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## Invited Commentary

# Invited Commentary: A Landmark Study Launched in a Public Health Maelstrom

**Eric A. Engels*, Charles S. Rabkin, and James J. Goedert**

* Correspondence to Dr. Eric A. Engels, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6E226, Bethesda, MD 20892 (e-mail: engelse@exchange.nih.gov).

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The acquired immune deficiency syndrome (AIDS) epidemic was first recognized in 1981, and it quickly became a public health emergency. In a 1987 paper in the *American Journal of Epidemiology* (*Am J Epidemiol*. 1987;126(2): 310–318), Richard Kaslow et al. described the launch of the Multicenter AIDS Cohort Study (MACS), a cohort study of homosexual men in 4 US cities, the purpose of which was to better understand the natural history of AIDS and its determinants. The MACS enrolled participants through a range of community contacts. These efforts facilitated rapid recruitment, but given the targeted approaches, participants tended to comprise high-risk social networks. At baseline, 4%–26% of participants at the 4 sites reported having a sexual partner who had developed AIDS. Kaslow et al. also described baseline testing for the causative agent of AIDS, the human immunodeficiency virus (HIV). HIV seroprevalence was remarkably high, ranging from 11%–26% across age groups in Pittsburgh to 38%–53% in Los Angeles. The major turning point in the epidemic occurred in 1995–1996 when combination antiretroviral therapy was introduced, effectively blocking HIV replication and markedly reducing AIDS morbidity and mortality. The MACS cohort continues to be followed actively 3 decades after its launch and has proven to be an important resource for information on HIV infection and AIDS.

AIDS; epidemic; HIV

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study.

In the spring of 1981, astute clinicians recognized the significance of an outbreak of life-threatening opportunistic infections and malignancies among otherwise healthy young adults in the United States, most of whom were urban homosexual men. The Centers for Disease Control and Prevention (then the Centers for Disease Control) summarized these cases (1, 2), and a *New England Journal of Medicine* paper by Michael Gottlieb et al. garnered widespread attention (3). Immunologic evaluation revealed that affected individuals had profound deficiency of cell-mediated immunity—specifically, a marked depletion of CD4+ T-lymphocytes (3, 4).

The next year was charged with urgency and uncertainty, with additional reports of cases in heterosexual injection drug users and Haitian immigrants to the United States (5, 6). Soon, the Centers for Disease Control and Prevention presented evidence of a likely blood-borne virus based on 3 cases among geographically dispersed patients with hemophilia A (7). The Centers for Disease Control and Prevention worked with members of the public health community and the National Institutes of Health to develop a surveillance definition for what became known as the acquired immune deficiency syndrome (AIDS) (8). The early history of this rapidly expanding, highly lethal, and bewildering epidemic is well described in Randy Shilts's engaging front-line perspective, *And the Band Played On* (9).

Immediately after the initial recognition of AIDS, epidemiologists in the United States, Denmark, and the Netherlands established cohort studies of homosexual men, injection drug users, and people with hemophilia (10–12), which eventually contributed substantially to the identification of the determinants and natural history of AIDS. However, Richard Kaslow and Alfred Saah of the extramural program of the National Institute of Allergy and Infectious Diseases (part of the National Institutes of Health) recognized that these initial cohorts would be too small to detect biologically relevant associations that were modest in magnitude. Their insights and efforts led to

establishment of the Multicenter AIDS Cohort Study (MACS), which was launched in 1984.

The rationale and design of the MACS were detailed by Kaslow et al. in an important paper published in the *American Journal of Epidemiology* in 1987 (13). The overarching goals of the MACS were to "1) describe the early pathophysiologic events in the course leading to AIDS-related conditions [and] AIDS…, 2) define and quantify the factors suspected of initiating or modulating the immunopathologic process leading to AIDS…, [and] 3) provide access to a repository of biologic specimens with detailed epidemiologic data for investigators with promising ideas for research" (13, p. 311). MACS investigators sought to enroll approximately 1,000 homosexual men in each of 4 US urban areas (Baltimore, Maryland/Washington, DC; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania). Participants were to be evaluated semiannually for at least 2–3 years. Baseline and follow-up questionnaire data and biospecimens were collected.

In setting up the MACS, the investigators recognized that homosexual men were a key population to study because the high attack rate of AIDS in this group would provide a sufficient number of cases for epidemiologic evaluations. However, it was also clear at the outset that there was no straightforward way to identify a completely representative sample of all homosexual men, given the private nature of sexual behaviors and the societal stigma associated with homosexuality. Moreover, the public health urgency in establishing the cohort and addressing the AIDS crisis argued for expedience. MACS researchers therefore reached out to enroll men through a wide range of contacts with community activists, social venues, and medical professionals who provided care to homosexual men. These efforts facilitated rapid recruitment, but given the targeted approaches, participants were not randomly selected and tended to be part of social networks.

