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Identifying the Appropriate Comparison Group for HIV-infected Individuals

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Abstract

Purpose of Review—HIV-infected individuals are living longer as a result of effective treatment. Age-related comorbidities now account for the majority of morbidity and mortality among treated HIV-infected adults. Previous findings regarding the age at, and risk of, these comorbidities have been mixed, sparking debate in the field. Discerning potential differences in the occurrence and burden of age-related comorbidities among treated HIV-infected adults as compared with uninfected adults of the same age requires careful selection of the appropriate uninfected comparison group.

Recent Findings—The validity of comparisons to HIV-uninfected populations is threatened when differences in demographic, clinical, and lifestyle characteristics between HIV-infected and uninfected adults are not considered. Identifying a pool of HIV-uninfected individuals from existing secondary data resources and employing selection methodologies may be a novel approach to reduce threats to internal validity. Issues related to identifying data sources, understanding inclusion criteria, determining measurement error, and threats to inference are discussed.

Summary—The development of clinical interventions targeting age-related comorbidities will rely on deriving valid inferences from appropriate comparison groups. The use of secondary data resources and selection methodology to create the appropriate uninfected comparison group is an attractive approach in the setting of finite resources, but are not without limitations.

Keywords

HIV-uninfected; HIV infection; aging; harmonization; causal inference

INTRODUCTION

Age-related comorbidities among persons living with HIV (PLWH) are becoming increasingly important in North America and Europe. The population attaining older age continues to rise because of extended life expectancy [1–4] and HIV infection is now treated as a chronic disease [5–7]. An increasing number of studies are evaluating whether the

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CONFLICTS OF INTEREST
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comorbidity burden is increased with HIV infection and whether targeted preventive and treatment guidelines are necessary for the management of these patients. Ultimately, these studies aim to determine how the onset age, incidence, severity, and treatment response of age-related comorbidities in PLWH compare to what would have occurred in these individuals had they not been infected with HIV.

There are a number of challenges to identifying a relevant HIV-uninfected comparison group including logistics of identifying a relevant population, differences in measurement of outcomes, and analytical issues. Uninfected adults in the general population are different from PLWH in terms of demographic characteristics, prevalence of traditional risk factors for age-related comorbidities, lifestyle, and socioeconomic factors. These differences must be accounted for in the design and analysis of epidemiologic studies in order to produce valid inferences of the impact of treated HIV on age-related comorbidities. Comparisons of populations that differ from this ideal in variables that are determinants of age-related comorbidities are subject to epidemiological confounding. Here, we discuss several challenges and possible solutions to identifying appropriate uninfected comparison groups.

WHAT IS THE IDEAL UNINFECTED COMPARISON GROUP?

The ideal comparison group would be defined as those individuals who are identical to HIV-infected adults in all aspects with the exception of their HIV status. Achieving this ideal is a theoretical aspiration but can be facilitated by enrollment of individuals from the same source population as the HIV-infected individuals. Some US interval and clinical cohort studies have enrolled an uninfected group that can be described as similar to their HIV-infected counterparts. The Multicenter AIDS Cohort Study (MACS) [8] the Women's Interagency HIV Study (WIHS) [9, 10], and the AIDS Linked to the Intravenous Experience Study (ALIVE) [11] have explicitly enrolled individuals who are HIV-uninfected at similar locations and have similar demographic characteristics. The Veterans Aging Cohort Study (VACS) identified HIV-infected individuals in care and selected an uninfected comparison group to match their demographic characteristics [12].

If studies have not enrolled HIV-uninfected individuals, what are the alternatives? The use of the general population as the (often times presumably) uninfected control group has been common practice in the US and Europe, due to the availability of these data through population-based studies, routine health information systems, and registries [13–19]. HIV-infected adults have been shown to have an increased risk of cardiovascular disease [20**, 21**], renal impairment [22, 23], malignancies [24–30], bone disorders [31], and multimorbidity [32–35] as compared to uninfected adults. Although these data may be readily available, differences in demographic characteristics, traditional risk factors, lifestyle factors, and socioeconomic factors in PLWH and the general population suggest the general population is not an appropriate comparison group.

