

# Addressing Research Priorities for Prevention of HIV Infection in the United States

Sten H. Vermund,<sup>1</sup> Sally L. Hodder,<sup>2</sup> Jessica E. Justman,<sup>3,7</sup> Beryl A. Koblin,<sup>5</sup> Timothy D. Mastro,<sup>8</sup> Kenneth H. Mayer,<sup>9,10</sup> Darrell P. Wheeler,<sup>6</sup> and Wafaa M. El-Sadr<sup>3,4</sup>

<sup>1</sup>Institute for Global Health and Departments of Pediatrics, Medicine, Preventive Medicine, and Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, Tennessee; <sup>2</sup>Department of Medicine, University of New Jersey Medical School, University of Medicine and Dentistry, Newark; <sup>3</sup>International Center for AIDS Care and Treatment Programs, Mailman School of Public Health, Columbia University, <sup>4</sup>Harlem Hospital Center, <sup>5</sup>New York Blood Center, and <sup>6</sup>Hunter College School of Social Work, City University of New York, New York, and <sup>7</sup>Bronx-Lebanon Hospital Center Clinical Research Site, Bronx, New York; <sup>8</sup>Family Health International, Durham, North Carolina; <sup>9</sup>Department of Medicine, Miriam Hospital and Brown University School of Medicine, Providence, Rhode Island; and <sup>10</sup>Fenway Community Health Center, Boston, Massachusetts

More than half a million Americans became newly infected with human immunodeficiency virus (HIV) in the first decade of the new millennium. The domestic epidemic has had the heaviest impact on men who have sex with men and persons from racial and ethnic minority populations, particularly black persons. For example, black men who have sex with men represent <1% of the US population but 25% of new HIV infections, according to Centers for Disease Control and Prevention estimates published in 2008. Although black and Hispanic women constitute 24% of all US women, they accounted for 82% of HIV infections among women in 2005, according to data from 33 states with confidential name-based reporting. There is a nearly 23-fold higher rate of AIDS diagnoses among black women (45.5 diagnoses per 100,000 women) and a nearly 6-fold higher rate among Hispanic women (11.2 diagnoses per 100,000 women), compared with the rate among white women (2.0 diagnoses per 100,000 women). Investigators from the HIV Prevention Trials Network, a National Institutes of Health–sponsored collaborative clinical trials group, have crafted a domestic research agenda with community input. Two new domestic studies are in progress (2009), and a community-based clinical trial feasibility effort is in development (2010 start date). These studies focus on outreach, testing, and treatment of infected persons as a backbone for prevention of HIV infection. Reaching persons not receiving health messages and services with novel approaches to both prevention and treatment is an essential priority for control of HIV infection in the United States; our research is designed to guide the best approaches and assess the impact of bridging treatment and prevention.

More than 1 million persons in the United States are currently infected with human immunodeficiency virus (HIV), of whom an estimated one-quarter are unaware of their HIV infection status. There were an estimated

56,000 new HIV infections during the past decade, with no evidence of a decrease in this number during this period [1]. Because attempts to develop a number of biological and behavioral prevention measures against HIV infection have been largely disappointing to date, there is intense global interest in pursuing research in innovative strategies for prevention of HIV infection.

## CURRENT US HIV DYNAMICS AND NEED FOR A RESEARCH RESPONSE

The HIV epidemic in the United States is geographically localized and is further focused in specific populations, creating hot spots of transmission nested in sexual and/or drug use risk networks. Two populations at highest

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Reprints or correspondence: Dr Sten H. Vermund, Vanderbilt Institute for Global Health, 2215 Garland Ave (319 Light Hall), Nashville, TN 37232-0242 (sten.vermund@vanderbilt.edu).

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risk are men who have sex with men (MSM), particularly black MSM, and women of black or Hispanic race/ethnicity [2, 3]. HIV transmission also persists among white MSM and drug users. The advent of antiretroviral therapy (ART) and the decrease in the rate of HIV-related mortality in the United States have led at-risk persons to view prevention of HIV infection to be less urgent than it was previously [4]. Failure to lower the incidence of HIV infection in the United States during the potent antiretroviral therapy era likely reflects this complacency about HIV infection, in addition to a systemic failure to effectively reach the persons at highest risk with risk-reduction interventions and persons with recognized or unrecognized HIV infection with ART.

