



Special Article

The Changing Science of HIV Epidemiology in the United States

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In 1984, a large prospective study of the natural history of human immunodeficiency virus (HIV) infection, the Multicenter AIDS Cohort Study (MACS), was established; 10 years later, the Women's Interagency HIV Study (WIHS) was launched. Motivated by the merger and redesign of these long-standing HIV cohort studies in 2019, we review ways in which HIV epidemiology in the United States has transformed over the lives of these studies and how this evolution has influenced planning for enrollment and follow-up. We highlight changes that have occurred in the 3 major domains that are central to epidemiologic science: changes to key populations at highest risk for HIV, refinements in measurement and shifts in the outcomes of interest, and a new era in the tools and approaches that epidemiologists use to synthesize evidence from measurements made on populations. By embracing foundational principles with modern methods, the epidemiologic approach of analyzing the causes and distributions of diseases in contemporaneous populations will continue to advance HIV science over the next decade.

HIV epidemiology; inference; measurement; population

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study; MWCCS, Multicenter AIDS Cohort Study/Women's Interagency HIV Study Combined Cohort Study; PLWH, people living with human immunodeficiency virus; WIHS, Women's Interagency HIV Study.

In 1984, the Multicenter AIDS Cohort Study (MACS) (1, 2) was established to investigate the epidemiology of what soon thereafter became known as human immunodeficiency virus (HIV) infection. The study enrolled men who have sex with men, reflecting the group at highest risk at the time, and focused on acquired immunodeficiency syndrome (AIDS) as a primary outcome (3). Ten years later, a prospective cohort study among women, the Women's Interagency HIV Study (WIHS) (4) was established using similar methodology. With continuous support from the National Institutes of Health and the substantial contributions from thousands of participants, operational staff, and research scientists, these 2 multicenter studies have been the source of more than 2,400 peer-reviewed publications and have made seminal contributions to the understanding of both the natural and treated history of HIV infection in the United States (5).

In 2019, the 2 cohort studies were merged into a single new prospective study: the MACS/WIHS Combined Cohort

Study (MWCCS) (5). With 13 clinical sites across the United States, as well as a single data analysis and coordination center located at Johns Hopkins University (Baltimore, Maryland), the study research team worked for more than a year to define the research goals and methods of the new MWCCS. The study design and methods that emerged reflect dramatic changes that have occurred in the epidemiology of HIV in the United States since the original MACS and WIHS studies were designed. HIV in the United States now affects a range of key populations, and its epidemiology is influenced by both a spectrum of prevention efforts and the successes of the HIV care continuum (6). Among people living with HIV (PLWH), mortality has declined significantly; however, life expectancy remains lower relative to the general population (7), reflecting the impact of HIV as well as the risks among the vulnerable and disadvantaged populations at highest risk for acquiring it. Now that HIV is managed more as a lifelong chronic disease, it is important to understand whether those living with HIV are at increased risk for other comorbidities,

particularly as the projected age distribution of the HIV-infected population in the United States continues to shift toward older adults (8).

A complete review of the ways in which HIV epidemiology has changed since the MACS and WIHS were established could fill volumes. Here we focus on selected ways in which the science of HIV epidemiology in the United States has evolved and influenced the design of the new MWCCS. We structure the paper along the lines of 3 key domains that are central to the “epidemiologic approach” (9): populations, measurement, and inferences made via population comparisons.

POPULATIONS RELEVANT TO HIV EPIDEMIOLOGY

The story of the earliest days of the US HIV epidemic is well documented (10, 11). At the time the MACS was planned (before the antibody test for HIV was available), the investigators focused on recruiting men who have sex with men, representing the group with highest risk, to permit meaningful longitudinal inquiry in a reasonable period of time (1). The subsequent discovery of the virus enhanced understanding of its routes of transmission and allowed for a better picture of how HIV was acquired among other populations. In 1996, women accounted for 20% of AIDS cases, up from 7% reported in 1984 (12). By the late 1990s, there was a greater recognition of the spread of HIV to minority populations. In 1999, African Americans, despite representing only 13% of the US population, accounted for 49% of US AIDS-related deaths, a rate 10 times that for white Americans (13). The populations most vulnerable to HIV are those with unequal opportunities and/or social exclusion, who have poor access to services coupled with the overlapping epidemics of substance abuse and incarceration. Incarcerated persons who inject drugs, for example, have 6 times the prevalence of HIV compared with noninjecting prisoner populations (14). The MWCCS brings together 2 cohorts, one of men (MACS) and one of women (WIHS), and complements other studies of HIV, such as those focused on persons living with drug use (15), transgender adults (16), or pediatric HIV (17).

