustained viral suppression, improved CD4 cell counts, and are living longer, we need an expanded approach to clinical care and research. This approach must embrace the complex and overlapping etiologies of morbidity and mortality among those in treatment and address the total health care needs of the individual.

Epidemiology

Two phenomena are driving the aging of the HIV epidemic; people are living longer on treatment, and middle aged and older individuals are becoming infected with HIV. In high-income countries, a 35 year old HIV infected individual initiating treatment at a CD4 count below 100 cells is expected to live to be 62 years old; if that same individual starts treatment at a CD4 count above 200, he is expected to live an additional 10 years, to 72.[3] Based upon more recent analyses, we have reason to believe that life expectancy would be even longer were this individual to start treatment at a CD4 count above 350 or 500 cells.[4, 5] These estimates underscore the importance of early treatment and the profound effect timely treatment has on aging with HIV. As a result, the number of adults over 50 living with HIV in the United States has grown 14% per year between 2004-2007. A third of adults living with HIV were 50 or older in 2009.[6, 7]

With increasing HIV prevalence among older individuals, we are also seeing a rise in incidence. Twenty-one percent

of new domestic AIDS cases in 2007 were among those 50 years and over.[8] While some concern has been raised that erectile dysfunction medications might be fueling increasing incidence among men who have sex with men (MSM),[9] a newer study among a larger mixed sample of MSM and heterosexual men found that regardless of HIV status, individuals who use erectile dysfunction medications do not report higher rates of risky sexual behavior.[10]

Instead, we are likely seeing an increased probability of transmission at each exposure due to increased prevalence of HIV among older individuals. The issue is not higher rates of risky behavior, but higher risk of transmission given exposure, similar to the situation among some urban African-American populations.[11]

A 35 year-old who starts treatment with a CD4 count of 200 has a life expectancy of 72.

As the numbers of individuals over 50 living with HIV are rising, our capacity to provide care is declining—both among those trained in HIV and among those trained in geriatrics. Few individuals are trained in both disciplines. Similarly, despite the rising numbers of individuals aging with HIV who will require assisted living, nursing home, and hospice placement, staff at these facilities have no formal training and little experience in providing care. Due to these constraints in capacity and training, HIV care may be "mainstreamed" into primary care. However, the spectrum of disease and its appropriate treatment are not the same among HIV-positive and negative individuals. Unless the staff of these facilities receive formal training and guidance on special issues regarding HIV, the potential for major mistakes is substantial.

The Changing Spectrum of Disease

The spectrum of clinical disease seen among HIV-positive individuals utilizing medications has changed dramatically since the advent of combination treatment. AIDS defining conditions are increasingly rare,[12] and the association of particular AIDS defining conditions with CD4 cell count is variable.[13]

Age and CD4 count at treatment initiation are major determinants of life expectancy,[14] but these relationships are complex. Due to better adherence, older adults have a better initial viral response to treatment than younger individuals. However, their CD4 response at one year is not as strong; they require two years of therapy to catch up with younger individuals.[15] Older adults living with HIV have more comorbid disease than their younger counterparts.[16] Whether this added burden of non-AIDS disease is the price of success or a manifestation of living with HIV long term has become an interesting research question.

Several observational studies have used cause of death analyses to study non-AIDS events[17-19] and generally found that approximately 50-60% of deaths are from "non-AIDS" causes. These studies did not use a standard criteria for AIDS and "non-AIDS" deaths, had substantial amounts of missing data, and often relied on death certificates. Cause of death analyses cannot detect important morbidity among the living and accurate attribution is difficult without an autopsy which is rarely performed;[20] thus, these findings are difficult to interpret.

Cohorts have compared rates of comorbid disease among HIV-positive and negative individuals to determine whether non-AIDS conditions may be associated with HIV status. Many of the earliest comparisons were made to population-based samples like the Framingham Risk Score or the Surveillance Epidemiology and End Results (SEER) cancer registry. Because HIV-positive individuals differ with respect to important risk factors (e.g., alcohol, cigarette and drug use; prevalence of obesity; prevalence of wasting; socio-economic status; and the prevalence of hepatitis C virus (HCV) coinfection) population-based comparators are likely not appropriate. In addition, several studies reported prevalence of non-AIDS conditions at a particular cross section.[21–23] These studies demonstrated higher prevalence of depression, substance use, liver and renal disease, and multi-morbidity and lower prevalence of vascular disease, diabetes, and hypertension than among uninfected, demographically similar individuals in care. However, the risk of prevalent disease at the start of treatment is not the same as that of incident disease after long term exposure to treatment.