In 2008, the National Institutes of Health–funded HIV Prevention Trials Network (HPTN) completed a systematic review of the available literature and an analysis of available data on the prevalence of HIV infection and reported new HIV infections in the United States [5]. On the basis of this review, an HPTN Domestic Prevention Research Agenda was developed [6]. In addition, on the basis of results of the analysis of available data on reported new HIV infections in the United States, approximately one-half of the newly reported cases were detected in MSM and one-quarter of the cases were in women of color. Because of their disproportionate disease burden, these populations needed to be considered as special priorities for efforts for prevention of HIV infection. For example, black MSM represent <1% of the US population but 25% of the new HIV infections [5]. HIV infection in US women is distributed in highly skewed geographical venues. Although black and Hispanic women constitute 24% of all US women, they accounted for 82% of HIV infections among women in 2005, on the basis of data from 33 states with confidential name-based reporting [7–9]. In addition, the increased risk among women of color is dramatically shown by the nearly 23-fold higher rate of AIDS diagnoses among black women (45.5 diagnoses per 100,000 women) and nearly 6-fold higher rate among Hispanic women (11.2 diagnoses per 100,000 women), compared with the rate among white women (2.0 diagnoses per 100,000 women) [7, 9].

The HPTN is also exploring new research concepts for other key populations that have a heavy HIV burden in the United States, such as nonminority MSM. For many at-risk persons, drug use and intercurrent mental health problems (eg, depression) may play a major role in potentiating the spread of HIV infection. Future prevention clinical trials that address these primary drivers of risk-taking behavior and poor adherence could be helpful in enhancing prevention of HIV infection.

As a most urgent priority, HPTN investigators have focused on black MSM and women at risk as 2 relatively neglected populations at highest risk in the domestic US HIV epidemic. Several questions were identified that required urgent attention before beginning large studies on effectiveness of efforts for

prevention of HIV infection in these latter populations. What are accurate estimates of the incidence of HIV infection in these populations? How can persons at risk who are least likely to be engaged in programs for prevention of HIV infection be reached? What are the types of prevention interventions that are likely to be feasible, acceptable, and effective for these individuals? How can individuals with unrecognized HIV infection be connected to HIV testing services? How can those with known HIV infection be linked and engaged in HIV care? How can those receiving ART achieve complete viral suppression? To address these knowledge gaps, several critical feasibility studies have been designed and launched (Figure 1).

### BLACK MSM: HPTN 061 PROTOCOL (BROTHERS STUDY)

The HPTN 061 protocol (BROTHERS study) was designed to assess the feasibility of a community-level, multicomponent intervention for reducing the incidence of HIV infection among black MSM (protocol chairs are B.A.K., K.H.M., and D.P.W.). In recognition of the importance of this study and the fact that black MSM represent a neglected population for HIV risk reduction efforts, a diverse team was constituted in the design and implementation of this study inclusive of individuals from the target population as community representatives and investigators.

The protocol uses innovative community outreach methods to recruit black MSM into a longitudinal study in a clinic-linked community setting, enabling prompt linkage to services of recruited men and their partners, as indicated. The recruitment approaches used are both conventional (ie, direct enrollment of sexually active black MSM) and complex (ie, enrollment of persons who are part of the sexual and/or social network of directly recruited individuals). Men are therefore recruited in 1 of 2 ways: directly from the community (ie, community-recruited participants) or as sexual network partners referred by participants (ie, referred participants). A subset of community-recruited and referred participants are considered to be index participants, because they were newly identified with HIV infection through the study or had previously diagnosed HIV infection but were not receiving HIV care. These index participants are asked to refer network members into the study. A random sample of HIV-uninfected participants is re-

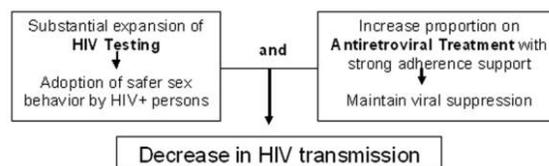


Figure 1. Test, link, and care hypothesis

cruited as a subset of those considered as index participants. Another component of the study includes conduct of focus groups (~18–24 participants per site) and qualitative interviews (up to 30 participants at each site).

**Field research plans the BROTHERS study.** The study began in mid-2009 and will continue for 12 months of participant accrual and up to 12 months of follow-up for each participant, with study visits at 6 and 12 months. Assessments include behavioral and psychosocial assessments and screening for HIV and sexually transmitted infections (STIs). At least 2418 participants (403 per site) will be enrolled from 6 cities: San Francisco, Los Angeles, Atlanta, Boston, New York City, and Washington, DC (Table 1).