As the MWCCS considers expansion and further enrollment, the characteristics of those eligible for inclusion in the study is of keen interest. Two important considerations include enrollment of individual who are not infected with HIV and representativeness versus homogeneity.

Enrolling HIV-uninfected individuals

The MACS and WIHS enrolled men and women who were free of HIV infection at enrollment. These individuals contribute in two ways. First, acquisition of HIV at a subsequent study visit can be determined. By providing an anchor for the time of infection, studies of the antecedents of acquisition of HIV can be undertaken, as can studies of the natural history of disease without the impact of bias (18). However, in the current era, when behaviors have changed and prevention strategies are becoming increasingly effective (19), the occurrence of individuals with defined

windows of HIV acquisition will be rare. For example, infection is now estimated at 0.71% per year among men who have sex with men overall, and 1.8% annually among black men who have sex with men (20), and risk among women is lower (0.20% per year in the WIHS). Given the small number of new seroconversions that will occur without a substantially larger enrollment, the MWCCS will not be suited to efficiently study factors associated with HIV acquisition in the United States, pointing to the need for alternative study designs (e.g., case-control studies).

A second consideration for including HIV-uninfected individuals has been the inclusion of a comparison group for the PLWH. MACS and WIHS recruitment efforts for individuals free of HIV have attempted to minimize differences from PLWH by using specified eligibility criteria (e.g., reported high-risk behaviors) and/or recruitment from similar geographic locations (e.g., sexually transmitted diseases clinics). However, epidemiologic confounding might occur because uninfected adults might be different in terms of various factors that we cannot control for at the time of recruitment (e.g., comorbidities and demographic, lifestyle, and socioeconomic factors). These differences must be accounted for in the design and analysis in order to produce valid inferences of the impact of treated HIV on age-related comorbidities (21).

Representativeness versus homogeneity

The MWCCS aims to be relevant to the contemporaneous epidemiology of HIV in the United States. The degree to which new enrollment should reflect the underlying population structure of the US epidemic is not obvious. We could use national statistics as the basis for enrollment. For example, male persons continue to account for 81% of all diagnoses of US HIV infection among adults and adolescents, predominantly among gay and bisexual men. (8) Female persons account for 19% of all diagnoses, predominantly through heterosexual contact. People of color remain at elevated risk of HIV infection in the United States, with blacks representing 43% of new HIV infections and Hispanics representing another 25% of new infections (22). Infection rates are highest in the South and Northeast.

On the other hand, the MWCCS is a research study with a broad set of specific aims that focus on heart, lung, blood, and sleep comorbidities as well as other conditions known to co-occur with HIV disease, including mental and neurologic illnesses, diabetes, kidney failure, liver diseases, and certain cancers. The study is striving to characterize the occurrence and predictors of these conditions with sufficient statistical power. Broad inclusion criteria for reenrollment could result in recruitment of key populations, such transgender people, people who inject drugs, and prisoners, whose epidemiology might be dissimilar from the majority of the cohort. While understanding HIV among these populations is of high importance, the overall statistical strength of the cohort might be diminished if only small numbers of persons with these characteristics are enrolled.

MEASUREMENT ISSUES IN HIV

Measurements at the biological level

There have been dramatic improvements in how we measure HIV infection, which is important because HIV viral load measurement is a key indicator of response to treatment, transmission risk, and risk for disease progression. While current ART regimens can suppress HIV, long-lived viral reservoirs remain; hence lifelong therapy is required to avoid HIV reactivation (23). The ability to precisely measure HIV viral load is critical to track the true size of the viral reservoir and to evaluate strategies for HIV remission.

Recent advances have allowed more accurate measurement of the viral reservoir, including the ability to detect single RNA or DNA molecules (24) as well as nanotechnology methods to analyze 1 provirus at a time (25). These continuing laboratory advances in measurement provide opportunities for new epidemiologic questions about HIV transmission, treatment, and reservoir. The MWCCS provides an optimal environment in which to assess the clinical importance of such new measurements by linking them to clinically relevant outcomes.

Measurements at the individual/clinical level

While lifespan and quality of life have increased for PLWH, there is increasing awareness that HIV-infected individuals are at increased risk for a range of outcomes not previously appreciated. (26) The outcomes we measure among PLWH have changed as a range of chronic morbidities has been shown to be elevated among HIV-infected individuals, including many outcomes not historically seen among individuals with HIV who, early in the epidemic, died prior to developing these age-related outcomes. Examples include cardiovascular disease (27, 28), pulmonary disease (29), neurocognitive disease (30), diabetes (31), and cancer (32, 33). Low-level viremia, even among suppressed patients, might be driving an inflammatory response that could be contributing to these conditions.

