

Responding to an Evolving U.S. Epidemic: An HIV Prevention Research Agenda

Developed by:

**The Domestic Prevention Working Group
of the HIV Prevention Network (HPTN)**

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EXECUTIVE SUMMARY

The US has experienced a substantial decline in AIDS-related morbidity and mortality due largely to the introduction of highly active antiretroviral therapy. In contrast, little progress has been achieved over the last 10 years in reducing the number of new HIV infections. Recent epidemiological estimates indicate that HIV incidence in the US is likely higher than previously assumed, lending a renewed sense of urgency among policy-makers and other stakeholders to develop more effective HIV prevention strategies. With effective vaccines and microbicides years or even decades from being available, refining and improving prevention efforts and testing new prevention interventions represent a major public health research priority. Evidence of significant transmission of drug-resistant virus in the US further underscores the need to strengthen HIV prevention efforts in general and among those with HIV who have been on antiretroviral therapy (ART).

The HIV/AIDS burden is most pronounced among some of the country's poorest and most disenfranchised populations, including Black and Hispanic men and women, men who have sex with men (MSM), particularly Black MSM, and young people. Use of both non-injecting substances (e.g., use of crack-cocaine or stimulants), and alcohol play important roles in HIV transmission and acquisition. While HIV incidence has declined in injection drug users (IDUs), both non-injecting drug-users and IDUs continue to be at higher risk of acquiring and transmitting HIV.

HIV prevention clinical trials in the US are inherently challenging for several reasons: the overrepresentation of the epidemic in specific populations that may be hard-to-reach; its occurrence both in diverse venues (e.g., urban communities as well as the rural South) and in specific geographically-defined "hot spot" areas; and the relatively low overall HIV incidence rates. Some populations at highest risk for HIV in the US (e.g., Black women and Black MSM) do not consistently report higher risk behaviors than their white counterparts. Nonetheless, Blacks experience higher risks of acquisition than Whites due to the greater likelihood of having a partner already infected with HIV or their higher probability of exposure to HIV because of higher HIV prevalence in some sub-populations. Finally, the paucity of research conducted to date over the past decade on the incidence of HIV in selected populations-at-risk in the US, particularly women, hampers efforts to conduct US-based HIV prevention studies.

In recent years, much HIV prevention research has focused on international settings where the epidemic is often generalized and with high HIV incidence. The changing typology of new HIV infections in the US and increasing HIV incidence rates in some populations suggest new imperatives to undertake US specific prevention research. Renewing HIV prevention in the US requires a fresh look at the characteristics of the epidemic, creative recruitment strategies for populations-at-risk, overcoming institutional barriers that limit the range of

feasible interventions for particular subpopulations (e.g., incarcerated and paroled individuals) and the development and use of innovative intervention tools and strategies.

A major focus of the prevention research agenda to date has been on the development and testing of new biomedical interventions. There is growing recognition that we may be several years away from an efficacious vaccine and/or microbicide and that no single intervention is likely to be effective for everyone. Intervention designs that integrate infectious diseases principles and behavioral and social theory can attack transmission cycle in several ways and achieve synergism, analogous to how different drug classes attack viral replication itself. Interventions that consider real-world practices and are appropriately tailored for the specific setting/population in terms of socio-economic circumstances and epidemiological characteristics are more likely to reduce HIV transmission than a “one size fits all” approach. For example, Black MSM have proven hard to reach with conventional messages targeting identified MSM communities. Thus, increasing attention is warranted towards behavioral interventions and combination biomedical-behavioral interventions that are tailored for specific populations.

Thus far, most evidence-based HIV risk reduction behavioral intervention research in the US has used behavioral endpoints, i.e., self-reported behavior change, rather than biomedical endpoints, i.e., HIV or sexually transmitted infection (STI) incidence. Further, none of the studies identified in our literature surveys have followed participants for longer than 18 months. The majority of validated interventions target HIV-uninfected individuals, with few studies evaluating interventions that aim to promote safer behaviors among people living with HIV. Few studies have been evaluated rigorously for their effectiveness in field environments beyond in the research settings. In addition, few studies intervene at a community level or attempt to address the role of social networks in HIV transmission. Most importantly, no public health application of study results has demonstrated a discernable impact on the annual rate of new HIV infections in the US.

Studies aimed at the prevention of HIV transmission in the US have focused largely on the individual for both biomedical and behavioral risk-reduction approaches. Dyadic, social network, and community interventions have rarely been tested. To strengthen future HIV prevention efforts, novel research designs are needed to focus on social factors that increase vulnerability to HIV infection in the US. These include gender-power relationships, poverty, homelessness, non-injection substance use, mental illness, prior incarceration (including through the juvenile justice system), unrecognized risk activity that is disconnected from usual routes of risk reduction education, and a history of domestic violence or victimization. Only by recognizing these social co-factors and addressing them in the research design and program implementation will the potential impact of individual risk reduction be realized.

The research approach proposed by the HIV Prevention Trials Network (HPTN) seeks to focus on populations that can have a measurable impact on US incidence rates, should interventions prove efficacious and be implemented successfully. Analysis of 2005 CDC HIV diagnosis data from 33 states with HIV reporting systems at that time suggest that an estimated 50% of infections occur in MSM (estimated to be equally divided between Black/Hispanic and white MSM). An additional 32.5% are attributable to high risk heterosexual contact (15.5% in Black/Hispanic women, 13% in Black/Hispanic men, and 4% in white women), and 17.5% are due to other or unknown risks, including IDU or multiple risk factors such as IDU and high risk heterosexual sex combined (10% Black/Hispanic men, 6% Black/Hispanic women and 1.5% in white women). It is noteworthy that while these data are based on newly diagnosed HIV infections (most without an AIDS diagnosis), they do not represent HIV incidence per se. The data represent only those individuals who availed themselves of HIV testing opportunities, a potentially non-representative sub-population. Nonetheless, these epidemiological data can help guide investigators in the selection of target populations that will have the largest impact on transmission of HIV in the US. As evidenced from these data, MSM, particularly Black MSM, and Black and Hispanic women who acquire HIV through heterosexual route are priority populations for future research. Furthermore, modeling data suggest that half of all new infections occur in persons ages 15-24 years of age; a focus on adolescents and youth adults is also essential.