Another key feature of the study is the assessment of the feasibility and acceptability of use of peer health system navigators in this population. The success of such an intervention in engaging disenfranchised populations was first demonstrated in the United States by Freeman [10] >20 years ago, when they found increased mammography use by African American women through use of trained peer assistance. More recently, HIV-infected persons were found to be more likely to be retained in care and have suppressed plasma HIV RNA when health system navigators were available to assist them [11]. The HPTN study aims to determine whether peer health system navigation can assist with primary and secondary prevention of HIV infection and whether this model is highly acceptable among black MSM.

**Study objectives and outcomes for the BROTHERS Study.** The key study objective is to assess the feasibility of recruiting

and engaging black MSM into prospective research studies designed to test novel approaches to reduce the risk and incidence of HIV infection. Engagement of participants includes referral of up to 5 sexual partners by index participants for study enrollment; HIV risk reduction counseling, testing, and referral for HIV care, as needed; STI testing and referral for care; screening for drug use, mental health problems, partner and/or homophobic violence, and counseling and referral for care as indicated; and engagement with peer health care system navigators to facilitate uptake of health care and other services.

Key study outcomes include effectiveness in recruitment and retention of black MSM; uptake of the intervention by black MSM, specifically the proportion of enrolled participants who agree to HIV testing, agree to STI testing, and use peer navigation; and estimation of the following key measures: the proportion of participants who received a new diagnosis of HIV infection at enrollment, change in condom use from enrollment to week 52 of follow-up, change in HIV RNA level at week 52 among HIV-infected participants who initiate potent ART, change in prevalence of STIs from enrollment to week 52, and satisfaction of black MSM with intervention components.

Secondary objectives are also seen as important components of the HPTN 061 protocol and include collection of samples, behavioral data, and HIV test results to improve laboratory measures of incidence of HIV infection in cross-sectional surveys; estimation of incidence rates of HIV infection under intervention conditions; estimation of the effects of the intervention on incidence of HIV infection through mathematical modeling; description of social and sexual networks of black

**Table 1. Clinical Research Sites (CRS) for HPTN 061 (BROTHERS) and HPTN 064 (ISIS) Studies to Reduce HIV Transmission in the United States**

Study, CRS
HPTN 061
The Fenway Institute CRS, Boston, MA
Ponce de Leon Center CRS, Atlanta, GA
Hope Clinic CRS, Emory Vaccine Center, Decatur, GA
UCLA Vine Street CRS, Los Angeles, CA
Harlem Prevention CRS, New York, NY
New York Blood Center/Union Square CRS, New York, NY
San Francisco Vaccine and Prevention CRS, San Francisco, CA
George Washington University CRS, Washington, DC
HPTN 064
New Jersey Medical School- Adult CRS, Newark, NJ
Ponce de Leon Center CRS, Atlanta, GA
Hope Clinic CRS, Emory Vaccine Center, Decatur, GA
Johns Hopkins University AIDS CRS, Baltimore, MD
Harlem Prevention CRS, New York, NY
Bronx-Lebanon Hospital Center CRS, Bronx, NY
University of North Carolina AIDS CRS, Chapel Hill, NC
Wake County Health and Human Services CRS, Raleigh, NC
George Washington University CRS, Washington, DC

MSM based on individually self-reported network data; description of risk behaviors of sexual network members of participants, especially those who receive a new diagnosis of HIV infection or who received a diagnosis previously but were not receiving care; assessment of attitudes of participants toward other interventions for prevention of HIV infection; examination of individual, interpersonal, cultural, institutional, and geographic-specific processes that influence study participation and uptake of intervention components; and understanding of how and to what extent stigmatization and discrimination (and other emergent themes) influence HIV testing and access to care by geographic region. Because black MSM represent a neglected population for HIV risk reduction efforts, black MSM from communities and universities were engaged to help guide the efforts of the BROTHERS study investigators.

