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Justification for a new cohort study of people aging with and without HIV infection

A.C. Justice^{a,b,*}, C.S. Landefeld^c, S.M. Asch^d, A.L. Gifford^e, C.C. Whalen^f, and K.E. Covinsky^c

^a Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, University Drive C 11E-124 (130-U), Pittsburgh, PA 15240, US

^b Veterans Aging Cohort Study (VACS) Center, Division of General Internal Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

^c VA San Francisco Healthcare System and University of California San Francisco School of Medicine, Division of Geriatrics, San Francisco, CA, USA

^d VA Los Angeles Healthcare System and University of California Los Angeles School of Medicine, Division of General Internal Medicine, Los Angeles, CA, USA

^e VA San Diego Healthcare System and University of California San Diego School of Medicine, Division of General Internal Medicine, San Diego, CA, USA

^f Case Western Reserve University School of Medicine, Division of Infectious Diseases and Department of Epidemiology, Cleveland, OH, USA

Abstract

This supplement contains a series of papers supporting the justification, design, and implementation of a longitudinal cohort study of an aging HIV-positive and HIV-negative veteran population called the Veterans Aging Cohort Study (VACS). Although the papers cover a wide range of topics and several papers address methodologic issues not unique to a study of aging veterans, all are motivated by a unifying set of assumptions. Specifically: (a) HIV/AIDS is a chronic disease in an aging population; (b) conditions among HIV-positive and -negative patients in care have overlapping etiologies; (c) individuals with pre-existing organ injury are at increased risk for iatrogenic injury; (d) cohort studies are uniquely suited to the study of chronic disease complicated by aging, comorbid conditions, drug toxicities, and substance use/abuse; (e) VACS is well positioned to study HIV as a chronic disease in an aging population

Keywords

Cohort study; People aging; HIV-positive; HIV-negative

*Corresponding author. Tel.: 412-688-6957; fax: 412-688-6916. Amy.Justice@med.va.gov (A.C. Justice).

1. HIV/AIDS is a chronic disease in an aging population

AIDS and aging were once mutually exclusive conditions; the AIDS epidemic began in young adults who died before they had time to age [1]. Yet, even early in the epidemic, there were links between HIV and aging. Clinicians spoke of AIDS as rapidly accelerated aging because AIDS, like aging, was associated with progressive physical and mental disability and, eventually, death. Further, even though the age range of those diagnosed with AIDS was limited, increasing age was consistently associated with poorer survival [2,3]. Finally, many of the same variables that predicted shorter survival in aging such as limitations in activities of daily living, anemia, and cognitive difficulty also predicted shorter survival in AIDS [4,5]

Since the advent of potent multidrug antiretroviral therapies the connection between AIDS and aging has become more direct. Two recent trends are rapidly adding to the numbers of middle-aged and older people with HIV infection. First, because of more effective antiretroviral treatment, those infected with HIV early in adulthood are aging. Estimates for expected survival based upon short-term, post-HAART data depend upon baseline CD4 cell count, but suggest that median survival from diagnosis may exceed 15–20 years—roughly twice the expected survival from diagnosis prior to 1992 [6]. Thus, someone diagnosis at 35 years of age (the median nationally) can now expect to live to 50 or 55 years of age. In contrast, before 1992, a similarly diagnosed individual could expect to live to 40 or 45 years of age. Second, a growing number of older people are newly infected with HIV. In 1999 alone, 78,197 people over the age of 50 were newly diagnosed with AIDS, accounting for 10.6% of all cases reported to the CDC that year; 10,002 people (1.4% of all cases) were over 65 years of age [7]. These two trends would suggest the prevalence of HIV infection among older people is rising; while 10% of new AIDS cases occur in those over 50 years of age, 14% of all people living with AIDS are over 50 years of age. Further, the number of persons 65 years of age and older at AIDS diagnosis has grown 10-fold in the last 10 years (from 1,008 to 10,002) [7].

In sum, people are growing older with HIV; older people are contracting HIV infection; HIV is now a chronic disease in an aging population characterized by complex long-term treatment, and related and unrelated comorbid conditions. Much can be learned from approaching chronic HIV infection with an aging perspective.