Based on analysis of available data, review of the literature, and assessment of the expertise and experience of the network, the HPTN supports the need for a focused and innovative approach for new domestic prevention studies with the following areas of emphasis:

- Specific communities with the highest rates of HIV transmission,
- HIV-infected persons, particularly those who are unaware of their HIV status and not engaged in clinical care,
- Focus on social and sexual networks, not merely on individuals,
- Recognition of changing patterns of drug use and their consequences for sexual and injection risk behavior (e.g., stimulant use)
- Use of multi-component interventions as with combinations of behavioral and biomedical approaches,
- Use of biological endpoints, including HIV seroincidence, whenever technically feasible and practical,
- Long-term follow-up of study participants to determine durability of interventions, and
- Development of targeted feasibility studies to inform larger efficacy trial designs.

In this document, we focus on non-vaccine, non-microbicide research and present a comprehensive compendium of a research agenda to guide reductions in domestic HIV incidence through the following:

- A description of the status of the HIV epidemic in the US as a basis for our focus on the most severely affected populations,
- An update on non-microbicide, non-vaccine interventions, emphasizing those suitable for HIV prevention in the US,
- A summary of epidemiological and behavioral data that are salient for prevention trial design,
- A discussion of the limitations of existing prevention interventions and specific research gaps, and
- An examination of key research questions that merit further investigation.

In summary, the continued alarming rates of HIV infection in the US among MSM, the continued expansion of HIV among Black and Hispanic women, and the limited effectiveness of current prevention efforts to lower the annual number of new HIV infections compel a renewed commitment to the development and implementation of a robust domestic HIV prevention research agenda. The HPTN is well-positioned to conduct clinical trials in these areas, having completed successfully multi-site studies in diverse populations and settings, including HIVNET 015 (EXPLORE, a risk reduction trial in MSM) and HPTN 037 (a network-level risk reduction study in IDUs). We seek to realize this agenda through partnerships with sister clinical trials networks, as well as other organizations sharing the prevention mission both domestically and internationally.

HIV prevention clinical trials must address the localized nature of the domestic HIV epidemic and focus on marginalized populations that have not been reached by conventional prevention approaches. This will require unprecedented community partnerships, innovative scientific initiatives, and sustained support for HIV endpoint trials, when possible, and for multi-year follow-up. The HPTN is eager to embrace these challenges.

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I. Background

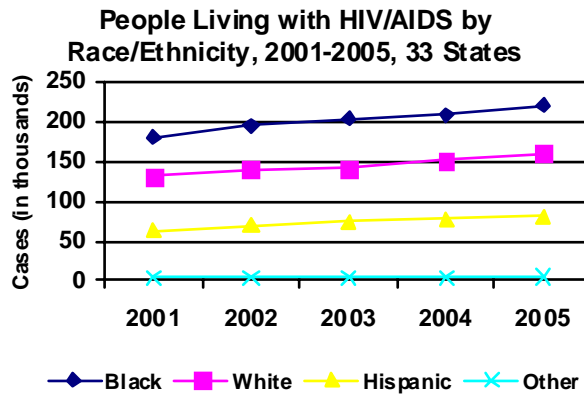
The HIV Prevention Trials Network (HPTN) is dedicated to the conduct of clinical trials that generate new tools and/or strategies to control the HIV epidemic in the U.S. and around the world. It seeks to prevent new HIV infections through control of sexually transmitted infections (STIs), behavioral and substance use interventions, use of antiretroviral drugs for prevention of HIV transmission and acquisition, and other public health measures. It is committed to the effective incorporation of emerging prevention mechanisms and tools as soon as they can be validated with rigorous research designs.

An important component of this effort is reducing the number of new infections in the US. Over the last decade, no decrease in the annual number of new HIV infections among Americans has been detected, and emerging evidence indicates that HIV incidence may be on the rise. As the epidemic has evolved in recent years, the proportion of African-American men and women among the newly infected has steadily risen. The African-American communities most heavily affected by new HIV infections disproportionately suffer from multiple social and economic disadvantages that contribute to HIV-related vulnerability and increase the complexity of HIV prevention programming.

In this document, we provide an overview of the current status of the epidemic in the US and a description of key populations that experience high rates of HIV infection and have important unmet prevention needs. We identify factors that increase risk of infection and describe trial design and methodological issues pertinent to prevention research. Based on analysis of available data, we present the HPTN's proposed approach to these challenges. The approach proposed by the HPTN builds on a network's comparative advantage: the expertise and experience of its investigators; knowledge of, and linkages with, affected populations and community advocates; and an existing infrastructure that supports the rigorous design, implementation, and analysis of large, multi-site clinical trials. In addition to the approach proposed by HPTN, we also identify pressing prevention research questions, providing guidance on the key components of a potential future comprehensive prevention research agenda. We conclude with our perspective on how to move forward towards the successful design and implementation of a comprehensive domestic prevention research effort.

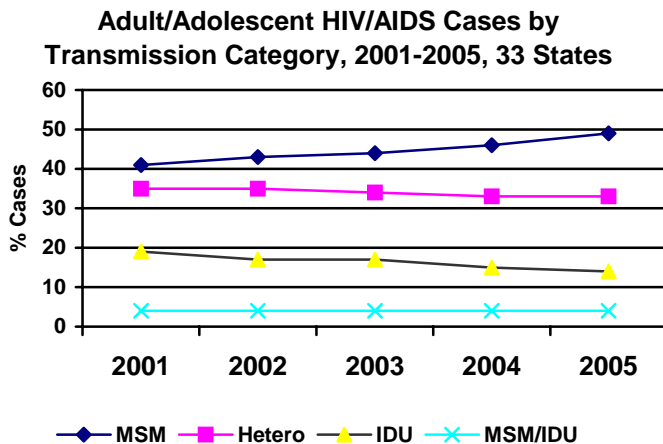
II. Current Status of the HIV Epidemic in the US

As of the end of 2003, CDC estimated that between 1.04 million and 1.19 million people in the US were living with HIV infection (including both AIDS diagnoses and the estimated 24-27% of HIV-infected individuals who are unaware of their HIV serostatus). (Glynn, 2005) Starting in the early 1990s, and until recently, the CDC has estimated that domestic HIV incidence has remained relatively stable, with roughly 40,000 new HIV infections occurring annually in the U.S. However, using more recent epidemiological methods that have emerged over the last several years (see discussion below in this section), CDC is reportedly soon to announce that annual HIV incidence may be higher than the current annual estimate. The number and proportion of new HIV/AIDS diagnoses are highest in the Northeast but are increasing in the South, with rates in other regions are stable or decreasing slightly. (Reif, 2006; Qian, 2006)



Source: CDC, 2007

HIV/AIDS disproportionately affects Blacks, who in 2005 had a population-based rate of HIV/AIDS diagnoses that was 2.5 higher than Hispanics and eight times higher than whites. For background, the US Census Bureau 2006 estimates for



Source: CDC, 2007

the US population as a whole were that 12% of the population was Black, non-Hispanic, 13% was Hispanic, and 69% was white, non-Hispanic.