### **THE WOMEN'S HIV SEROINCIDENCE STUDY (ISIS): HPTN 064 PROTOCOL**

The HPTN 064 protocol (ISIS study) is designed to estimate incidence rates of HIV infection among women at risk for HIV acquisition in the United States and to determine the feasibility of enrolling and following at-risk women (protocol chairs are S.L.H. and J.E.J.). Measurement of the incidence of HIV infection in this study will be determined through the traditional multisite, prospective observational cohort design of determining rate of HIV seroconversion over time and by use of novel laboratory assay algorithms to estimate recent infection rates of HIV infection retrospectively at the time of enrollment. Both quantitative and qualitative methods will be used for assessment of behavioral issues in the study. Semistructured interviews of participants and focus group discussions with women enrolled in the cohort will be conducted, as will focus groups that include men recruited from the same communities.

A key innovative component of this study is the choice of a venue-based, time-space sampling recruitment strategy. Venue-based, time-space sampling is a cross-sectional survey of persons who attend venues in locally defined geographic areas and has been used to obtain large and diverse samples of MSM [12–14] and heterosexual persons [15]. The use of venue-based, time-space sampling in ISIS permits the enrollment of women at high risk for HIV acquisition in a systematic and reproducible manner and reflects the geographic patterns of the HIV epidemic in the United States. Building on HIV surveillance data and community poverty rates, priority prevention areas with potentially high incidence rates of HIV infection are identified in neighborhoods in several locations in the United States. In these defined neighborhoods, ethnographic work identifies venues, such as playgrounds, laundromats, and grocery stores, where potential participants are approached. Women are enrolled on the basis of geographic criteria (residence in specified census tracts) and their own or

their partners' behavioral characteristics. This recruitment strategy will result in the enrollment of more women with the highest geographic and behavioral risk profiles, rather than women who are primarily interested in enrolling in a clinical trial.

**Field research plans for the ISIS study.** The study aims to recruit 2000 women from 10 geographically distinct communities in the Atlanta, Georgia (metropolitan area); Baltimore, Maryland; Newark, New Jersey; New York, New York (Bronx and Manhattan), Chapel Hill and Raleigh, North Carolina (metropolitan area); and Washington, DC (Table 1). By assuming that there are ~40 HIV infections, the sample size provides a very precise (95% confidence interval,  $\pm 0.006$  infection per 100 person-years) estimate of annual incidence of HIV infection. Qualitative data will be collected from subsets of enrolled women from 4 (2 urban and 2 nonurban) of the 10 participating communities. In the first subset of women, focus groups will be conducted to explore ways to enhance recruitment of at-risk women for subsequent prevention trials. Incentives, barriers, and facilitators to enrollment and retention (eg, child care and transportation) will be discussed, as will convenient times and locations for participation in interventions for HIV infection. In a second subset of women, semistructured, recorded interviews will be conducted with ~30 women in each of 4 communities to identify social, structural, and contextual factors likely to affect women's HIV-related decision making. In addition, male focus groups will explore barriers and facilitators to male-mediated factors of prevention of HIV infection, such as male perceptions of community-level HIV testing efforts.

**Study objectives and outcomes for the ISIS study.** The study duration is 2 years, with accrual for 1 year and follow-up for 6–12 months. Interventions to be provided include HIV testing, counseling for risk reduction, and referrals for drug use, domestic violence, mental health problems, and HIV care, as needed. In addition to the primary objective of estimation of the overall incidence rate of HIV-1 infection, important secondary objectives are as follows: evaluation of new laboratory assays and algorithms for determination of cross-sectional incidence of HIV-1 infection, including use of combined laboratory methods and statistical adjustments based on population CD4<sup>+</sup> cell count and ART coverage characteristics, with anticipation of future large-scale, cross-sectional studies on interventions for HIV infection in women and/or men [16]; estimation of recruitment and retention rates for use in the design of future interventional trials; description of sexual behaviors, alcohol and drug use, prevalence of domestic violence, and mental health indicators of women at risk of HIV acquisition; assessment of women's preferred recruitment and retention strategies for future studies; description of social, structural and contextual factors in a subgroup of women to inform future intervention studies; estimation of prevalence rates of HIV in-

fection among women who have not reported previously testing positive for HIV; and exploration of facilitators and barriers to HIV testing among men residing in areas with high risk to inform future intervention studies

Past efforts to recruit women at high risk into clinical trials for prevention of HIV infection in the United States failed to identify women with >0.5% seroincidence per annum [17–21]. This study aims to use an innovative multidimensional approach based on 3 elements: community, individual, and partner characteristics. It is anticipated that the majority of women recruited in the study will include black or Hispanic individuals, reflecting the characteristics of the US HIV epidemic among women (Table 1).