Underscoring the co-occurrence of HIV and many other comorbidities, a recent US study of PLWH receiving health care showed high prevalence of hypertension (31%–76%), hyperlipidemia (22%–50%), and endocrine disease (22%–54%) (31). Aging with HIV poses a set of challenges that includes decreased physical function, increased frailty, and increased incidence of geriatric conditions, including multimorbidity. As the population of PLWH ages, the prevalence of comorbidity will continue to increase (31).

As noted above, the MWCCS will focus on HIV-related comorbidities and aging with HIV. The study aims to maintain a rigorous process for complete assessment and adjudication of outcomes of clinical importance. Our criteria for an outcome to be routinely obtained and validated are: 1) the outcome should be clinically important for the MWCCS research aims; 2) the outcome should have clear criteria for validation of the diagnosis; and 3) those criteria should be ascertainable from a standard medical record (or testing done as part of the study). The outcomes of interest include hospitalizations, AIDS-defining conditions, cardiovascular

outcomes, chronic obstructive pulmonary disease, malignancies, anal dysplasia, sepsis, pneumonia, and fractures. Further, one of the design strengths of the MWCCS is our ability to launch protocols for measures that are not routinely collected in clinical care. This is reflected in the priorities of our study to collect echocardiograms for characterizing cardiovascular disease, pulmonary function tests for precursors of pulmonary disease, the Composite International Diagnostic Interview (CIDI) responses for understanding mental health, measurements of physical functioning and frailty as precursors to disability, and neurocognitive batteries to examine motor and neurocognitive abnormalities. Understanding subclinical manifestations of HIV allows us to extend the science of HIV.

Measurements at the population level

As of 2008, all 50 states, the District of Columbia, and 6 US-dependent areas had implemented confidential name-based reporting of HIV infection. In 2017, the Joint United Nations Program on HIV/AIDS agreed upon a set of HIV epidemic transition metrics to help measure progress in reducing the public health burden of HIV (Table 1). Among PLWH in the United States who complete each step of the HIV care continuum (i.e., are diagnosed, retained in care, and adhere to ART), 85%–90% of treated PLWH achieve viral suppression (6, 34). However, only approximately 86% of all PLWH in the United States know that they are HIV-infected, (34) and not all engage in care, so the proportion of all infected individuals that actually achieve viral suppression is much lower (35, 36). This highlights remaining needs for improvement in each step of the HIV care continuum (35, 36) (Table 2).

Although the MWCCS is an observational study, and as such we do not specifically offer treatment, we closely monitor these variables among our participants, including reasons for missed health-care visits and barriers to perfect ART adherence. Our large database, linking back as far as 35 years, will enable us to investigate and track predictors of these measures on an individual basis.

INFERENCES FROM POPULATION COMPARISONS

The scientific and public health response to HIV from the early 1980s through today benefited from the important advances in epidemiologic science that had been accumulating for more than a century (37). There are numerous examples in HIV that illustrate the “traditional” path for epidemiologic inquiry that is often taught in our introductory courses (i.e., initial observations from case studies and ecological analysis, followed by more rigorous observational studies and, when possible, randomized clinical trials, followed by further studies evaluating effectiveness and feasibility). This includes the evolving evidence of the benefits of early initiation of antiretroviral therapy for preventing death (38, 39), male circumcision in reducing the risk of HIV acquisition (40, 41), and the use of combination approaches for the prevention of HIV transmission (42–44).

Table 1. Comparison of Estimated Key Epidemiologic Measures of the Human Immunodeficiency Virus Epidemic, Compared With the Joint United Nations Programme on HIV and AIDS 2020 Benchmarks, United States and Globally

