MACS Turns 25: The Influential HIV Study Continues

As the Multicenter AIDS Cohort Study (MACS) turns 25 years old, it has much to celebrate. Leading to the identification of long-term nonprogressors and the discovery of CCR5 as a receptor used by HIV to infect CD4 cells, MACS is one of the most influential HIV studies in the world. Researchers, activists and participants share what MACS has meant to them and the contribution it has made to the well-being of people with HIV.

May 12, 2009 By David Evans

This year marks the silver anniversary of the Multicenter AIDS Cohort Study (MACS), the longest-running HIV study in the United States. Twenty-five years since its launch, the National Institutes of Health (NIH)–funded MACS has produced some of the most important discoveries regarding the pathogenesis, treatment and prevention of HIV. But it's not all science—midway through its third decade, MACS researchers and participants have developed a close familial bond.

Since 1984, MACS researchers at four universities—Johns Hopkins in Baltimore, the University of Pittsburgh, Northwestern University in Chicago and the University of California in Los Angeles (UCLA)—have enrolled 6,973 HIV-positive and HIV-negative gay and bisexual men. Though many have died, moved away or simply dropped out of the study, roughly 2,700 are still alive and actively participating in the study. Most of the original researchers are still in charge of their study sites.

Among the 1,100 or so MACS-derived scientific papers that have been published is research that led to the validation of viral loads tests as a marker of disease progression, the identification of long-term nonprogressors and the identification on CCR5 as a receptor that HIV uses to infect CD4 cells. "This has been an invaluable resource for finding out key information about the natural history of HIV infection," says Gregg Gonsalves, a longtime AIDS activist who interacted with MACS researchers in the early 1990s.

Beginnings

Danny K., who prefers that his last name not be used, has been a Northwestern study volunteer since 1984. He's always felt that participating in the MACS has meant being part of something valuable to the community. He remembers being recruited for the study at the Howard Brown clinic in Chicago when he was just 26. Though he says he was aware of AIDS, he and his peers thought of it more as a disease of older men, or men who used lots of drugs. "When you're in your

20s," he says, "40 seems ancient."

He doesn't remember joining the MACS as an HIV study so much as a study of young sexually active gay men, and he says that several of his friends also joined the study at that time.

The MACS researchers hit the ground running, suggests John Phair, MD, the principal investigator at Northwestern. Soon after the virus was discovered in 1984, an initial and vital task of the MACS was to confirm HIV as the cause of AIDS. So the MACS volunteer samples were tested for HIV antibodies. "It turned out that about 40 percent of the cohort over the four cities were infected [at the first blood draw]," Phair says, "But when we first started doing the antibody test, we had nothing to offer, so we made it optional for men to find out their status."

Danny says he didn't find out he was HIV positive until 1989, after Retrovir (zidovudine) became more widely available. It was then that he learned he'd been positive at least since his first study visit back in 1984. Though the result didn't surprise him, he says, it did change his life. He compares living with HIV to living under a dark cloud. An active participant in the Chicago Gay Men's Chorus, Danny worried that he'd become ill like some of his fellow chorus members. "Somebody would get sick on a Friday and go into the hospital and then be dead by our Sunday rehearsal," he recalls. "I didn't know if that would be me."

Important Findings

It turned out that Danny was what researchers considered a "slow progressor." In fact, one of the most important research contributions of the MACS was a better understanding of why some people progress quickly to AIDS, whereas others progress more slowly—or not at all.

Gonsalves recalls a meeting with Anthony Fauci, MD, head of the National Institute of Allergy and Infectious Diseases, in the early 1990s. He and fellow activist Mark Harrington, along with a New York City physician named Joseph Sonnabend, explained to Fauci that Sonnabend had a small group of patients with HIV who didn't seem to have disease progression. They wanted Fauci to explore this phenomenon—and it was the MACS that took up the question.

Phair says he and other MACS researchers confirmed the existence of these nonprogressors and, through collaborations with other laboratories, discovered a CD4 cell coreceptor called CCR5 that is critical for viral infection of cells and offers a clue to why some people can resist becoming infected. Phair and others found that people whose cells can't make any CCR5 receptors are highly resistant to HIV infection. Those with CD4 cells studded with a lower-than-normal number of receptors tend to have slower disease progression. This early research on nonprogressors and CCR5, Gonsalves says, led directly to the development of the entry inhibitor Selzentry (maraviroc).

Other early scientific achievements included confirmation that unprotected anal sex was responsible for 90 percent of the new infections taking place in the study. Still another early paper described how a person's risk for developing Pneumocystis pneumonia (PCP) greatly increased when his or her CD4 count fell below 200. This led to the first guidelines for people to take

preventive treatment for PCP.

Charles Rinaldo, PhD, a professor of medicine and the principal investigator at the University of Pittsburgh, says one of the most important and influential papers to be published came in 1996. Rinaldo, along with John Mellors, MD, and others published data from the MACS that clearly demonstrated how a person's risk for illness and death increased as his or her CD4 count dropped and viral load increased. These data remain key to the rationale for starting antiretroviral therapy and became the foundation for HIV treatment guidelines for years to come.

Most recently, the MACS has turned its focus to the influence of HIV and ARV therapy on the aging process in people with HIV. "HIV-infected men are living pretty close to normal life spans if they take their medication," Phair says. Following the MACS volunteers, "we can see the effect of controlled HIV infection, and the therapy, on the aging process of HIV-positive men, because we can compare them to uninfected men who are not taking therapy."

This finding—along with other ongoing research into the effects of HIV and its treatment on aging and organ health—prompted the NIH to renew funding for the MACS for several more years.

Like a Family

It was around 1995, with the introduction of protease inhibitors, that Danny met a man named John, who was to become his lover and a big influence on his life. Though John had very advanced HIV disease at the time, the new drugs gave them four and a half years together before John died.

Danny remembers going to see the AIDS Memorial Quilt from the NAMES Project in Chicago in 2001 and being overwhelmed. On one side, he says, were quilts from the earliest days of the epidemic in Chicago, including a quilt panel for his best friend. On the other side of the building were the newest panels, including a panel Danny had made for John.

"What I was looking at visually was unimaginable. My best friend was in one corner and my lover was in the other, with 10 years of everybody dying in the middle," Danny says.

Unfortunately, death has been a significant part of the natural history of HIV disease, and it has touched not only the participants, but also the researchers. Three of the early researchers—Frank Polk, David Imagawa and Janice Giorgi—have all passed away since the study began, though not of HIV. Phair says the deaths these researchers, and his patients, have been a huge loss. "They were my friends as well as my colleagues," he says.

Roger Detels, MD, principal investigator of the UCLA site, says one of participants had a tremendous impact on his life and ultimately became a friend. Detels says, "I was having trouble with some of the local gay groups over the study recruitment in the early days, and Rand Schrader, who was the head of the community advisory board and the first openly gay judge in California, told me, 'You worry about the science, and I'll take care of everything else.' And he did!"

Detels says most of his staff at the UCLA site have been with him for 20 years and some for nearly 25. “They’re pretty extraordinary people,” he says.

The UCLA site recently had a party to commemorate 25 years of the MACS and invited all of its study participants. He says the study volunteers gave the staff a standing ovation, and that over the years he’s gotten dozens of testimonials from participants praising the staff. He says they’ve all become like a family.

Phair also has high praise for the participants who’ve continued showing up every six months for 25 years. “None of this would be possible without the loyalty and dedication of the men who signed on,” he says. “They have given time and blood and sweat and tears, and their contribution to this has been so inspiring.”

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