Blacks accounted for 49% of new HIV/AIDS diagnoses in 2005 in the 33 states with mature HIV reporting systems. (CDC, 2007) The racial/ethnic profile of the population of people living with HIV/AIDS has undergone

major changes over the course of the epidemic; while whites accounted for 47% of AIDS diagnoses between 1981-1995, Blacks and Hispanics together comprised 70% of AIDS cases between 2001-2004. (CDC, 2006a)

Women accounted for 15% of AIDS cases between 1981-1995; in contrast, they represented 27% of AIDS diagnoses from 2001-2004. (CDC, 2006a) The proportion of new HIV/AIDS diagnoses among women appears to have stabilized in recent years, although the epidemic has continued to expand among poor, Black women in the South. (Holmes, 1997) Between 2001 and 2005, the number of diagnoses nationally declined 1% for men and 19% for women, with males representing 73% of all HIV/AIDS diagnoses in 2005. Blacks and Hispanics made up 79% of all females living with HIV/AIDS at the end of 2005. Sexual intercourse with men was the source of infection in 72% of living HIV/AIDS cases among women in 2005. (CDC, 2007)

Men who have sex with men (MSM) represent the largest transmission category for HIV/AIDS diagnoses reported in 2005 (49% of new cases), with heterosexual transmission accounting for 32% of new cases. From 2001 and 2005, cases among MSM increased in the 33 states with mature reporting systems, while the number of diagnoses for other risk groups declined. Whites accounted for 50% of MSM living with HIV/AIDS as of December 2005, although MSM also represent the largest share of living cases among Black and Hispanic males. (CDC, 2007)

Analysis of 2005 CDC HIV diagnosis data from 33 states with mature HIV reporting systems suggests that an estimated 50% of infections occur in MSM (estimated to be equally divided between Black/Hispanic and white MSM). An additional 32.5% are attributable to high risk heterosexual contact (15.5% in Black/Hispanic women, 13% in Black/Hispanic men, and 4% in white women), and 17.5% are due to other or unknown risks, including IDU or multiple risk factors such as IDU and high risk heterosexual sex combined (10% Black/Hispanic men, 6% Black/Hispanic women and 1.5% in white women). These data are based on newly diagnosed HIV diagnoses (not AIDS) and do not represent the true incidence of HIV. They represent only those individuals that availed themselves of HIV testing opportunities, with attendant biases of this selected subpopulation. Nonetheless, these limited epidemiological data can help guide investigators in the selection of target populations that will have the largest impact on transmission of HIV in the US. As evidenced from these data MSM, particularly Black MSM and Black and Hispanic women who acquire HIV through heterosexual route are priority populations for future research.

As of December 31, 2005, nearly 20,000 young people between ages 13-24 were living with HIV infection in the 33 states with mature HIV reporting systems. This number understates the actual extent of infection among young people as it omits infections in about one-third of the states and does not account for the considerable number of young people who are unaware of their HIV infection. (CDC, 2007a) Blacks account for 55% of infections among young people 13-24,

with heterosexual females and young MSM accounting for the majority of new infections among young people. Risk factors for young people include early initiation of sexual activity, lack of awareness of the risk associated with unprotected sex, low rates of HIV testing, and the silence and stigma often associated with same-sex attraction among young people. (CDC, 2006f)

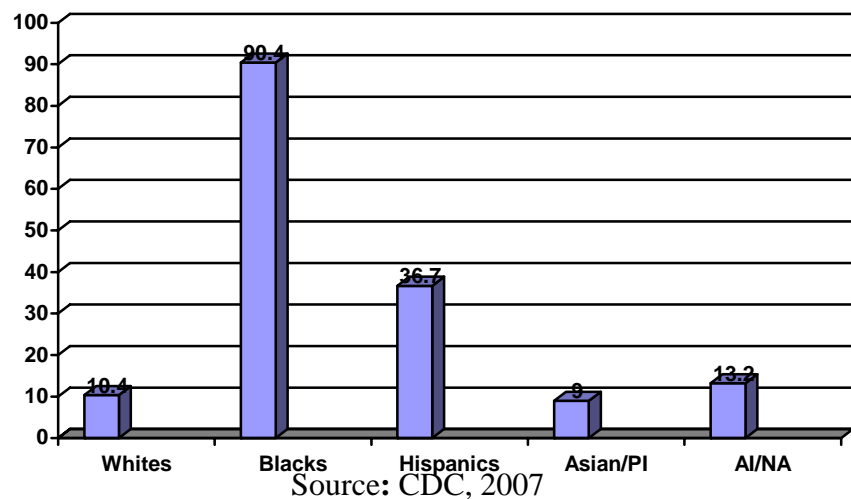
Although transgender individuals have long been known to be at risk for HIV infection, reliable data on the extent of HIV infection and on the frequency of sexual and drug-using risk behaviors in this population have been limited. A survey by the New York City Department of Health and Mental Hygiene of the “house ball” community found that 18% of male-to-female transgender individuals were HIV-infected.

As a result of improvements in HIV treatments, HIV-related mortality has fallen sharply over the last decade. Two-year survival for people diagnosed with AIDS rose from 44% from 1981-1992 to 85% from 1996-2000. (CDC, 2006a)

Improvements in survival have been more marked for HIV-infected whites than for Blacks. The combination of stable HIV incidence and declining mortality due to improved treatments has resulted in a slow but steady increase in HIV prevalence, as reflected in CDC’s increase in 2005 of its estimate of national HIV prevalence. (Glynn, 2005)

A growing proportion of new HIV infections involve transmission of drug-resistant HIV. Among new infections identified in a CDC-sponsored study of MSM in six US cities, evidence of drug resistance was present in 16% of the cases. (Eshleman, 2007) In New York City, nearly one in four (24%) treatment-naïve individuals with recent HIV infection were resistant to one or more classes of drugs in 2003-2004, with especially high resistance to non-nucleoside reverse transcriptase inhibitors. (Shet, 2006)

