Published in final edited form as:

Curr Opin HIV AIDS. 2014 July ; 9(4): 291–293. doi:10.1097/COH.0000000000000081.

Aging and HIV: An Evolving Understanding

Amy Justice, MD, PhD and Julian Falutz, MD, FRCPC

The increasing availability of effective antiretroviral treatment (ART) has dramatically extended life expectancy for those with HIV infection¹. As a result, people are aging with HIV², but data on this new phenomenon remains somewhat limited and opinions vary. Some experts contend, now that we are successful at suppressing HIV-1 RNA, that HIV research and health care resources should be exclusively dedicated to ensuring access to ART and developing an effective vaccine. They argue against spending limited resources on complex issues of aging with HIV since many of these issues have bedeviled aging researchers for decades. Some also suggest that routine care of virologically suppressed patients can be managed in more patient-centered and financially less expensive primary care settings³. Others take a different view, suggesting that the pathophysiologic processes and socioeconomic supports of aging are substantially altered among those with HIV and that these alterations offer unique opportunities for scientific discovery and improved clinical management. They suggest that aging with HIV is an untapped laboratory for discovery that offers unique insights into larger issues of aging. They point out that treatment strategies among those aging with HIV are only beginning to take shape, offering a unique opportunity to use evidence to inform care. Many clinicians also argue that enough unique and challenging aspects related to the ongoing management of HIV remain, suggesting a continuing role for the HIV specialist⁴.

Probably the strongest data in support of the view that patients aging with HIV in the context of virologic suppression and adequate immune recovery are no different than aging uninfected persons comes from a recent meta-analysis of HIV life expectancy data. Among those with HIV-1 RNA suppression and CD4 counts above 500 cells/mm³, the studies find no difference in life expectancy compared with demographically similar uninfected individuals¹. Importantly, the majority of those in care with HIV infection do not achieve this level of immune reconstitution. According to recently updated analyses from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a cross cohort study encompassing most of the large HIV cohort studies in North America, more than 95% of whom are on ART, the median CD4 cell count in 2011 below 500 cells. Thus, less than half of those aging with HIV have a normal life expectancy (www.naaccord.org/dossier/NA-ACCORD_Dossier_20140325.pdf). Further, whether long-term HIV effects of microbial translocation, viral reservoirs, and chronic inflammation among suppressed patients will alter these estimates with time is not yet known^{5, 6}.

Corresponding Author: Amy Justice, Professor of Medicine and Public Health, Yale School of Medicine, Building 35A, Room 2-212 (11-ACSLG), 950 Campbell Avenue, West Haven, CT 06516, amy.justice2@va.gov.

Conflict of Interest Statement:

Amy Justice has no conflict of interest.

Julian Falutz has no conflict of interest.

Another common argument from HIV and aging ‘skeptics’ is that any increased risk we observe for non AIDS conditions among those with HIV compared to demographically similar uninfected individuals can be explained by differential health behaviors (more smoking, drinking, and drug use) or by suboptimal antiretroviral therapy (exposure to mono and dual therapy as well as exposure to antiretrovirals with known toxicity collectively known as the “D drugs”, i.e., the thymidine NRTIs). Certainly alcohol use, smoking, and both illicit and prescription drug abuse are more common among those aging with HIV^{7, 8}. Similarly, mental health issues play a role⁹. However, the SMART study¹⁰ and a number of observational studies controlling for important health behaviors such as smoking, alcohol, and drug use^{11–14}, have demonstrated that ART, on average, decreases risk for and progression of non AIDS defining organ system disease including anemia, cardiovascular disease, liver disease, and renal disease. While ART toxicity continues to play a more minor role in adverse outcomes, it does not appear to be a major driver of excess risk for the so called HIV Associated Non AIDS defining conditions or HANA^{15–19}.

At least some of the incident metabolic complications occurring after ART initiation, previously attributed to ART toxicity, may be partially explained by a general return to health characterized by weight gain²⁰ and inevitable increases in lipids and glucose intolerance or frank diabetes¹⁵. Determining what is healthy and unhealthy weight gain after ART is a unique challenge.

A further possibility that has yet to be carefully explored is that toxicity from non HIV medications may explain some of the observed excess risk for organ system disease and adverse outcomes seen among those aging with HIV²¹. In resource rich settings, those aging with HIV are also taking a growing number of non ART medications that likely interact with ART and easily cross the numeric threshold for polypharmacy established in the geriatric literature. As a result, they are at increased risk of adverse drug reactions further^{22–24}. Whether decreasing the number of non ART medications through prioritization and consideration of behavioral alternatives to medications for common aging related conditions such as sleep disorders, reflux esophagitis, and chronic pain improves outcomes remains to be seen.