2. Conditions among HIV-positive and -negative patients in care have overlapping etiologies

As the population of people with HIV infection and AIDS is aging, the overall profile of HIV-associated complications has changed dramatically [8]. Until very recently Pnuemocystis pneumonia, Kaposi's sarcoma, and Myco-bacterium were consistently the most common conditions in HIV-positive populations in the developed world [9–11]. Now, multiple groups are reporting dramatically lower prevalence for these conditions and increased prevalence for conditions such as bacterial pneumonia [8].

Even more remarkably, “non-HIV”-related complications such as hepatitis [12,13], hyperlipidemia [14,15], and diabetes [16–19] are now more common than HIV-related

conditions among HIV-positive people in care. In many cases these conditions appear to have multiple and complex etiologies (Fig. 1).

For example, hepatitis has become a common cause of morbidity and mortality among those infected with HIV [20,21]. This increased rate of hepatitis-related morbidity and mortality likely represents the combined effects of hepatotoxicity of multidrug antiretroviral therapy, and other therapies (e.g., treatment with statins) [17], increased susceptibility due to aging, chronic coinfection with Hepatitis B and/or C, and chronic alcohol abuse.

Mental health comorbidities like depression [22] and cognitive impairment [23] follow the same pattern. Depression is common among the elderly and especially common among older individuals with chronic diseases, including HIV. Elderly men are almost twice as likely to commit suicide as younger adults. Older individuals also have a higher risk of cognitive impairment overall, and older HIV-infected patients may be at particularly high risk.

Alcohol use is also associated with psychiatric and cognitive comorbidity, and may be higher among middle-aged and older people with HIV than is currently appreciated [24,25]. Finally, several antiretroviral therapies are known to cause peripheral neuropathy, and this may be of particular concern with advancing age [23].

Thus, a new set of questions now needs to be addressed. What are the consequences of long-term exposure to HIV treatment? What conditions are comorbidities of aging and substance use (e.g., drug, alcohol, and cigarette use)? To what extent do HIV infection, HIV treatment, aging, and substance use and other patient behaviors interact to cause these comorbidities or to accelerate their course? Finally, which of these comorbidities are consequences of HIV infection but have not previously been appreciated as such because people did not live long enough with HIV infection to develop them?

3. Patients with pre-existing organ injury are at increased risk for iatrogenic injury

Based largely upon two landmark studies [26,27], the Institute of Medicine has estimated that between 44,000–98,000 people die in U.S. hospitals annually as a result of medical error. If true, these estimates rank medical error as the eighth leading cause of death—ahead of motor vehicle accidents (43,458 deaths), breast cancer (42,297 deaths), or AIDS (16,516 deaths) [28]. Although the report also recognized the growing importance of out-patient management, and the likelihood that substantial morbidity and mortality is also occurring in clinics and physician offices, good out-patient data are not generally available.

Medical harm occurs when the patient experiences an adverse consequence from a medical error or from approved medical practice that has an untoward effect on the patient. Medical harm is much more common among those with chronic disease who have greater exposure to medical care and greater susceptibility to injury due to pre-existent organ injury. Exogenous factors that predispose individuals with chronic disease and HIV to medical harm include under diagnosis and delayed diagnosis due to symptom denial, symptom attribution to age alone, and atypical presentations [29,30]. Endogenous factors associated

with increased risk of medical harm include diminished reserves, especially in cognitive, renal, and hepatic function [29,30]. Because people are growing older with HIV, because older people are contracting HIV infection, and because HIV is now a chronic disease characterized by complex long-term treatment and comorbid conditions, people aging with HIV infection are likely to be at a dramatically increased risk for medical harm. Yet little is known about the association of medical errors and age in HIV.

The most common types of medical harm result from adverse drug events [29]. Adverse drug events include preventable adverse events (those due to error) and nonpreventable events, also called adverse drug reactions. Risk of adverse drug events of both kinds increases with age, prescription of multiple drugs, and increasing comorbidity [29], all factors that are increasingly common in an aging HIV population. Drug-induced delirium deserves special attention in the HIV setting. Medications are among the most common causes of delirium [29], particularly among older patients with underlying chronic diseases. Other common causes for delirium are infections, metabolic derangement, and alcohol or drug withdrawal.

By studying medical harms in HIV-positive and HIV-negative aging individuals we may be able to more clearly identify the relative roles played by both endogenous and exogenous factors, and in turn, take steps to minimize medical harms in both populations.

