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The multicenter AIDS Cohort Study, 1983 to …

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SUMMARY

The Multicenter AIDS Cohort (MACS), initiated in 1983 at the Johns Hopkins School of Public Health, the University of Pittsburgh School of Public Health, Northwestern University School of Medicine, and the UCLA School of Public Health, continues to conduct studies and publish key papers on the natural history of untreated and treated HIV infection in 6972 men-who-have-sex-with-men. Through May 2011, 1,490,995 specimens have been collected, 86,883 person-years of data accrued and 1195 scientific papers published in international journals.

Keywords

HIV; AIDS; Cohort

The Multicenter AIDS Cohort Study (MACS)[1] was initiated in 1983 when four investigators [Roger Detels (UCLA), John Phair (Northwestern University), Frank Polk (Johns Hopkins University) and Charles Rinaldo (University of Pittsburgh)], funded by the National Institute of Allergy and Infectious Diseases to conduct cohort studies of men who have sex with men, agreed to join forces and collaborate to investigate the natural history of acquired immunodeficiency syndrome (AIDS). In 1986, they were joined by Alvaro Muñoz (Johns Hopkins University) who directed the newly funded data coordinating centre, now directed by Lisa Jacobson. Twenty-eight years later (2011), the MACS continues to investigate the natural history of untreated and treated human immunodeficiency virus (HIV)/AIDS in a cumulative total of 6972 men in the four centres.

From the original five investigators, the MACS has expanded to involve more than 100 independent investigators who have used data and specimens established by the MACS over the 28 years of follow-up. As the MACS has expanded, it has developed a complex organizational structure to facilitate the management of data and specimens, and the wide

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range of studies investigating epidemiological, immunological, virological, genetic, behavioural, clinical and pathological factors involved in the natural history of HIV/AIDS.

To ensure that the MACS is at the cutting edge of research on HIV/AIDS, the following working groups have been established: behavioural; biomarker; cardiovascular; laboratory; data; genetics; hepatitis; malignancy/pathology; metabolic; renal; and viral immune. Each is chaired by an investigator with expertise in the area. The community advisory boards at each centre have provided key advice to ensure the success of the MACS.

The men in the MACS are followed at 6-month intervals, at which time they complete a questionnaire soliciting information about their medical history, behaviour, quality of life, depression, activities of daily living, and medications including antiretroviral drugs and compliance. They are also tested for neuropsychological function and have blood collected. Blood specimens are divided into serum, plasma and cells. An aliquot is tested for HIV antibody(seronegative men only), T-cell subsets and viral load. Aliquots of the cells, serum and plasma, as well as Epsteine–Barr virus-transformed B-cell lines and peripheral blood mononuclear cell pellets, are stored at central and local repositories. Data and specimens are available to qualified investigators who apply and have their proposal approved by the principal investigators. The men are followed for seroconversion, AIDS, cerebrovascular disease, cardiovascular disease, kidney disease, liver disease, lung infections, malignancies, neurological complications, changes in cognition and mortality. Outcomes that are ascertained continuously are listed in Table 1.

As of May 2011, the MACS had accumulated almost 87,000 person-years of follow-up, incorporating 8920 variables, 1,490,995 repository aliquots, over 100,000 CD4/CD8 measurements, 130,000 person-visits and over 35,000 HIV RNA measurements (Table 2). The MACS has documented seroconverters, long-term seropositive men with minimal decline in CD4 levels, seropositive men experiencing rapid decline in CD4 levels, long-term survivors with low (<50) CD4 cells, highly exposed persistently seronegative men, seropositive men on treatment and older infected men. Thus, the MACS has data and specimens documenting the entire natural history of HIV/AIDS from pre-infection, through infection, pre-treatment and treatment, to cause-specific death.

The strengths of the MACS include comparable comparison groups of similar risk to those of interest (e.g. uninfected men, infected men not on treatment); standardized, complete longitudinal data and specimens collected uniformly across centres before and after infection and treatment; rigidly standardized laboratories and physical examinations; an extensive repository of blood and other specimens; and genetic data for predicting infection, disease outcome and response to therapy.

Over the 28 years of its existence, the MACS has published 1200 papers on a wide range of host, behavioural, environmental and virological factors influencing the acquisition, natural history and clinical management of HIV infection. These have greatly expanded understanding of the processes involved in infection, and understanding of human immune responses and viral behaviour in the human host.