Claims of “accelerated aging” are largely overstated and heighten concern and anxiety in many older patients. Increased risk of complications at all ages is not the same as premature aging. Many HIV infected and uninfected patients complain of feeling “old beyond their time”⁹, but the characterizations of aging with HIV as accelerated are largely based on biomarker data and/or clinical data employing inappropriate comparators^{25, 26}. Age differences that at first appeared pronounced, diminish substantially when the underlying distribution of age in the samples compared is matched²⁷. Comparing community based controls to clinic based patients is always biased toward higher estimates of disease in the clinic sample. While those with HIV infection appear to have more co-occurring conditions²⁸ (also called multimorbidity) including hepatitis C, substance use addiction to tobacco, alcohol and psychoactive drugs, and to have somewhat higher levels of the frailty related phenotype²⁹, it is not clear that HIV patients infection achieving immuno-virologic control are subject to greater levels of frailty³⁰ or functional compromise. Further, the current understanding of HIV Associated Neurologic Disease (HAND) is problematic since

many factors included are not unique to HIV. For example, many measures of neurocognitive performance are strongly associated with organ system components of the VACS Index but are not associated with CD4 count or HIV-1 RNA³¹. These risks will increase as the HIV population ages beyond 65 years of age, an age after which cerebrovascular disease, dementia, both vascular and non-vascular related, and affective disorders occur more often¹⁸.

An important subgroup among those supporting the relevance of aging concerns in HIV focuses on aging with and without HIV in resource limited settings³². In this setting, aging, among the general population, is a relatively new phenomenon and the HIV epidemic is a generalized one. How limited resources can be used to effectively address the growing population of both aging HIV infected individuals and newly infected older individuals will provide a unique and important challenge³³. Among these challenges is that of simply characterizing aging with, and without, HIV in this data limited setting.

We are only beginning to comprehend aging and HIV. The median age among those living with HIV has crossed 50 years in specific settings such as the US Veterans Administration Healthcare System, New York City, and San Francisco. More will follow. Whether investments in this line of research will lead to important biologic insights and improved clinical management remains uncertain. There are tantalizing clues about overlapping roles of chronic viral infection, hypercoagulability, inflammation, immune dysregulation and senescence^{5, 6, 34, 35} as well as the critical importance of more integrative scientific thinking across diseases, medical and research disciplines, and ages^{22, 36, 37}. Outside HIV research, there is a growing appreciation for the importance of other chronic viral infections including hepatitis C and cytomegalovirus. Perhaps the questions at this juncture are: can studying aging with HIV inform the study of aging more generally; can this focus provide unique insights into modifiable roles of chronic inflammation, multimorbidity, and frailty in the course of particular disease processes and in the overall aging process; and can it improve care of those aging with HIV? We believe that the answers to these questions will be a resounding, “yes”, but only time will tell.

To further inform the discussion, we invited 18 papers from colleague with diverse backgrounds who think that there is something special about the study of aging and HIV. Some of these papers focus on particular organ systems including the immune system³⁴, gastrointestinal system⁶, liver¹⁹, cardiovascular system¹⁷, kidney¹⁶, skeletal system³⁸, and central nervous system¹⁸. Some focus on health behaviors and substance use^{8, 9}. Others are focused on more integrated issues of aging including metabolism¹⁵, multimorbidity²¹, geriatric syndromes³⁵, frailty³⁶, and functional status²⁸. Still others focus on systems and approaches to care³⁷. Finally, we begin the collection with an updated description of the demographics of aging with HIV² and end with a cautionary paper on how to identify appropriate uninfected comparators²⁶ and an article focused on pressing research questions⁵.

Acknowledgments

FINANCIAL DISCLOSURE April 2014:

- Consulting: Theratechnologies Canada Inc.