Measurement	Calculation	UNAIDS Benchmark	Current US (2016–2017) ^a	Current Global (2016–2017) ^b
<i>Measures of Disease Burden and Treatment</i>				
PLWH	No. of known PLWH		991,447 ^c	36,900,000
	No. of estimated PLWH (including those not diagnosed)		1,122,900 ^c	
<i>Using Antiretroviral Therapy</i>				
PLWH	No. of PLWH currently on treatment		700,000	21,700,000
% PLWH accessing ART	% of PLWH currently on treatment		62%	59%
<i>UNAIDS Goals Related^{a,d}</i>				
Know HIV serostatus	% PLWH who know status	90%	86%	75%
On treatment	% on treatment among diagnosed with HIV	90%	72%	79%
	% on treatment among all PLWH			59%
Virally suppressed	% virally suppressed among those on therapy	90%	85% ^a	81%
	% virally suppressed among all PLWH		60% ^a	47%
<i>Measures of Epidemic Spread and Future Disease Burden</i>				
New HIV infections	No. of new HIV cases per year		38,281 ^c	1,800,000
HIV incidence rate	No. of new HIV cases per 1,000 population per year	To be set locally	0.12 ^c	0.3 ^e
HIV incidence reduction (2010–2016)	Percentage reduction in number of new HIV cases	75% by 2020	8–11% ^f	12% ^e
Incidence:prevalence ratio	(No. of new HIV cases per year)/(No. of PLWH aged ≥15 years in same pop), × 100	0.03	0.04 ^g	0.05
<i>Measures of Care Delivery and Mortality</i>				
Incidence:mortality ratio	(No. of new HIV cases per year)/(No. of PLWH aged ≥15 years who die per year), × 100	1.0	3.0 ^h	1.7 ^e
Mortality rate	No. of deaths per 1,000 people diagnosed with HIV per year		0.05 ^c	
AIDS-related mortality rate	No. of AIDS-related deaths per 1,000 population per year	To be set locally		25.5
AIDS-related mortality reduction (2010–2016)	Percentage reduction in AIDS-related deaths	75% by 2020	18% ^{a,i}	32% ^d

Abbreviations: AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; HIV, human immunodeficiency virus; PLWH, people living with human immunodeficiency virus; UNAIDS, Joint United Nations Programme on HIV and AIDS.

^a Centers for Disease Control and Prevention (34).

^b UNAIDS (71).

^c Centers for Disease Control and Prevention (72).

^d UNAIDS (73).

^e Ghys et al. (74).

^f Bonacci and Holtgrave (75).

^g Centers for Disease Control and Prevention (76).

^h Centers for Disease Control and Prevention (77).

ⁱ Percentage reported here for the US mortality reduction is the reduction in the overall death rate 2010–2015 among persons with diagnosed HIV infection, not the reduction in AIDS-related deaths.

Since the beginning of the epidemic, there have been notable changes in the tools and approaches that epidemiologists use to synthesize evidence from measurements made

on populations and draw scientific inferences. HIV has been an important incubator for these approaches as well as a beneficiary. We highlight 3 epidemiologic areas that are

Table 2. Status at Each Step in the Human Immunodeficiency Virus Care Continuum in the United States, 2019

Step in HIV Care Continuum	Status
Diagnosis	14% of HIV-infected individuals are not aware of their serostatus (34)
Linkage to care	85% of PLWH are now linked to care within 3 months of diagnosis (34), up from 59%–80% several years ago (35, 36)
Retention in care	40%–57% of diagnosed PLWH are retained in care (34, 36)
ART adherence	86% of PLWH in care report being adherent, but estimates including undiagnosed PLWH and those not engaged in care are closer to be 24–37% (78)
Viral suppression	85%–90% of treated PLWH now achieve viral suppression. However only approximately 60% of diagnosed PLWH are virally suppressed (6, 34), suggesting that its approximately 51% when including undiagnosed PLWH (79)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PLWH, people living with human immunodeficiency virus.

particularly relevant to future observational studies that have shown significant evolution and have influenced our design of the MWCCS.

New options for traditional study designs

“Traditional” interval cohort studies, like the MWCCS, that implement protocols that specify the timing and type of data collection have been a mainstay of epidemiologic inference for over 80 years (45). With the rise of electronic medical and administrative records, clinical cohort studies have arisen to capitalize on the opportunity to utilize these data for epidemiologic inference (46). HIV study has benefited tremendously with the establishment of studies using clinical populations and measurements, such as the single-site Johns Hopkins Clinical Cohort Study (47) as well as multicenter studies such as the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort Study (48).

A further development has been the growth of “collaborative” and pooled studies (49). These “supercohorts” exceed traditional meta-analyses of published studies and aggregate individual-level data from multiple cohort studies to provide a powerful design that facilitates research that would otherwise not be possible. These designs might have increased power for rare outcomes, rare exposures, and analyses of specific subgroups, as well as greater potential for drawing inferences from study populations that are more diverse in person, place, and time. The MWCCS, for example, participates in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (50), which represents one region of the “International Epidemiologic Databases to Evaluate AIDS (IeDEA)” project (51).