A particularly useful feature of the MACS afforded by the longitudinal database and the repository of specimens dating back to 1984 is the ability to identify factors involved in the infecting process and the human immune response to infection, by performing cutting-edge assays not available in the mid-1980s to specimens collected before onset of the various outcomes of HIV infection. This has been particularly useful in looking for predictors of AIDS malignancies and the course of HIV infection leading to AIDS (e.g. long-term survivors with minimal CD4+ cell decline, persistently negative high-risk individuals). Space does not permit a full exposition of all the scientific advances that the MACS has

contributed. However, a short list of scientific advances made by the MACS is included in Box 1

The success of the MACS should be attributed first and foremost to the commitment of the 6972 men who have endured repeated questioning about the most personal aspects of their behaviour, collection of biological specimens, and implementation of invasive procedures every 6 months in order to contribute to the elimination of this deadly disease. Other factors that have contributed to the success of the MACS include the dedication of the staff, many of whom have been with the study for more than 20 years; the decision to establish a repository of specimens; consistent funding from the National Institutes of Allergy and Infectious Diseases and the National Cancer Institute; reaching out to other qualified investigators; and the commitment of the investigators to remain on the cutting edge of HIV/AIDS research.

Box 1 Examples of contributions of the MACS to the advancement of science

- Imagawa *et al., N Engl J Med* 1989;320:1458–62[2]

  Study: isolation of HIV from seronegative men

  Interpretation: 27 men cleared the virus

- Detels *et al., J Acquir Immune Defic Syndr* 1994;7:1263–9[3]

  Study: resistant vs susceptible men who have sex with men

  Interpretation: CD8 cells may modulate outcome of HIV exposure

- Moore *et al.,* AIDS 1996;10:175–80[4]

  Study: Kaposi's sarcoma-associated herpesvirus infection prior to onset of Kaposi's sarcoma

  Interpretation: evidence that HHV8 infection precedes Kaposi's sarcoma, and HIV induces accelerated ageing of T-lymphocytes

- Effros *et al., AIDS* 1996;10:F17–22[5]

  Study: shortened telomeres in the expanded CD28−/CD8+ cell subset in HIV disease implicate replicative senescence in HIV pathogenesis.

  Interpretation: evidence that HIV leads to senescence of immune cells

- Zimmerman *et al., Mol Med* 1997;3:23–36[6]

  Study: CCR5 confers protection.

  Interpretation: 100% absence of CCR5 receptor on CD4 cells confers 100% protection

- Mellors *et al., Ann Intern Med* 1997;126:946–54[7]; Li *et al., Am Statistician* 2003;57:193–9[8]

  Study: likelihood of developing AIDS in 3, 6 and 9 years.

  Interpretation: viral load is a better predictor than CD4 level in early infection

- Detels *et al., JAMA* 1998;280:1497–503[9]

  Study: effectiveness of HAART.

Interpretation: HAART delays onset of AIDS as used outside the clinical setting

- Giorgi *et al., J Infect Dis* 1999;179:859–70[10]

  Study: predictors of short- and long-term survival after reaching <50 CD4+ T cells/mm^3

  Interpretation: activation is a more important determinant of survival at low CD4+ levels than viral load

- Kaplan *et al., AIDS* 2008;22:1615–24[11]

  Study: association between CD4+ T-cell count (cells/μl) and prevalence of carotid lesions among participants in men (MACS) and women (Women's Interagency HIV Study)

  Interpretation: decreasing CD4+ levels are associated with increasing risk of cardiovascular disease

- Cao *et al., JAIDS* 2009;50:142[12]

  Study: premature ageing of T-cells is associated with HIV-1

  Interpretation: HIV-1 infection is associated with a shift toward aged conformation of T-cells; i.e. HIV induces accelerated ageing of T-lymphocytes

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Table 1

Continuously ascertained outcomes.

Seroconversion
Clinical outcomes
• AIDS diagnosis
• Non-AIDS diagnosis
– Cardiovascular disease
– Kidney disease
– Liver disease
– Lung infection, bacteraemia, septicaemia
– Malignancies
• Mortality

AIDS, acquired immunodeficiency syndrome.

Table 2

Multicenter AIDS Cohort Study database (as of May 2011).

Publications (published and in press)		1195
Participants		6972
Person-years		86,883
Variables		8920
Repository aliquots (plasma, serum, cells, urine)		1,490,995
	HIV+	HIV−
Person-visits	56,352	72,566
CD4 measurements	51,798	57,808
HIV RNA measurements	34,149	1206

HIV, human immunodeficiency virus.

RNA, ribonucleic acid.