4. Cohort studies are uniquely suited to the study of chronic disease complicated by comorbid conditions, drug toxicities, and substance use/abuse

Cohort studies and randomized trials offer completely complimentary scientific insights [31–37]. Whereas cohort studies are designed to study clinical phenomena observationally and can thereby observe the entire range of variation in etiologies and outcomes present in the clinical population, randomized trials are designed to resolve a particular focused scientific question. By design, cohort studies are meant to be broad, inclusive, open to detect the unexpected, and hypothesis generating [38,39]. On many occasions, cohort studies can also definitively answer a clinical question when there is no substantial unadjusted confounding [31,32]. In contrast, randomized trials typically exclude many times the patients that they enroll [33,34,36]. This is done to enroll patients who maximize the chance of response to the treatment. However, this also means that important populations of patients, patients with comorbid conditions, older and sicker patients, and minority patients are omitted. In addition, randomized trials often include clinical care that is not routine and unlikely to occur in actual clinical practice. This is again done to maximize the chance of a favorable response, but substantially reduces the chances that a similar response will be seen in the course of routine medical care [40].

If we are to understand the separate and combined effects of HIV infection and its treatment, aging, patient behaviors, and risk factors on patient outcomes we must be able to compare and contrast groups with and without a range of these conditions, of a wide range of ages, with and without HIV infection. If we are to understand the role of depression [22] or other

psychiatric or cognitive diseases [22,23] in undermining a patient's ability to adhere to medication we must also consider the role of active substance use, homelessness, severity of illness, the strength of the relationship with the provider, and the complexity, chronicity, and toxicity of the medical regimen [25]. If we are to understand why older people with HIV infection die faster than their younger counterparts [41] we must first be able to determine that age alone does not explain the differences observed by comparing rates of mortality among appropriate matched HIV-negative individuals. If we are to understand the high rate of clinical hepatitis [24] among HIV-positive patients in care we need to study the relative effects of Hepatitis C infection, alcohol consumption, and drug toxicity in both HIV-positive and -negative patients.

Cohort studies allow us to study conditions in all their diversity—rather than attempting to stratify on particular variables or excluding patients less likely to benefit from a particular intervention (as is commonly done in randomized trials) [32]. Randomized trials are more appropriately targeted to questions cohort studies have previously helped to define that cannot be resolved through observational data. Further, cohort studies are substantially less expensive than randomized trials. Perhaps most importantly, cohort studies are more readily able to follow patients for long enough intervals to study long-term patient outcomes such as survival.

We are in the midst of a new wave of the HIV epidemic in which new conditions are emerging and the etiologies of patient outcomes are likely to be multifaceted. Cohort studies are needed to conduct surveillance of the disease, define appropriate questions for further research, and identify sensible management strategies applicable to a wide range of patients from amidst the diversity of clinical practice.

5. VACS is uniquely positioned to study HIV as a chronic disease in an aging population

In the setting of multifaceted etiologies and complicating conditions, it is increasingly important to link a broad range of data sources on the same patient to understand the full range of conditions present [42,43]. The only way to do this is to have data for the same patient from multiple sources that can be linked and analyzed together. Data needed include medical records, surveys, blood and tissue, and neuropsychiatric and cognitive testing. Full medical record data includes laboratory data, pharmacy data, diagnostic codes, and utilization data. In the past, extracting data in a valid and systematic manner from medical records was a challenging task for scientific and logistical reasons. As a result, many cohort studies have implemented an expensive parallel system of record keeping and laboratory assessment. Further, because these systems are completely independent of the patients' medical records and are collected at a separate clinical site, there is no opportunity to use the medical record as a means of additional surveillance. Because the proposed cohort is based upon the VAs national electronic medical record, this cohort study can be conducted at a substantial savings.

Although a great deal of valuable data is efficiently available in the medical record, certain critical data elements are missing. Survey data are needed to supplement the medical record.