HIV/AIDS Case Rates (per 100,000 pop) by Race/Ethnicity, 2005, 33 States



HIV Prevention Successes and Challenges

Important successes in the prevention of HIV infection have been achieved in the US. As prevention efforts were brought to scale in the US, annual HIV incidence declined from more than 150,000 new infections per year in the mid-1980s to an estimated 40,000 by the late 1990s. (CDC, 2006c) Following the development and widespread implementation of programs to prevent mother-to-child transmission, the estimated number of perinatally-acquired HIV infections declined from a peak of 1,650 new infections in 1991 to an estimated range of only 144-236 in 2002. (CDC, 2006b) As a result of improvements in blood screening technologies, the risk of HIV transmission as a result of a blood transfusion may be as low as one per 2 million blood donations. (Dodd, 2002) In addition, implementation of harm reduction programs in numerous locales throughout the U.S. has contributed to sharp declines in new HIV diagnoses among injection drug users. (Institute of Medicine, 2006)

More than 50 behavioral interventions have been demonstrated to be effective in promoting safer behaviors among various risk groups, although few of these approaches have been evaluated for their effect on biological endpoints (i.e., HIV or sexually transmitted infection (STI) incidence), and none has been sufficiently scaled up to permit an assessment of impact on HIV incidence. (CDC, 2006c)

Yet there remains an urgent need to improve our ability to prevent new HIV infections in the US. As noted, no decline in the rate of new infections has been detected over the last decade, and there is evidence that HIV incidence is higher than earlier estimates suggested. The rate of new infections is greatest at this stage of the epidemic in the Southern part of the U.S. although significant transmission continues in other regions, most notably highest rates remain in the Northeast and Mid-Atlantic states. New infections in the South are concentrated among poor, heterosexual Blacks, with an especially notable burden among women, whose vulnerability to HIV infection typically stems less from their own levels of risk behavior but from the sexual and drug-using behaviors of their male sexual partners. In some US cities with large gay communities, increasing infection rates have been observed among older, white MSM, in addition to the alarmingly high HIV incidence among Black MSM. (New York City Department of Health and Mental Hygiene, 2005) In New York City, recent report indicates an alarming increase in HIV infections among MSM <30 years of age with a doubling of infections among MSM between ages of 13-19 years. (New York City Department of Health and Mental Hygiene, 2007)

The frequency of unprotected anal intercourse among MSMs appear to have increased in recent years, reflected most vividly in the sharp rise in syphilis diagnoses in this population in recent years. (Task Force on Community Preventive Services, 2007) The trend toward riskier sexual behaviors in the MSM population has been variously attributed to optimism regarding HIV

treatments, prevention fatigue, and increased use of methamphetamine and other drugs in conjunction with sexual intercourse. (AmFAR, 2006)

Especially worrisome are signs that an increasing proportion of individuals with newly acquired HIV infection harbor resistance to one or more classes of antiretrovirals. Among MSM testing HIV-positive in six US cities, 15.9% had evidence of resistance to antiretrovirals, with 3.6% exhibiting signs of resistance to multiple classes of antiretrovirals. (Eshleman, 2007) These troubling behavioral and epidemiological trends among MSM may in part reflect a lack of access to prevention services for Black MSM in particular, as well as the curtailment of prevention efforts in the broader MSM population. Identification of new effective MSM-focused prevention interventions is needed to address an evolving epidemic.

The magnitude of the failure in the US to reduce the number of new HIV infections over the last decade is especially evident when placed in the context of the global epidemic. A number of low- and middle-income countries – most notably Thailand, Kenya, Uganda, Haiti, Zambia and Zimbabwe – have reported decreases in HIV incidence and prevalence in recent years. (Global HIV Prevention Working Group, 2007) The inability of the world's wealthiest and most powerful country to record similar achievements underlines the urgent need to sharpen and strengthen domestic HIV prevention efforts.

Key Recent Developments

The HIV prevention field has been affected in recent years by a number of medical developments, changes in the sociocultural environment in which risk behavior occurs, and improvements in the capacity of public health authorities to respond to the epidemic. For example, the treatment advances of the last 12 years have produced complicated and still not fully understood behavioral and epidemiological dynamics. With studies indicating that people diagnosed with HIV typically take steps to avoid exposing others to the virus (CDC, 2006d; Hays, 1997), CDC in 2006 revised its HIV testing recommendations to endorse routine HIV testing in health care settings. (CDC, 2006d) It has also been hypothesized, though not definitively confirmed, that antiretroviral therapy may reduce patients' infectivity by lowering viral load in genital secretions and plasma. (Porco, 2004) By contrast, evidence suggests that confidence in the ability of antiretrovirals to prevent HIV disease progression may partly be responsible for recent increases in HIV risk behaviors among men who have sex with men. (Stolte, 2004)

There have been notable improvements in recent years in the capacity of public health authorities to track the US epidemic, including recent infection trends. Use of assays such as the IgG capture BED-enzyme immunoassay, while certainly with its own limitations, have enabled researchers to identify recent infections among those found to be HIV-infected, providing insights regarding population differences in HIV incidence. (Schwarcz, 2007) HIV reporting is also

becoming more useful for purposes of HIV prevention planning and program targeting, as the percentage of recent infections among the newly diagnosed is growing over time. (Bennani & Torian, 2006)

Technologies for the prompt and accurate diagnosis of HIV infection have improved in recent years. Whereas HIV was almost universally diagnosed in the epidemic's early years via the ELISA/Western Blot antibody test, an expanding array of testing technologies now exist, including rapid tests, home collection kits, p24 antigen testing, detection of viral nucleic acid, and viral culturing. Together, these technologies have reduced the "window period" between HIV exposure and diagnosis of infection, as well as increased the accuracy of diagnostic efforts, with these gains most vividly seen in major improvements in the ability to prevent HIV-infected donations from entering the nation's blood supply.

In recent years, researchers have devoted extensive efforts to evaluating the HIV prevention efficacy of various "new prevention technologies," with the hope that behavioral interventions might soon be buttressed by a spectrum of biomedical or technological prevention tools. While studies in Africa indicate that adult male circumcision significantly reduces female-to-male sexual HIV transmission (see discussion below under biomedical interventions), trials to date have failed to demonstrate the effectiveness of vaginal microbicides, female diaphragms, use of acyclovir to treat herpes simplex virus (HSV), and pre-exposure antiretroviral prophylaxis (PrEP). (Gray, 2007) However, several trials are ongoing to investigate the HIV prevention potential of antiretroviral prophylaxis following sexual exposure (PEP), as well as PrEP for sexual exposure, use of antiretrovirals in serodiscordant couples, administration of acyclovir to reduce the contribution of Herpes simplex type 2 (HSV-2) infection, various preventive vaccine candidates, and additional vaginal microbicide products. (Global HIV Prevention Working Group, 2006.)