- Advisory Boards: Serono USA
- Speaker Bureaus: none

Reference List

1. Sabin CA. Do people with HIV infection have a normal life expectancy in the era of combination antiretroviral therapy? *BMC Med.* 2013; 11:251. [PubMed: 24283830]
2. Costagliola D. Demographics of HIV and aging. *Current opinion in HIV and AIDS.* 2014; 9(4)
3. Chu C, Selwyn PA. An epidemic in evolution: the need for new models of HIV care in the chronic disease era. *J Urban Health.* 2011; 88(3):556–566. [PubMed: 21360244]
4. High KP, Brennan M, Clifford D, et al. HIV and Aging: State of Knowledge and Areas of Critical Need for Research. A Report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *Journal of Acquired Immune Deficiency Syndrome (JAIDS).* 2012; 60(Supplement 1)
5. Hunt P. HIV and ageing: emerging research issues. *curr opin.* 2014; 9(4)
6. Kotler DP. HIV enteropathy and aging: GI immunity, mucosal epithelial barrier and microbial translocation. *Current opinion in HIV and AIDS.* 2014; 9(4)
7. Green TC, Kershaw T, Lin H, et al. Patterns of drug use and abuse among aging adults with and without HIV: A latent class analysis of a US Veteran cohort. *Drug Alcohol Depend.* 2010; 110(3): 208–220. [PubMed: 20395074]
8. Fiellin D. Substance use in older HIV-infected patients. *Current opinion in HIV and AIDS.* 9(4) 14 A.D.
9. Rourke S. Psychosocial, mental health and behavioral issues of aging with HIV. *Current opinion in HIV and AIDS.* 2014; 9(4)
10. Strategies for Management of Antiretroviral Therapy (SMART) Study Group. El-Sadr W, Lundgren J, et al. CD4+ Count-Guided Interruption of Antiretroviral Treatment. *New England Journal of Medicine.* 2006; 355(22):2283–2296. [PubMed: 17135583]
11. Anderson JP, Tchetgen EJ, Lo RV III, et al. Antiretroviral Therapy Reduces the Rate of Hepatic Decompensation among HIV- and Hepatitis C Virus-Coinfected Veterans. *Clin Infect Dis.* 2013
12. Wyatt CM, He C, Parikh C, et al. VACS Diabetes and CKD. *Journal of Acquired Immune Deficiency Syndrome (JAIDS).* In press.
13. Moore RD, Forney D. Anemia in HIV-infected patients receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2002; 29:54–57.
14. Freiberg MS, Chang CC, Kuller LH, et al. HIV Infection and the Risk of Acute Myocardial Infarction. *JAMA Intern Med.* 2013:1–9.
15. Martinez E. Update on metabolic issues in HIV patients. *Current opinion in HIV and AIDS.* 2014; 9(4)
16. HIV, Wyatt C.; Kidney, Aging. *Current opinion in HIV and AIDS.* 2014; 9(4)
17. Freiberg M. CVD risk in an aging HIV population - not just a question of biology. *Current opinion in HIV and AIDS.* 2014; 9(4)
18. Brew B. The effects of HIV and aging on brain functions: proposing a research framework and update on last 3 Years' findings. *Current opinion in HIV and AIDS.* 2014; 9(4)
19. Rockstroh JK. Liver fibrosis in HIV: which impact has HIV itself, long-term drug toxicities and metabolic changes or other comorbidities? *Current opinion in HIV and AIDS.* 2014; 9(4)
20. Lakey W, Yang LY, Yancy W, Chow SC, Hicks C. Short communication: from wasting to obesity: initial antiretroviral therapy and weight gain in HIV-infected persons. *AIDS Res Hum Retroviruses.* 2013; 29(3):435–440. [PubMed: 23072344]
21. Capeau J. Emerging clinical issues related to management of multi organ comorbidities and polypharmacy. *Current opinion in HIV and AIDS.* 2014; 9(4)
22. Edelman EJ, Gordon K, Akgun K, et al. HIV+ individuals on ART are at risk of polypharmacy: More medication increases mortality. 2013
23. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC. The next therapeutic challenge in HIV: polypharmacy. *Drugs Aging.* 2013; 30(8):613–628. [PubMed: 23740523]

24. Holtzman C, Armon C, Tedaldi E, et al. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med*. 2013; 28(10):1302–1310. [PubMed: 23605401]
25. Pathai S, Bajillan H, Landay AL, High KP. Is HIV a Model of Accelerated or Accentuated Aging? *J Gerontol A Biol Sci Med Sci*. 2013
26. Gange SJ. Identifying the appropriate comparison group for HIV-infected individuals. *Current opinion in HIV and AIDS*. 2014; 9(4)
27. Shiels MS, Althoff KN, Achenbach C, et al. Age at cancer diagnosis in HIV-infected individuals in North America compared to the general U.S.population. XIX International AIDS Conference. 2012 Ref Type: Abstract.
28. Guaraldi G. Multimorbidity and functional status assessment. *Current opinion in HIV and AIDS*. 2014; 9(4)
29. Desquilbet L, Jacobson LP, Fried LP, et al. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. *J Gerontol A Biol Sci Med Sci*. 2007; 62(11):1279–1286. [PubMed: 18000149]
30. Althoff KN, Jacobson LP, Cranston RD, et al. Age, comorbidities, and AIDS predict a frailty phenotype in men who have sex with men. *J Gerontol A Biol Sci Med Sci*. 2014; 69(2):189–198. [PubMed: 24127428]
31. Marquine MJ, Umlauf A, Rooney AS, et al. The Veterans Aging Cohort Study Index is Associated With Concurrent Risk for Neurocognitive Impairment. *J Acquir Immune Defic Syndr*. 2014; 65(2):190–197. [PubMed: 24442225]
32. Mills EJ, Barnighausen T, Negin J. HIV and aging—preparing for the challenges ahead. *N Engl J Med*. 2012; 366(14):1270–1273. [PubMed: 22475591]
33. Justice AC, Braithwaite RS. Lessons learned from the first wave of aging with HIV. *AIDS*. 2012; 26(Suppl 1):S11–S18. [PubMed: 22781174]
34. Tsoukas C. Immunosenescence and aging in HIV. *Current opinion in HIV and AIDS*. 2014; 9(4)
35. Chirch LM. HIV and aging: a clinical journey from Koch's Postulate to the chronic disease model and the contribution of geriatric syndromes. *Current opinion in HIV and AIDS*. 2014; 9(4)
36. Rockwood K. Biologic ageing, frailty, and age-related disease in chronic HIV infection. *Current opinion in HIV and AIDS*. 2014; 9(4)
37. Boyd C. Patient-centered care for people living with multimorbidity. *Current opinion in HIV and AIDS*. 2014; 9(4)
38. Mallon P. Ageing with HIV: osteoporosis and fractures. *Current opinion in HIV and AIDS*. 2014; 9(4)