### **THE TEST AND TREAT PLUS STUDY: HPTN 065 PROTOCOL**

Persons who are unaware of their HIV infection are more likely to receive a diagnosis at advanced stages of HIV disease and, thus, are likely to have had uncontrolled HIV replication with consequent high plasma and genital tract HIV RNA levels for many years without access to ART [22, 23]. Suppression of plasma HIV RNA to undetectable levels through ART may lead to decreased risk of HIV transmission, offering a public health benefit in addition to the personal health benefits of ART [24–34]. In addition, several studies have revealed that individuals who know their HIV-positive status are likely to adopt safer behaviors [35, 36] and, thus, reduce the risk of transmitting HIV to others. Therefore, potentially effective interventions to decrease incidence of HIV infection in a community could involve a combination of interventions, including intensive HIV testing efforts for early identification of HIV, linking HIV-infected individuals with access to ART, and providing adherence support to maintain viral suppression, in combination with other prevention efforts (Figure 1). One model based on parameters relevant to the HIV epidemic in South Africa suggested a substantial impact on the trajectory of the global epidemic if testing and early ART are widely implemented [37]. Assumptions of near-universal testing and treatment of all seropositive persons are fanciful; however, other modelers are critical of the methods used [38]; the concept will require prevention clinical trials to assess definitive impact.

**Expanded HIV testing and treatment coverage to prevent HIV transmission.** On the basis of these promising elements for a cohesive strategy for prevention of HIV infection, the HPTN has embarked on the design of a test and treat study that aims to determine the feasibility of such a strategy. The study involves expanded HIV screening and testing to identify individuals with HIV infection who are unaware of their status and, then, using ART to decrease risk of HIV transmission. The study builds on ongoing efforts by community service providers and social mobilization to expand HIV testing, the

community of HIV providers engaged in HIV care and treatment, and the wealth of available HIV surveillance data to investigate various elements of this strategy. Key elements of enhanced test and treat (Test, Link, and Care-Plus Study [HPTN 065]) include substantial expansion of HIV testing with a goal of universal offering of testing to populations for which testing is likely to have a high yield, linkage of those identified with HIV infection to health care sites using an innovative approach, prompt evaluation for ART eligibility and optimization of ART initiation, provision of interventions to decrease risk of HIV transmission from those with HIV infection to others, and support for achievement of suppression of viral replication through an innovative approach.

The test and treat study (cochaired by W.M.E.-S. and Bernard Branson of the Centers for Disease Control and Prevention), has an expected launch in early 2010. The proposed study aims to use an innovative approach to show the feasibility of embarking on a large test and treat study through use of a community-focused approach, nested comparison of innovations, and use of HIV surveillance data from the target communities. Implicit in the overarching test-and-treat approach are the following questions. Can a substantial increase in HIV testing coverage be accomplished? Will this effort identify those with undiagnosed infection in a community? Can persons with HIV infection be effectively linked and engaged in HIV care? Can use of ART achieve a decrease in community viral load? Consequently, will these efforts result in a decrease in the incidence of HIV infection [37, 39, 40]?

**Need for new prevention research for MSM.** While focusing on the aforementioned studies, the HPTN is exploring new research concepts for some of the other key populations that bear a heavy HIV burden in the United States, such as white and Hispanic MSM who will not be targeted in the BROTHERS study, which is focused on black MSM. For many of these men, drug use (eg, methamphetamine and excessive alcohol) and intercurrent mental health problems (eg, depression) may play a major role in potentiating HIV transmission and, thus, need to inform design of future prevention trials. All of these efforts build on previous HPTN studies in the United States that addressed behavioral and biological risk reduction among MSM [41], injection drug users [42], and at-risk women [43–46]. The aforementioned studies demonstrate the importance of working through networks, such as the HPTN, to address questions in a variety of venues and with a large enough sample size to derive meaningful results to guide the next stages of community- or individual-level clinical trials.

Stemming the HIV epidemic in the United States will require concerted research efforts, innovation, and perseverance; assessment of complex multicomponent strategies rather than traditional assessment of one intervention; embarking on critical feasibility studies; working at a community level rather than

at a facility or research site level; working with diverse constituencies; use of new design methods; and establishment of meaningful partnerships with communities that are often disenfranchised or stigmatized. We are optimistic that this research partnership has begun the journey toward our common goal and public health imperative [47].

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