Prevention practice, as well as research focus in the field, significantly shifted after 2003, when the CDC launched its *Advancing HIV Prevention* initiative. In a departure from prior prevention efforts, which primarily targeted prevention services to individuals who were uninfected or unaware of their HIV status, *Advancing HIV Prevention* prioritized funding for initiatives that promote timely knowledge of HIV serostatus, link HIV-infected individuals to care, and provide tailored prevention services for HIV-positive people. The initiative is based in large part on strong evidence that most HIV-positive people avoid risky behaviors after their diagnosis and on the hypothesis that antiretroviral therapy reduces the risk of infection by lowering the patient's viral load. (CDC, 2003)

The majority of ongoing HIV prevention research efforts are occurring in the international arena in resource-limited settings. The latter studies are of critical importance to confront the massive global HIV epidemic. These studies also can potentially provide important insights and tools to control of the domestic HIV epidemic. However, findings from international prevention studies may not

always have direct relevance to the US HIV epidemic, particularly in view of the key difference between the two epidemics, a localized one in the US versus a generalized one in many resource-limited settings. For example, in the context of relevance of recent circumcision studies conducted in Africa, data indicate that rates of infant circumcision are much higher in the US than in most countries in Africa, while lower background prevalence of HSV-2 and other STIs in the US may limit the generalizability to the US of ongoing HSV-2 and other STI control trials in Africa. In addition, the societal and social context in which sexual and drug using behaviors occur and the different community norms may limit the direct relevance of interventions found to be effective in international settings to domestic settings and vice versa.

These factors – the important cultural and epidemiological differences between the US and other societal contexts, as well as the fact that most HIV prevention research is currently taking place in international settings -- all underscore the importance of a domestic HIV prevention agenda that is tailored to the special circumstances pertinent to the US. At the same time, opportunities for gaining insights through bridging studies that are conducted at both domestic and international HPTN sites should continue to be pursued.

Limitations of Available Epidemiological Data

Although significantly improved over earlier stages of the epidemic in the US, our epidemiological understanding of important aspects of the HIV/AIDS epidemic remains imperfect. While special epidemiological studies (such as the CDC-sponsored Young Men's Survey) have yielded insights on HIV incidence among MSM in certain urban areas, limited data exist on the rate of new infections among women in the US or among key subpopulations of women of interest (Black and Hispanic women from communities with high HIV prevalence). The use of new types of assays has permitted more elegant estimates of HIV incidence of certain populations of convenience, such as users of public HIV testing services, but the population-wide applicability of such findings is often unclear due to various selection biases. Due to the patchwork quality of state testing and disease reporting policies, HIV prevalence estimates are also often suspect.

Data on the size and geographic distribution of key populations are also lacking. No definitive, data-driven estimates currently exist regarding the number of sexually active MSM in the US, the number of individuals who actively inject drugs, the proportion of key communities at risk who use non-injection drugs or engage in risky sexual behaviors, and the number and geographical distribution of HIV-infected individuals who were previously incarcerated.

* * *

In summary, the HIV epidemic in the US continues unabated, with annual seroincidence now estimated to be higher than originally assumed. MSM and women are most heavily affected, accounting for nearly 75% of new HIV/AIDS diagnoses in 2005. Among racial/ethnic groups, Blacks have a notably higher HIV/AIDS burden, with substantial impact on Hispanics, as well. While important research has demonstrated the efficacy of a number of behavioral prevention interventions, these studies have focused on demonstration of an effect on self-reported risk behaviors and have yet to be tested to determine their ability in the field to reduce incidence of HIV or other sexually transmitted infections. In addition, no current studies are focused on HIV or STI incidence as an endpoint in the US. Although existing prevention strategies may have helped prevent a more severe expansion of HIV infection in the US, no decline in the annual number of new HIV infections has been noted in the US for the past decade.

Among MSM, the risk behavior category responsible for the largest number of new HIV infections in the US, strong evidence has emerged of an increase in unprotected anal intercourse (although Black MSM are disproportionately vulnerable to HIV even though they are less likely than whites to engage in risky sexual acts). Most alarmingly, recent data indicate an increase in incidence of HIV infection among young MSM in urban communities. In the context of women at risk, efforts to study various interventions have been hampered by the lack of precise information on populations at risk or the availability of accurate up-to-date incidence data to guide study design. Evaluations of prevention interventions for at-risk women should focus on specific communities in the US with high HIV prevalence. Renewed interest in domestic HIV prevention has emerged in recent years with the recognition of the need to address specific research gaps and to vigorously pursue efforts to identify effective interventions to prevent further spread of HIV in the US.

III. Current Status of HIV Prevention Research

Research to date has identified numerous efficacious strategies to reduce HIV risk behaviors. These include:

- *Behavioral interventions* that work at the individual, group and/or community level to promote changes in HIV risk behaviors and thereby help to reduce the number of new HIV infections. Existing behavioral interventions typically aim to affect cognitive constructs, individual skills and motivations, and/or social norms.
- *Biomedical interventions* that reduce the biological probability of transmission and can be used in combination with behavioral interventions. Interest in biomedical interventions to reduce the risk of HIV transmission or acquisition has gained prominence with enhanced understanding of the pathogenesis of

HIV infection, the role of co-morbidities, and the availability of antiretroviral medications and other products with anti-HIV activity.

- *Structural interventions* that aim to favorably alter the environment in which risk behavior occurs, regardless of the knowledge, attitudes or social patterns of individuals at risk.

As we describe below, an array of more than 50 behavioral interventions for various populations has been validated, as well as a limited menu of biomedical and structural interventions. However, key populations lack validated prevention methods, critical research questions remain unaddressed, and methodological weaknesses of much prevention research to date limit the confidence of policy makers in the evidence base for HIV prevention.

Prevention researchers in the US confront major challenges. In the setting of a generalized epidemic as in sub-Saharan Africa, the incidence of HIV and related risk behaviors enable inclusion of a large proportion of the population into prevention trials, given high background incidence. In contrast, the US epidemic is highly concentrated in particular vulnerable populations, including the very poor, users of illicit drugs, and MSM. Identifying and accurately characterizing populations that merit research attention can often be difficult, in part because HIV incidence and risk behaviors in populations may change radically over time. This is evidenced most strikingly by the epidemiological and behavioral changes exhibited by IDUs in the US. Groups at highest risk of HIV infection are often multiply disadvantaged, and some affected communities have little history of successful partnerships with medical or social science researchers. Institutional or legal issues – such as rules governing correctional facilities or the public policy preference in the US to prioritize criminalization over rehabilitation with respect to drug use – may also hamper research efforts and limit the range of permissible prevention strategies.