For the MWCCS, the selection of appropriate study groups is of paramount importance for valid inferences. In many studies of individuals with HIV on therapy, it is necessary to collect data from both untreated PLWH and HIV-uninfected persons to properly distinguish the consequences of HIV infection alone from the consequences associated with both HIV infection and therapy. Disentangling HIV disease and HIV treatment in the United States is now virtually impossible: The number of PLWH who have

not yet initiated antiretroviral therapy is increasingly small given guidelines for early initiation after diagnosis. Of more importance from an epidemiologic perspective, confounding by indication (52) is strong; the characteristics of individuals not on therapy (i.e., they typically are healthier) compared with those who might have discontinued therapy (e.g., due to adverse events) complicate comparisons.

Refinement and expansion of statistical tools

Prospective cohort studies like the MWCCS offer the ability to collect longitudinal data for the study of individual changes over time as well as the opportunity to implement nested studies for the purpose of elucidating factors related to the occurrence of important events (e.g., fast or slow progression, development of particular comorbidities, success or failure following initiation of therapy). Analytical techniques to handle the within-individual correlation that arises from such measurements, (53) missing and censored responses (54), nonlinear patterns (55), and even all of these issues together (56) are now part of the standard toolkit for statistical analysis of data from HIV studies.

Further, the toolkit for time-to-event data has also been expanded considerably with a full armamentarium of parametric, semiparametric, and nonparametric approaches that allow for handling a variety of issues that arise in HIV studies, including internal and external time-dependent covariates (57), left and right censoring (58), and multivariate survival outcomes (59). Further, when studying nonfatal outcomes, death is a principal competing risk that precludes the occurrence of age-related comorbid events. In competing-risk settings, it is well known that the complement of the standard Kaplan-Meier survival estimates (with competing events treated as censored observations) will overestimate the cause-specific cumulative incidence. For these situations, it is important to integrate approaches that have been developed for competing risks (60, 61).

Causal Inference

One of the most profound differences in how epidemiologists approach inference in the last two decades is through

the increased refinement of causal inference concepts and tools. Causality is a vital concept throughout all of science, and philosophers and scientists have been working for centuries on refining the definitions and characteristics of “cause” (62). More recently, there has been a recognition that causal concepts such as “confounding,” “mediation,” and “randomization” are distinct from statistical concepts (63), and causal inference has grown into a rigorous independent field. Concomitant with the rise of these concepts, a new set of analytical tools is now available to modern epidemiologists (64). The counterfactual/potential outcomes framework has been particularly important for development of tools that are alternatives to multivariable regression, such as propensity scores, marginal structural models, and g-computational approaches. Observational HIV studies have been a particularly strong setting for the development and refinement of these methods (65, 66).

HOW CAN EPIDEMIOLOGY REMAIN CONSEQUENTIAL FOR HIV SCIENCE?

In the past decade, the question of consequentiality (67) has arisen within the discipline. The above review provides strong evidence that epidemiology has been consequential for HIV science in leading to improvements in health.

Looking toward the next 25 years, we believe that epidemiology will continue to have an important impact through focus on the 3 essential domains used as a framework for this review (9). The epidemiologic frameworks for characterizing the hierarchy of target, source, and study populations, as well as the tools to evaluate and address selection between them, continues to be critical. These approaches will be increasingly relevant and in need of further refinement as we expand our notion of populations at risk for HIV. Future epidemiologic research will increasingly use populations constructed from those individuals who contribute data to repositories of electronic health records, social media, and search engines (68).

The type and level of measurement relevant to those at risk for HIV and PLWH has expanded considerably, and assessing measurement validity and reliability will be key contributions by epidemiologists. Studying HIV will require the adaptation of evolving tools to a host of new measurements, such as those that reflect the social environment as well as those derived from wearable devices and mobile phone applications. For example, e-health apps were shown in recent randomized trials to increase HIV knowledge and motivate safer behaviors among men who have sex with men, as shown by lower incidence of sexually transmitted infections (69, 70). Finally, epidemiologists will need to be at the forefront for adapting these methodologies to unique questions in HIV science and continuing to assess their accuracy, precision, and effectiveness.

From the identification of cases through surveillance to randomized trials of new preventive and therapeutic interventions, much of the success reported over the last 25 years has benefited from, if not been a direct result of, robust use of the epidemiologic approach. The epidemiologic approach of analyzing the causes and distributions of diseases in

populations to identify and implement new ways to prevent and control disease will continue to inform HIV science in the future.

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