Moreover, as a result of the recruitment strategy, the baseline characteristics of MACS participants, which were described by Kaslow et al. (13), reflected a high degree of sexual activity and thus high risk of acquiring the infectious agent of interest. At the 4 separate MACS sites, 21%–35% of the men had had 500 or more homosexual partners over their lifetimes, 83%–90% had engaged in receptive anal intercourse, 40%–67% had a history of gonorrhea, 11%–31% had a history of syphilis, and 53%–72% had evidence for prior hepatitis B virus infection. Most worrisome, 4%–26% reported having had a sexual partner who had developed AIDS. Thus, an admitted design tradeoff of the MACS involved sacrificing population representativeness in favor of efficient recruitment of a large number of high-risk individuals.

In 1983–1984, around the time that the MACS began recruitment, human immunodeficiency virus (HIV) was discovered as the causative agent of AIDS by Luc Montagnier at the Institut Pasteur in Paris and Robert Gallo at the National Institutes of Health (14, 15). The Gallo laboratory developed a prototype blood test to detect anti-HIV antibodies (16). The paper by Kaslow et al. includes a description of baseline HIV test results of MACS participants (13). HIV seroprevalence was remarkably high, ranging from 11%–26% across age groups in Pittsburgh to 38%–53% in Los Angeles.

Kaslow et al. noted 2 key ethical issues that they considered when designing the MACS (13). First, because of the sensitive information collected regarding sexual behaviors, use of illicit drugs, and health, it was especially important for the researchers to ensure the participants' confidentiality. Second, the investigators were reluctant to provide participants with the results of immunologic assays (e.g., CD4 counts) and HIV antibody testing because of concern about inducing fear and despondency. As the researchers wrote, "In some centers, specific test results were made available only upon request of the participant and then only through qualified study staff… In others, results were provided more routinely but were likewise accompanied by careful explanation" (13, p. 314). In the early years of the epidemic, there was no treatment for HIV, and a diagnosis of AIDS was usually a death sentence. Indeed, by January 1992, 40% of the men who had had prevalent HIV infection documented at entry into the MACS had developed AIDS, and the median survival time after development of AIDS was only 16 months (17). These horrific statistics illustrate both the wisdom of Kaslow et al. in establishing the MACS as a scientific resource and the devastating toll of this disease on homosexual men and other vulnerable communities.

The major turning point occurred in 1995–1996, when more than a decade of basic science research yielded accurate assays to detect and quantify HIV in blood (18, 19) and combinations of antiretroviral drugs that effectively blocked HIV replication, enabling partial recovery of immunity and marked reduction in HIV-related morbidity and mortality (20). When the MACS began and the paper by Kaslow et al. was written, these developments were unforeseen and a decade in the future.

Remarkably, the MACS cohort continues to be actively followed 3 decades after its launch. The study has proven to be an important resource for elucidating HIV infection and AIDS, attesting to the vision of Kaslow and Saah and the productivity of the MACS team and collaborating researchers. As of June 2016, the MACS has led to 1,442 research publications (21). Moreover, 841 papers abstracted in Web of Science (accessed January 3, 2017) cite Kaslow et al. (13), and 4 of these papers have in turn been cited more than 1,000 times each:

1. Fahey et al. (1990), in which researchers validated serum levels of neopterin and β2-microglobulin, in combination with the CD4 T-cell count, as biomarkers of AIDS risk (22);
2. Dean et al. (1996), in which they described the profound protection against HIV infection by a genetic variant of a co-receptor for HIV on CD4 T-cells (23);
3. Mellors et al. (1996), in which the authors identified the level of HIV circulating in plasma (i.e., HIV viral load) as a strong prognostic indicator (24); and
4. Mellors et al. (1997), in which they established the combined measurement of HIV viral load and CD4 T-cell count as a highly accurate predictor of prognosis (25).

In additional important papers, researchers described receptive anal intercourse as a strong risk factor for the acquisition of HIV (26), estimated the impact of effective HIV therapy on the risk of AIDS and death (27), and characterized serum

markers of inflammation and immune activation as risk factors for AIDS-related lymphoma (28).

With the availability of effective HIV treatment, life expectancy has greatly increased (29). However, there remain substantial health issues for this population, reflecting the adverse effects of an imperfectly restored immune system and the high prevalence rates of smoking and substance abuse, coinfection with viruses that cause liver disease and cancer, and poverty and poor access to medical care. HIV epidemiology has evolved to focus on identifying barriers to HIV treatment and developing strategies for the prevention and treatment of chronic illnesses. In recognition of the need for data from a large and diverse sample of the population with HIV, the National Institutes of Health has encouraged the creation of regional consortia that pool together data from multiple cohort studies, including the North American AIDS Cohort Collaboration on Research and Design, to which the MACS contributes.

Over the 30-year period during which AIDS transitioned from a poorly understood, consistently fatal plague to a complicated but manageable chronic disease, the MACS has continued to play an important role in epidemiologic research. The article by Kaslow et al. (13) can still profitably inform epidemiologists today as they consider tradeoffs that are sometimes involved among public health urgency, patient priorities, and scientific inquiry. Moreover, the Kaslow paper illustrates the value of wide engagement with multiple stakeholders and careful planning for collaboration, which are required for long-term research success.

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Author affiliation: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Eric A. Engels, Charles S. Rabkin, James J. Goedert).

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