A growing body of work has analyzed incident disease and controlled for established risk factors. These studies have demonstrated that in addition to the expected associations with established risk factors, there is an increased risk for non-AIDS conditions among HIV-positive compared to HIV-negative subjects. Studies have demonstrated increased risk of particular non-AIDS cancers,[24, 25] pulmonary disease,[26, 27] intracranial hemorrhage,[28] and osteoporosis.[29, 30] Four studies have compared incident rates of cardiovascular disease among HIV-positive individuals to demographically matched controls.[31-34] These studies suggest a higher incidence among those living with HIV, but could not adequately control for substance use (i.e., smoking, alcohol, and cocaine). Further, it is not clear how completely these studies captured acute myocardial events occurring outside their particular healthcare facilities.

Taken as a whole, these studies have demonstrated that established risk factors and some new risk factors (HIV, HIV treatment, and in some cases, HCV coinfection)[35, 36] combine to determine the patient's overall risk of morbidity and mortality. Of note, while viral infection plays a role, behavioral risk factors, such as smoking in cardiovascular disease[37] and alcohol in liver disease,[38, 39] are often as or more important than HIV status or antiretroviral treatment toxicity. This may be especially true with newer regimens that are thought to have fewer toxicities.

While observational studies have provided important insights into the changing spectrum of HIV, no single study has done more to change our thinking about the pathophysiology of HIV and aging than the Strategies for Management of Anti-Retroviral Therapies (SMART) trial.[40] This landmark study compared continuous treatment to a structured treatment interruption intended to minimize treatment toxicity and provided several critical insights. First, combining the arms of the trial, there were more non-AIDS events than AIDS events and 81 of 96 AIDS events were considered "nonserious" opportunistic infections. Second, there were 1.7 times as many major coronary artery disease, renal, and liver disease events among those in the structured treatment interruption arm as among those receiving continuous therapy (65 vs. 39 events). Of note, CD4 count and viral load did not capture these differences.

The combined implication of this work is that, among those on treatment, HIV is part of a group of conditions which together drive morbidity and mortality. Individuals on antiretroviral treatment experience HIV as a complex chronic disease. For these individuals, all contributing causes of morbidity and mortality are important and worthy of intervention. Further, the overall process of disease among those living with HIV and utilizing treatment cannot be understood through the study of isolated parts. We need to develop approaches to understanding and intervening on the overall process.

What Can We Do to Prevent "Premature" Aging

There is likely much that can be done to slow the process of functional decline, loss of quality of life, and early mortality that is currently ongoing among HIV-positive persons currently utilizing treatment. We can begin by learning as much as possible from the study of aging (gerontology) and the medical specialty of geriatrics; then we must tailor their lessons to the special issues affecting people aging with HIV.

First, geriatricians will tell us that the term "premature" aging is a bit of a misnomer; it suggests that aging is inevitably associated with decline and that early decline is unique to those aging with HIV. Organ system injury and failure, functional decline, repeated hospitalizations and death are also observed at earlier ages among those with other chronic diseases such as diabetes and rheumatoid arthritis.[41] As with these other conditions, steps can be taken to regain or, preferably, maintain function and quality of life and thereby avoid a prolonged period of compromise prior to death.

Additionally, geriatricians will tell us that morbidity and mortality among those aging with HIV likely reflect the integrated whole of many conditions and disease processes—some tied to the "primary disease" and its treatment, and some associated with health behaviors and conditions more common among those with the primary condition but not necessarily causally associated (e.g., hepatitis C infection).[42, 43] Interventions that systematically identify and address multiple contributing factors are more likely to succeed. These will include early treatment as well as behavioral interventions to improve adherence; end cigarette and tobacco use, alcohol consumption and drug use; and avoid obesity and support regular exercise. Diagnosis and treatment of comorbid illnesses, in particular hepatitis B and C, and careful consideration of potential treatment toxicity from HIV and non-HIV medications are also important.