For example, in the US, HIV-infected adults are younger than the general population. In 2010, 13–24 year-olds comprised 16% of the US population, but 26% of all new HIV infections were within young persons [36]. Slightly less than half of the US population is male, but 70% of PLWH are male [37]. African Americans and Hispanic/Latinos make up

12% and 16% of the US population, respectively, but together they comprise more than half of all PLWH [36–38]. Being male and black are also traditional risk factors for some age-related comorbidities. Additional differences in risk factors include an increased prevalence of smoking [39, 40], substance abuse [41–43], hypertension [44, 45], dyslipidemia [46, 47], and diabetes [45, 48, 49] among HIV-infected adults compared to the general population. Differences in lifestyle factors include an increased prevalence of hepatitis C (HCV) infection in PLWH [50] and HCV is associated with a greater comorbidity burden [51, 52]. Finally, PLWH are more likely to experience socioeconomic factors such as social isolation [53], unstable housing [54], and food insecurity [55], which may be associated with age-related comorbidities. PLWH may also experience better screening for age-related comorbidities due to their frequent interaction with the healthcare system.

Taken together, comparing PLWH to the general population in the US and Canada will likely to result in an overestimation of the age-related comorbidity. This might be different in countries that have more generalized HIV epidemics [56] but in these settings the prevalence of HIV may be so high as to render general population comparisons irrelevant.

ALTERNATIVES TO THE GENERAL POPULATION: HARNESSING EXISTING DATA SOURCES

Justifying the enrollment of HIV-uninfected individuals to funding agencies in sufficient numbers can be difficult. The MACS initially enrolled a large number of HIV-uninfected individuals but trimmed enrollment before the era of effective therapy; subsequent efforts to re-enroll these men should be applauded. In 2010, the AGEhIV cohort commenced recruitment of infected and uninfected individuals in Amsterdam, with planned follow-up of two years [57]. Further, enrollment of uninfected groups through similar venues does not guarantee they are equivalent. In the WIHS, for example, HIV-uninfected women are several years younger than the HIV-infected cohort [9].

Existing data sources from longitudinal studies observing age-related comorbidity outcomes among uninfected adults are a potential alternative resource for establishing an appropriate uninfected comparison group. Efforts to harness existing data for secondary purposes have been seen in other fields. For example, the National Cancer Institute funds the Cohort Consortium which pools large quantities of cancer data and biospecimens to promote the study of genomic associations with cancers that cannot be addressed by a single cohort [58]. This consortium involves more than 40 cohorts across the world and has initiated numerous pooled analyses. Similarly, PhenX (funded by the National Human Genome Research Institute) seeks to integrate epidemiologic and genetics research by creating standardized, high-quality measures of exposures and phenotypes, and facilitate large-scale genomic research and genome-wide association studies (GWAS) that will promote cross-study comparisons [59]. Beyond genetics, the National Institutes of Health Big Data to Knowledge (BD2K) initiative is devised to engage biomedical researchers in accessing diverse datasets (e.g. imaging, phenotypic, molecular, exposure, heath, behavioral data) [60]. By establishing 6–8 large data centers of excellence, novel approaches, standards, and methods will be developed to harness rich data sources. The FDA-sponsored Sentinel Initiative, which uses a

distributed data model to assemble linked data on more than 100 million persons, is part of an early warning system for adverse drug reactions and medical product safety [61].

EPIDEMIOLOGICAL CONSIDERATIONS WHEN USING MULTIPLE EXISTING DATA SOURCES TO CREATE A POOL OF UNINFECTED ADULTS

This approach prompts careful consideration of what epidemiological issues will be faced, and therefore a transparent discussion of what limitations can materialize when pooling data from HIV-uninfected individuals.

Study population considerations

Understanding of the original research question that identified the source population and drove the participant recruitment and follow-up for the existing data source is essential. Clinical trials are often restricted to individuals who are healthier [62]. Observational studies of age-related outcomes are famous for recruiting based on geographic location, such as the Framingham study [63] or the Jackson Heart Study [64]. Understanding inclusion and exclusion criteria for enrollment into the existing studies is essential for understanding bias that may occur when data are pooled. If the existing pooled data sources are diverse in their study populations, the bias from any one source may be counter-balanced by another source. For example, selecting individuals from the Framingham study and the Jackson Heart Study may reduce the bias from over-representing either white and black participants from using each study separately. Finally, low retention or differential loss to follow-up may result in study populations that are no longer representative of the original recruits. Depending on whether healthy or sicker individuals drop out over time, this leads to an over- or underestimation of comorbidity occurrence, respectively.