Behavioral Interventions

CDC identified 24 intervention studies completed prior to 2000 that demonstrated efficacy and met CDC standards for methodological rigor. (CDC, 2001) Ten of these pre-2000 best evidence interventions target heterosexual adults, five target drug users, eight are designed for youth, and five target MSM. All but three of the best evidence interventions from pre-2000 research provide for delivery of the intervention in group sessions, while nine of the programs include one-on-one individual sessions (including three that are delivered exclusively through individual sessions). Only four of the 24 best evidence interventions documented prior to 2000 are designed to operate at a community level. Eleven of the 24 interventions are delivered in health care settings, eight in community or commercial settings, two in educational settings, and one in a correctional facility.

In addition to these best evidence interventions reported prior to 2000, CDC also found that research reported between 2000 and 2004 identified an additional 18 best evidence behavioral interventions. (Lyles, 2007) Eleven of the most recent best evidence interventions specifically target minority populations. Heterosexual adults are targeted by half of the best evidence interventions reported between 2000 and 2004. MSM and injection drug users are targeted by three and five of the most recent best evidence interventions, respectively. Three of the interventions target young people (including two specifically designed for Black youths), while four of the interventions specifically aim to promote safer behaviors among people living with HIV.*

Ten of the best evidence interventions documented between 2000 and 2004 are delivered exclusively through group sessions, five solely in one-on-one sessions, and three via both group and individual sessions. Nine of the interventions are delivered, at least in part, in clinical settings. Seven of the interventions involve the participation of a licensed professional, such as a therapist, registered nurse, or social worker. Six rely on the involvement of peers for delivery of the intervention to the target population.

Various efforts have focused on identification of best evidence behavioral interventions for specific subpopulations at risk of HIV infection. A recent best evidence review for interventions targeted to MSM identified four efficacious individual-level interventions, 13 group-level interventions, and three community-level interventions. (Herbst, 2007) On average, the interventions reduced the odds of reported unprotected anal intercourse by 27% to 43%. Group-level interventions increased the chances of condom use by 81% among MSM studied. All but three of these interventions were specifically designed for non-white MSM. Two of the interventions aimed to influence the behaviors of drug-using MSM, although studies produced conflicting results, with no evidence of significant behavior change.

As described above, the preponderance of “best evidence” interventions focus on promoting safer behaviors during heterosexual intercourse. A number of these approaches have been specifically designed for at-risk minority women, especially among the more recent interventions studied between 2000 and 2004. With respect to best evidence interventions for women, there are both individual and group sessions, as well as delivery in a range of venues, including community service organizations, outpatient psychiatric clinics, family medical clinics, and STI clinics. (Lyles, 2007) Among women-targeted HIV prevention interventions that have been validated during this decade, all use group sessions, with the number of sessions varying from four to 16. Five of the interventions rely on female facilitators, while one is delivered by psychotherapists.

* Five of the best evidence interventions target multiple populations.

CDC has identified 11 efficacious behavioral interventions to prevent HIV infection in young people. These include both group- and behavioral interventions, with delivery sites ranging from clinical settings to residential and community sites. Important prevention gaps remain for young MSM of color, and community-level and structural interventions targeting young people remain largely unevaluated.

A systematic review by Herbst et al. (2007) identified six behavioral risk reduction interventions for HIV-positive men with prevention efficacy in terms of behavior change. Delivery venues include both community and clinical sites, with three of the interventions relying on HIV-positive peers for delivery. Only one of the interventions for HIV-positive men has been demonstrated to be efficacious for MSM, who constitute the largest single group of people living with HIV.

As described below in Sections IV and V, important research gaps and methodological limitations of intervention studies to date have limited the reliability of the evidence base for behavioral HIV prevention. The vast majority of best evidence interventions focus on participants' skills, attitudes, and norms, largely neglecting other factors that increase the risk for the HIV acquisition, such as substance use, certain mental health conditions, and consequences of childhood sexual abuse). Validated behavioral interventions are either scarce or non-existent for key populations, including Black MSM, abusers of alcohol or non-injection drugs, and high-risk partners of individuals with low risk profiles. Best evidence behavioral models have not been rigorously evaluated to assess the feasibility of implementation in the field or to determine their impact on HIV incidence. Similarly, the sustainability of the behavioral gains documented in best evidence studies is unclear, as trial participants have typically not been followed longer than 12 months.

As individuals with undiagnosed HIV infection are 3.5 times more likely to transmit the virus than those who are aware of their infection. (Marks, 2006) HIV testing serves as an important pillar of HIV prevention. Although it is technically a biomedical, diagnostic intervention, the prevention benefits of HIV testing primarily stem from its impact on risk behaviors. A positive HIV test typically prompts newly diagnosed individuals to reduce their risk behaviors. (CDC, 2006d; Hays, 1997) In addition to its behavioral benefits, timely HIV diagnosis may help ensure that HIV-infected individuals obtain antiretroviral treatment in a timely manner, which might reduce the patient's infectivity by lowering viral load. While the prevention benefits from a positive test result are apparent, the behavioral benefits for the uninfected are less apparent. Indeed, among MSM, frequent testing appears to be associated with riskier sexual practices (Mackellar, 2002), while sero-sorting among people who claim to have HIV-negative status (perhaps based on long past test findings) may lead to riskier behavior and the potential for increased HIV acquisition. (Butler, 2007)

To maximize the HIV prevention benefits of testing, CDC in 2006 recommended that health care settings routinely offer HIV testing to patients. (CDC, 2006d) CDC has also strongly encouraged increased use of rapid HIV testing, which increases the likelihood that individuals who present for testing will actually receive their HIV test results. While the prevention benefits for a positive test result are apparent, evidence indicates that HIV counseling and testing has limited utility as a primary HIV prevention strategy for uninfected individuals. (Weinhardt, 1999) An important ongoing HPTN study is evaluating community promotion of HIV testing in sub-Saharan Africa (HPTN 043). However, it is uncertain whether ultimate findings will have direct relevance for the US epidemic due to major differences in the characteristics of the epidemic in the two settings.