Besides describing techniques to address the diverse etiologies that drive functional decline among those aging with complex chronic disease,[44, 45] the geriatric literature offers a general lesson for management. Geriatricians warn against the blind application of screening and treatment guidelines developed for application in a primary care population free of major comorbidity to those with complex chronic disease and multi-morbidity.[46, 47] Multimorbidity is the norm among those aging with HIV.[48] We must prioritize and tailor care for those aging with HIV based upon a careful assessment of their risk of morbidity or mortality, identification of risks which are modifiable, and targeted intervention based upon assessment and patient preferences.

We Need a New Way of Assessing Risk

The list of potentially helpful interventions is long and demanding for both providers and patients. Therefore, prioritization and tailoring of health care goals based upon a careful assessment of the individual risk of morbidity and mortality is essential.[49, 50] This assessment needs to go beyond CD4 count and viral load quantification. While a focus on CD4 count, viral load, and AIDS defining illnesses made sense when we had few effective antiretroviral therapies and mortality rates were high, it is no longer appropriate. As the SMART investigators have concluded, we now need to use a more nuanced approach which adapts research priorities to understand the role of HIV in a range of clinical diseases and enables clinicians to prevent and monitor for non-AIDS outcomes.

We must prioritize and tailor care for those aging with HIV based upon a careful assessment…and patient preferences.

The geriatric research community is sharply divided regarding the best means of measuring the overall health or vulnerability to injury of an individual.[51] A modified version of the frailty phenotype, the frailty related phenotype, has been applied among those with HIV infection with mixed success.[52, 53] Functional capacity, or the reported or observed

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ability of the individual to do certain physical activities, might be a more useful measure because functional capacity can be measured over a wider range of abilities, from activities of daily living like using the bathroom to extreme exertion like running uphill,[54] and has demonstrated a wider applicability to HIV-positive individuals in care.[55, 56]

The recently published Veterans Aging Cohort Study Risk Index (VACS Risk Index) offers a more comprehensive approach and direct insight into the likely contributing sources of injury. The VACS Index incorporates age, CD4 count, viral load, AIDS defining illnesses, hemoglobin, renal function, liver function, chronic hepatitis B and C, and diagnoses of alcohol and drug abuse and dependence.[57] It predicts short and long term survival among those starting treatment better than an index restricted to CD4 count, viral load, and AIDS defining illnesses.[58] The index has been developed and validated among veterans in care and the process is underway to validate it outside the Department of Veterans Affairs healthcare system. With further validation, indices such as the VACS Risk Index may prove a valuable tool to: 1) comprehensively assess risk of morbidity and mortality, 2) identify modifiable mediators of risk and 3) demonstrate the efficacy of early intervention.

However, additional work also needs to be done regarding how best to communicate the meaning of the index score both to people with HIV infection and to their health care providers. The VACS Project Team is developing a public website where individuals, or their health care providers, can enter clinical information and get the score and an interpretation. We would like feedback from people living with HIV and their providers on how to make this site more useful; the link can be accessed at www.vacohort.org.

Eventually, the use of a more comprehensive risk index can encourage patients and health care providers to think more broadly about the conditions contributing to the total burden of disease among those aging with HIV. This will help us recognize the inevitable tradeoffs between screening for and treating every possible comorbid condition and concerns about overly complex medical treatment which leads to increased rates of toxicity, drug interactions, and medical error. We must keep in mind that some conditions will have major impact on an individual's quality and quantity of life and others will not. Further, an overall index would allow us to uniformly measure benefit from health behavior changes including weight control, exercise, moderation or cessation of tobacco or alcohol, and discontinuation of drug abuse.

Conclusion

HIV and its consequences continue to play a central role in health outcomes. Additionally, those aging with HIV have different risks of other aging related conditions due to behaviors and conditions present previous to HIV. If we are to further extend the quality and quantity of life for those living with HIV and accessing treatment we must systematically recognize and measure overall organ system injury and its implication for the HIV-positive individual's risk of morbidity and mortality. Armed with this tool and a willingness to think more comprehensively about the cumulative effects of health behaviors, aging related comorbidity, and medication toxicity, we can continue to improve life for those aging with HIV.

It is likely too early to determine who should provide primary care to individuals aging with HIV. But it is clear that a greater dialogue is needed between those with expertise in antiretroviral therapy and geriatricians and generalists with expertise in the optimization of complex chronic disease management. Primary care guidelines will require adaptation and individualized tailoring if they are to have their intended effect of preventing disease and extending survival among those aging with HIV. Individual health behavior changes will likely be as important as new medications in improving overall health.

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