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Aging and HIV: An Evolving Understanding

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The increasing availability of effective antiretroviral treatment (ART) has dramatically extended life expectancy for those with HIV infection[1]. As a result, people are aging with HIV[2], 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 settings[3]. 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 specialist[4].

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 individuals[1]. 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].

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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]. Similiarly, mental health issues play a role[9]. However, the SMART study[10] 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 gain[20] and inevitable increases in lipids and glucose intolerance or frank diabetes[15]. 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 HIV[21]. 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 though 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 matched[27]. 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 conditions[28] (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 phenotype[29], it is not clear that HIV patients infection achieving immuno-virologic control are subject to greater levels of frailty[30] 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 RNA[31]. 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 often[18].

An important subgroup among those supporting the relevance of aging concerns in HIV focuses on aging with and without HIV in resource limited settings[32]. 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 challenge[33]. 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 system[34], gastrointestinal system[6], liver[19], cardiovascular system[17], kidney[16], skeletal system[38], and central nervous system[18]. Some focus on health behaviors and substance use[8, 9]. Others are focused on more integrated issues of aging including metabolism[15], multimorbidity[21], geriatric syndromes[35], frailty[36], and functional status[28]. Still others focus on systems and approaches to care[37]. Finally, we begin the collection with an updated description of the demographics of aging with HIV[2] and end with a cautionary paper on how to identify appropriate uninfected comparators[26] and an article focused on pressing research questions[5].

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