Biomedical Interventions

Few biomedical interventions have been demonstrated to have efficacy in preventing new HIV infections in the US. Cohort analyses have strongly correlated viral load with transmission risk (Quinn, 2000; Fideli, 2001), underscoring the HIV prevention importance of early HIV diagnosis, timely initiation of antiretroviral therapy, and strong treatment adherence. In a longitudinal observational study of 393 sero-discordant heterosexual couples, introduction of highly active antiretroviral therapy was associated with an 80% decline in the rate of sexual HIV transmission. (Castilla, 2005) However, no prospective study has validated therapeutic administration of antiretroviral drugs as an effective HIV prevention intervention. HPTN 052, a multi-country study that began enrolling in 2005, aims to assess and compare the impact of early and later initiation of antiretroviral therapy on subsequent HIV transmission among sero-discordant heterosexual couples.

The potential for antiretroviral therapy to play an important role in preventing new infections similarly underscores the overlap between biomedical and behavioral interventions, as initiatives to increase treatment adherence are vital to maximize the ability of available drugs to lower viral load and to minimize the risk of transmission of drug-resistant virus. Research to date has identified a variety of strategies to improve treatment adherence (Amico, 2006), although more effective interventions are needed to achieve adherence levels sufficient to prevent or significantly slow the emergence of drug resistance. (Chesney, 2006)

While the link between HIV risk and untreated STIs has been firmly established (Institute of Medicine, 1997) no study has documented the effectiveness of any particular STI control practice in preventing new HIV infections. (See discussion of biomedical interventions below.) Evidence is especially strong linking herpes simplex type 2 infection with increased risk of HIV acquisition. (Brown, 2007) However, unfortunately, HPTN 039, a five-country study of the impact of daily suppressive therapy for HSV-2 on HIV acquisition among individuals who are HIV-uninfected but seropositive for HSV-2 that enrolled women from international sites and MSM from three sites each in Peru and the US did not demonstrate

effectiveness of this intervention. (Celum, 2008) A similar study is ongoing with the goal of assessing effect of daily suppressive therapy for HSV-2 infection on transmission of HIV from co-infected patients to their HIV uninfected partners. .

As noted, evidence from studies as well as clinical practice has demonstrated the effectiveness of antiretroviral and other interventions in reducing the risk of perinatally-acquired HIV infection. Initiation of a four-week course of antiretrovirals following percutaneous exposure to HIV has similarly been shown to lower the risk of HIV transmission to health care workers. (Cardo, 1997) Although no studies have specifically assessed the effectiveness of antiretroviral prophylaxis following sexual or other non-occupational exposure, small studies have yielded promising indications of effectiveness. On the basis of these studies, observational data, findings from studies on prevention of mother-to-child HIV transmission, and biological plausibility, the CDC recommends use of antiretroviral prophylaxis following a non-occupational exposure where circumstances indicate a significant risk of transmission. (CDC, 2005c)

It has been similarly hypothesized that daily administration of antiretrovirals to HIV-uninfected individuals might prevent HIV infection by disabling or interfering with HIV when individuals are exposed to the virus. One antiretroviral agent currently under investigation is tenofovir, which has a long half-life and a favorable side effect profile. Studies have yet to validate the effectiveness of pre-exposure prophylaxis with use of antiretroviral drugs in preventing HIV infection, although efficacy trials for PrEP regimens containing tenofovir are currently underway in Thai injection drug users, African heterosexuals, and MSM in North and South America. While a study of PrEP conducted among high risk women in Ghana, Cameroon and Nigeria demonstrated the safety of daily oral tenofovir, effectiveness could not be demonstrated due to premature closure of enrollment at two study sites and limited number of HIV seroconversion events. (Peterson, 2007) With the exception of one safety study, ongoing research on PrEP is occurring in non-US settings.

Extensive studies have documented the effectiveness of needle exchange in reducing HIV risk behaviors and new HIV infections. (Vlahov, 1998) Substitution therapy (e.g., methadone maintenance, buprenorphine) has been shown to reduce illicit drug use and thereby potentially contribute to the prevention of HIV transmission through drug use. (Ward, 1999) Non-injection, non-opiate drugs have no validated pharmacological therapies. In particular, two factors discussed below that are highly pertinent to HIV transmission in the US – crack use, especially among heterosexuals in the South and in certain urban centers in the US, and stimulant use among MSM – lack any validated preventive or therapeutic regimen.

Results from randomized clinical trials conducted in Kenya, South Africa, and Uganda indicate that male circumcision reduces the risk of female-to-male sexual HIV transmission by roughly 60%. (Bailey, 2007; Gray, 2007; Auvert, 2005)

Some have suggested that adult male circumcision might also be a suitable prevention intervention for MSM in the U.S. This hypothesis has not yet been tested in the US, where the majority of males are already circumcised.*

Structural or Policy Interventions

Policy change to permit non-prescription, pharmacy-based sales of sterile syringes – a structural intervention – has proven effective in reducing the prevalence of needle sharing. (Groseclose, 1995) Otherwise, relatively few structural interventions have been validated in the US.

* * *

In summary, research to date has yielded important advances in the evidence base for certain HIV prevention interventions, but these have largely focused on behavioral rather than biomedical outcomes such as the incidence of HIV or STI. Relatively few “best evidence” behavioral interventions operate at a community level; few specifically address social networks or the socioeconomic context in which risk behavior occurs; and few have been assessed in the key populations of interest in the context of the US epidemic. In addition, many “best evidence” interventions depend on participants’ adherence to lengthy and exacting intervention protocols.

Alone among interventions studied to date, adult male circumcision has been demonstrated to have the most dramatic effect on the prevention of HIV acquisition in heterosexual men in resource-limited settings during sexual intercourse. However, the relevance of the findings to MSM and to the domestic HIV epidemic remains unknown. Needle exchange and expanded drug treatment access have helped reduce HIV seroincidence among IDUs, but these approaches have not been studied in clinical trials. In addition, few structural interventions have been studied.

Most importantly, few interventions of any kind have been proven efficacious in the prevention of HIV for key populations, including Black MSM and substance-using MSM. Although a number of interventions targeted women of color have emerged in recent years, both the small number of participants in these studies and limited range of available interventions fail to fully address the substantial risk faced by subpopulations of women at risk, particularly Black and Hispanic women. Most importantly only few utilize STI and non use HIV seroincidence as the endpoints. While important prevention studies that are ongoing outside the US may help inform prevention efforts in this country, the unique characteristics of the US epidemic, particularly its localized nature and the social context in which HIV is transmitted in the US, requires development of a robust research

* We are unaware of any study documenting the prevalence of circumcision among MSM generally or among key MSM subpopulations in the US.

agenda that specifically addresses the particular features of this country's epidemic.