Measurement considerations

Issues from unmeasured variables and measurement error can become magnified when data sources are extended beyond their original research goals and combined to form a pool for the comparison group. The degree to which data elements are collected is a function of a data source’s original research purpose.

Frequently, variables that are of particular importance in HIV research are unmeasured – this may include HIV status itself, a history of injection drug use, or smoking. These variables may not be considered relevant in many longitudinal studies that are not focused on HIV and therefore not collected. Because <1% of the population in the U.S. is HIV infected, it seems reasonable to assume individuals from non-HIV studies are uninfected if HIV is not directly measured. For variables that are typically collected across age-related comorbidity studies, such as smoking, the methods of data collection (e.g. surveys vs. medical record review), the intensity of data collection (e.g. categories and frequency of data elements), and data validation procedures may all vary between studies. Invariably, this complicates its standardization between multiple data sources [65]; the most crude measure of the data is the standard to which the data must be harmonized to reduce the occurrence of missing data.

Approaches for how outcomes are measured must be equally considered. For instance, the same clinical outcome of interest may be captured by International Classification of Diseases – Ninth Revision (ICD-9) codes, objective lab-based measures, or validation procedures that involve a central adjudication committee; each method has its own sensitivity and specificity. Further, detection of disease outcomes is likely to be different among a group of HIV-infected individuals receiving clinical care compared to HIV-uninfected adults in the general population, potentially biasing exposure-outcome associations in either direction. Careful consideration must be taken when deciding whether to include studies without validation processes for age-related comorbidity outcomes. Systematic under ascertainment of outcomes among existing data sources can threaten the validity of the treated HIV effect.

Harmonization of data across administrative, clinical, or interval cohort studies can be challenging; however, often the diversity in structures provide complementary information [66]. Establishing a list and definitions of basic variables needed from all potential existing data sources is a first-step to this harmonization challenge. Understanding not only the nuances between the variables collected in each study, but also the data collection and quality assurance of the variables within each existing data source is essential. Further, understanding the steps taken to assess data quality during phases of data collection, entry, and storage requires a detailed understanding of each study's protocol and interaction with study team personnel [67]. Although potential data management and analytic techniques may mitigate some measurement error, study inferences can still be impacted by heterogeneity in underlying data architecture [65].

Inference considerations

Merging multiple existing data sources may limit control for important confounders. In addition to the serious threat of unmeasured confounders, the most crude measure of each measured confounder will typically be the measure used in analysis across studies; residual confounding is likely to persist after adjustment. To reduce the influence of confounders, selection methodology using propensity and prognostic score methodologies [68, 69] can be employed to ensure the uninfected adults selected from the pool are similar to HIV-infected adults. Propensity and prognostic score methodologies cannot account for unmeasured variables, emphasizing the importance of discussing the pros and cons of these methodologies [70].

Studies using appropriate uninfected comparison groups and analytic techniques to preserve the internal validity of their inferences have demonstrated comorbidities occurring at the same ages (not younger) and with attenuated increased risk in PLWH compared to uninfected adults. The difference in the age distributions of PLWH and the general population has led to numerous studies reporting a younger age at diagnosis of age-related comorbidities. As described by Shiels and colleagues [71], this misleading observation can be the product of the differences in the age distribution in the HIV-infected and general populations, arguably the most powerful confounder of age-related diseases. Other studies have found no difference in age at diagnosis after accounting for differences in the age distribution [72]. A study conducted in the VACS suggests that HIV-infected adults have a

48% increase in the risk of myocardial infarction after adjustment for traditional risk factors [20**]; similarly, a study by Kaiser Permanente California suggests a 44% increase in risk [21**]. This effect is attenuated from previously published estimates of a minimum two-fold increase in risk among HIV-infected persons compared to the general population [73–76].