These include patient report of health related quality of life [44–46], symptom burden [47–50], alcohol and other substance use [51], adherence to medication [52–54], homelessness [55], and relationship with their provider [56–60]. Provider survey data is needed to understand the provider's assessment of severity and prognosis [61–65], the presence or absence of key comorbid conditions [8,66–72], and the provider's determination of whether or not the patient is adhering to their medication. If we are to understand provider behavior, we also need to determine whether or not the provider is aware of complications. Blood and tissue banking is needed to address important underlying mechanistic questions as they are defined by clinical observation and research. These include: evaluating surrogate markers, systematic studies of pathophysiologic markers of drug and alcohol toxicity; and evaluation of genetic predisposition to immune decline. Equally important to being able to conduct these studies is being able to tie results to a complete picture of the patients using the linked sources of data. In addition, formal neuropsychiatric and cognitive testing is needed to determine the prevalence of these conditions both among HIV-positive and HIV-negative patients in care.

Elements of this design are present in several important prior and current cohorts, but no other HIV cohort contains all these elements. In particular, no multisite cohort is collecting systematic prospective data on complications and a panel of general medical comorbid conditions, and no cohort is collecting parallel data on age–race–site-matched HIV-negative subjects. Further, few cohorts have access to electronic patient care records, and few are powered to analyze survival as a primary end point. The Veterans Affairs (VA) Health Care System is uniquely configured for such a study. The VA is the nation's largest public integrated healthcare system, providing care to 3.4 million unique patients during 695,000 in-patient episodes and 37 million out-patient visits annually. VA is the first large healthcare system to computerize its records and, today, has the largest electronic medical records system in the world that is fully integrated nation-wide. The VA has also become a leader in monitoring adverse drug events and medical error, and has instituted mechanisms that have substantially increased the recognition and reporting of these events [73]. Further, the VA is the largest provider of direct HIV services in the country. In 1999, the VA cared for more than 19,000 HIV-positive patients. Medical care for veterans with HIV infection encompasses all needed services and programs. Clinical guidance on the appropriate use of HIV therapies has been implemented across all VA facilities in the form of system-wide directive that uses the Public Health Service HIV and Opportunistic Infections Treatment Guidelines as VA standards. These guidelines lead to consistent care and the availability of all licensed HIV drugs and diagnostics across the VA health care system. Veterans with HIV tend to remain in the system because VA integrates acute and chronic medical care, access to all licensed HIV drugs and diagnostics, as well as programs for homelessness, substance abuse, mental health, and occupational/vocational rehabilitation. Because there are VA facilities throughout the country, many veterans are able to relocate and yet continue within the VA system by transferring their care to another VA site. As a result of staying within a single system, long-term follow-up is very strong in the VA, because the computerized record-keeping systems allow patients to be tracked wherever they are treated. Completely parallel data is available on HIV-negative veterans including all diagnoses, pharmaceutical usage, and laboratory and resource utilization. Equally important, the HIV patients cared for

by the VA system have been under-represented in prior research. Although clinical studies in HIV have primarily represented White men who have sex with men, the VA population is predominantly non-White, older, from lower socio-economic populations, and ethnically diverse.

6. Conclusions

The face of the HIV epidemic in the United States has changed dramatically since the advent of multidrug antiretroviral therapy that includes protease inhibitors and nonnucleoside reverse transcriptase inhibitors; people with HIV infection are now living long enough to experience HIV as a chronic disease with competing risks from aging, drug toxicity, and comorbid diseases and conditions. In addition, older people, already experiencing substantial comorbid disease, are contracting HIV infection. These comorbid medical and neuropsychiatric conditions substantially overlap with conditions associated with aging, drug and alcohol use and abuse, and antiretroviral drug toxicity. Further, an individual's susceptibility to iatrogenic injury from drug toxicity is likely determined by the degree of pre-existing compromise from HIV and comorbid conditions. The overlap and interaction among these conditions requires that they be studied as a whole. Cohort studies are well suited to this task. The VA health care system with its national electronic medical record provides is uniquely positioned for the efficient and effective study of outcomes among aging individuals with and without HIV infection. Thus, the time has come for a new paradigm in the study of outcomes in HIV infection. This paradigm calls for direct routine clinical surveillance and comparison of process and outcomes among individuals aging with and without HIV infection in the full context of aging, medical and psychiatric comorbidity, substance use and abuse, and drug toxicity. Because this paradigm calls for the study to be based in routine clinical care, it is also optimally situated for future clinical intervention trials targeted at modifiable mediators of clinical outcomes.

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Fig. 1.
Etiology of “non-HIV-related” comorbidity.