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Lessons learned from the 'ethical odyssey' of an HIV trial

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In the battle against HIV/AIDS conditions on the frontlines are constantly in flux as treatment, research and policy evolve. The landmark HIV Prevention Trials Network (HPTN) 052 study, which established that antiretroviral treatment in people who are HIV positive decreases the likelihood of transmitting HIV to their sexual partners, was no exception. One year after publication the study serves as a case study of ethical challenges faced at every stage of the research trial process in the new paper "Establishing HIV treatment as prevention in the HIV Prevention Trials Network 052 randomized trial: an ethical odyssey," published in the June 2012 issue of *Clinical Trials*.

HPTN 052 was designed to investigate two questions related to the use of antiretroviral treatment (ART). First, can ART be used to prevent sexual transmission of the HIV virus, and second, is earlier use of ART better for the health of someone who is already HIV positive? In 2007, the full trial began at 13 sites in 9 countries, with 1763 couples enrolled. In each couple, one partner was HIV-positive and one HIV-negative.

"HPTN 052 provides useful real-world examples of the types of ethical difficulties faced when conducting research that has profound implications for public health and how these difficulties can be managed in order to both protect the participants and do good science," says Jeremy Sugarman, MD, MPH, MA, co-author of the paper and deputy director for medicine of the Johns Hopkins Berman Institute of Bioethics.

To address the research questions, study participants were randomly assigned to two groups – one that would receive ART earlier, and the other at a later stage of HIV progression. This became a source of ethical tensions as the trial progressed and enthusiasm for earlier ART treatment grew, whereas previously it had been considered potentially unsafe. For example, in November 2009 the World Health Organization (WHO) issued new guidelines recommending that ART treatment begin earlier.

The deliberation and evolving guidance on ART treatment "brought into sharp focus the ethical tensions inherent to a moral obligation to intervene and the sometimes-conflicting need for gathering data to develop evidence-based practices," write Sugarman and his co-authors Myron S. Cohen, MD, and MaryBeth McCauley, M.P.H.

The authors point to the "constant threat" from observational and ecological study data, and the official guidelines they inspire, as posing a critically important ethical lesson of HPTN 052: whether and how a randomized trial should respond in light of them. "As these necessary changes were made, they threatened the very research that might support or refute the recommendations themselves," they write. The authors credit the Data and Safety Monitoring Board (DSMB), which met 11 times during the trial, for helping make critical calls as new developments arose during the trial, and maintaining essential communication with the investigators and Institutional Review Boards.

Yet even as HPTN 052 was being designed, ethical questions were raised as to the potential "coercion" of participants who would otherwise not have access to ART. The authors agree that "the unavailability of ART at the research sites reflected long-standing issues of global justice," but point out that initiatives coinciding with (but separate from) the trial by the WHO, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, as well as the President's Emergency Plan for AIDS Relief (PEPFAR) made ART much more widely available without having to enroll in

HPTN 052.

The authors also address the question of the study's potential to encourage unsafe sex for the sake of research results into the transmissibility of HIV, a common ethical issue raised in HIV research. The authors assert that "including a 'prevention package' is ethically obligatory," and should include methods known to be effective and accessible to participants.

"Throughout the course of the trial, the search for 'scientific truth' had to be weighed along with the rights and welfare of the subjects," said Sugarman.

Though some of the results of HPTN 052 were published in May 2011, the trial is still ongoing and will continue as planned until 2015, to assess long-term outcomes of early versus late ART treatment.

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