It is also important to be aware of differences in the amount of data collected between these two populations [66]. HIV-infected individuals participating in clinical cohort studies are being followed as a result of their HIV status. Caution must be taken when interpreting risk of comorbidity development, as this may be a result of increased opportunity for comorbidity detection among HIV-infected adults.

IDENTIFYING AND SECURING SECONDARY DATA SOURCES OF UNINFECTED ADULTS

To initiate a search of secondary data sources to create a pool of uninfected adults, one should first consider the outcome of interest and identify studies that will comprehensively allow for this outcome to be collected. Once known, studies can be pursued with the following preliminary steps:

- identification of potential existing studies through PubMed searches of the outcome of interest
- use of Internet search engines to identify existing studies described on academic institution websites
- search of the website for the Inter-university Consortium for Political and Social Research and similar consortiums relevant to the outcome of interest (this consortium maintains a data archive of over 500,000 files of social science research [77]).
- search of websites of specific funding agencies associated with the outcome of interest. For example, the National Heart, Lung, and Blood Institute's (NHLBI) Biologic Specimen and Data Repository, otherwise known as BioLINCC, promotes public use of over 100 NHLBI funded studies, including well-established longitudinal interval cohorts, such as the Multi-ethnic Study of Atherosclerosis (MESA), Framingham Study, and the Atherosclerosis Risk in Communities (ARIC) Study [78]. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) maintains a Central Repository that includes clinical data and documentation for NIDDK-funded studies, biospecimens collection, and a collection of genotyping data from GWAS and sequencing investigations [79]
- asking colleagues for suggestions of potential existing sources

Once an exhaustive inventory of potential data sources is compiled, the next step is to articulate the relevant source population at-risk of the outcome of interest, the nature of the data desired (for example, administrative or observational), and confounders that must be measured. These characteristics, as well as a crude rank of estimated cost in dollars and time (such as "high," "medium," and "low") to secure potential existing data from each source, will help narrow down candidate sources.

Once a feasible number of candidate sources have been identified, begin reaching out to the sources to secure data. As data are secured, initial tasks require becoming versed in protocols and procedures, determining the completeness of the data, and verifying variable definitions. Publicly available protocols, questionnaires, documentation, and data dictionaries are also important tools.

Following efforts to harmonize data and compile a pool of potential uninfected adults, selection methodology can be employed to increase the similarity between PLWH and the selected uninfected comparison group. Assistance from a statistician would be prudent to ensure the success of the applied selection methodology.

The process to produce a pool of uninfected individuals based on existing data and employ selection methods to increase the similarities among PLWH and the uninfected comparison group will require a lot of time, attention to reproducibility [80], and engagement of experienced data managers, statisticians, and scientific investigators; these efforts are essential, however, to understanding the treated HIV effect in the limited funding environment.

CONCLUSION

In summary, identifying the appropriate comparison group for HIV-positive individuals is a challenging but necessary effort. Establishing an ideal comparison group based on existing data sources is likely to be a feasible approach in an environment of finite resources compared to establishing cohorts of uninfected adults. Overcoming threats to validity through careful examination of existing data, aims to enlighten the understanding the treated HIV effect on age-related comorbidities. Research using the appropriate comparison group and analytic techniques to control for confounding can inform future intervention strategies to mitigate age-related comorbidity occurrence, through strategies such as age-specific screening guidelines or conventional risk factor management.

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Abbreviations

ART	antiretroviral therapy
HIV	human immunodeficiency virus
HCV	hepatitis C
PLWH	persons living with HIV
B2DK	Big Data to Knowledge

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KEY POINTS

1. To isolate the effect of treated HIV on age-related comorbidities, appropriate uninfected comparison groups are needed; it should not be assumed the general population is an appropriate comparison group
2. Identification and careful selection of existing data sources of uninfected adults followed for age-related comorbidity outcomes may fill this need.
3. Sound epidemiological principles for characterizing the source and potential selection biases in the choice of comparator populations, the accuracy and consistency of measurements of age-related outcomes, and inferential techniques that account for important confounders to ensure internal validity must all be considered when using existing data sources for the uninfected comparison population.