IV. Major Unmet Prevention Needs

Over the last 10-15 years, several notable changes have occurred in the rates and patterns of new HIV infections. While HIV has always heavily affected populations in the US that are socially marginalized, the epidemic has become increasingly concentrated in recent years among minority populations with high rates of poverty and social and medical co-morbidities. As explained below, the epidemic's expansion has increased the urgency of effective HIV prevention measures for MSM (particularly Black MSM) and Black and Hispanic women from high prevalence geographic areas, people living with HIV and residents of correctional populations who are paroled or otherwise released back into communities that may have comparatively high HIV prevalence rates. What has remained constant is the epidemic's continuing evolution, requiring the ongoing evaluation and adaptation of HIV prevention strategies to ensure their relevance in changed circumstances to the populations most at risk.

Heavily Affected Urban Neighborhoods, Rural Areas and Social Networks

HIV is not evenly distributed geographically but tends to be heavily concentrated in neighborhoods with particular characteristics in common. The HIV burden is especially severe in gay urban enclaves and in urban minority neighborhoods where poverty rates are high and economic opportunities scarce. In New York City, for example, while fewer than one in four whites with diagnosed HIV/AIDS live in zip codes where 20% or more of households are in poverty, nearly two out of three HIV-diagnosed Blacks and Hispanics live in poor neighborhoods. (New York City Department of Health and Mental Hygiene, 2007) In the Harlem district of Manhattan, where 2.6% of residents have been diagnosed with HIV or AIDS, people of color represent 93% of the population, 37% live in poverty, and the neighborhood's drug-related death rate is twice as higher as the New York City average. (New York City Department of Health and Mental Hygiene, 2006a)

The HIV-infected poor do not solely live in urban areas. In the Southern US, for example, where a significant number of infections are scattered among poor Blacks in rural areas. (Hammett, 2006) Even in the rural South, however, evidence indicates the presence of dense social networks among heterosexual African-Americans that contribute to high rates of STIs and HIV infection. (Adimora, 2006) In the rural South, evidence indicates that the epidemic is largely driven by conditions of poverty, high rates of incarceration, and the risk of rapid spread of HIV within social networks. (Adimora, 2006) Understanding of the social structures of at-risk communities in rural areas remains incomplete, as most HIV-related research to date has focused on urban areas.

While HIV infections among MSM exhibit certain geographic patterns, MSM are in many respects a non-geographic risk population, in that they are broadly distributed throughout the US, in both urban and rural areas and in communities both rich and poor. Significant numbers of HIV infections among MSM are clustered in heavily gay neighborhoods in urban areas. In the affluent, predominantly white neighborhood of Chelsea in Manhattan, for example, 4.3% of residents have been diagnosed with HIV or AIDS, a rate roughly 3.5 times higher than the citywide average. (New York City Department of Health and Mental Hygiene, 2006b) A random survey of young MSM (ages 23-29) in West Hollywood in 2000 found that 10% of participants were HIV-infected. (Johnson, 2001)

Substantial numbers of MSM also live in non-affluent neighborhoods where the majority of residents are people of color. In New York City alone as of December 31, 2005, more than 11,000 MSM resided in the less affluent boroughs of Brooklyn, Bronx and Queens. Even in the affluent borough of Manhattan, more than 20% of HIV-infected MSM live in the heavily minority, lower-income neighborhoods of Harlem and Washington Heights.

Developing effective prevention strategies for MSM is challenging, as behaviors, social networks, risk of infection, and openness to various HIV prevention strategies may differ markedly from one locale to another. Interventions to reduce harm associated with crystal methamphetamine use in urban gay centers, for example, are likely to differ markedly from strategies to prevent HIV infection among Black MSM living in small towns or rural areas of the South. To date, ethnographic research to characterize diverse subpopulations of MSM in the US has not been fully developed.

While HIV prevention trials and specific epidemiological studies have occasionally recruited volunteers from particular neighborhoods, most interventions have used a population-based approach that may fail to capitalize on geographic or community structures that may support prevention service delivery or influence social norms. Similarly, as noted below, relatively few studies have specifically aimed to address the impact of social networks or to use such networks to facilitate prevention service delivery.

Blacks

In comparison to whites with similar behavioral characteristics, young Blacks with low levels of risk behavior are 25 times more likely to be infected with HIV. (Hallfors, 2007) Unprotected vaginal intercourse is the source of the vast majority of HIV infections in Black women, while the primary transmission route for Black men is anal intercourse between males. (CDC, 2007) Blacks' vulnerability to HIV has increased over time; while the AIDS rate for Black males was 3.4 times higher than for white males in 1990 (CDC, 1991), it was nearly eight times higher in 2005. (CDC, 2007) Similarly, while Black women were 13

times more likely than white women to be diagnosed with AIDS in 1990 (CDC, 1991), this imbalance had expanded to 23:1 by 2005. (CDC, 2007) Blacks tend to experience higher rates of poverty, incarceration and incidence of sexually transmitted infections. (Millett, 2007; Hammett, 2006)

A number of interventions have proven efficacious in reducing risk behaviors among various sub-populations of African Americans, although none have been shown to decrease HIV incidence. (e.g., DiClemente, 2004) In view of the extraordinarily heavy HIV/AIDS burden experienced by Blacks and other minority populations, the spectrum of interventions with demonstrated HIV prevention efficacy is relatively limited. (Darbes, 2006) Proven HIV prevention strategies are notably lacking for Black MSM (see immediately below) and for Black heterosexual males. In addition, few of the studies that have evaluated interventions targeting African Americans have incorporated biomedical endpoints; most follow participants only for brief periods of time, precluding reliable conclusions on the long-term impact of prevention interventions; and many studied interventions include features that may inhibit their effectiveness in the real world, such as requiring participation in multiple, multi-hour sessions over several weeks. Efficacious intervention models that rely on Black social networks are also in short supply. As Blacks on average are less likely than other racial/ethnic groups to know their HIV serostatus (MacKeller, 2006), effective strategies to promote HIV testing are also needed for this population.

MSM

MSM account for the largest single share of new HIV cases among all risk categories. Following many years of decline, the proportion of MSM among diagnosed HIV/AIDS cases is on the rise. (CDC, 2007) Increases in HIV incidence among MSM have recently been identified in a number of high-income countries.

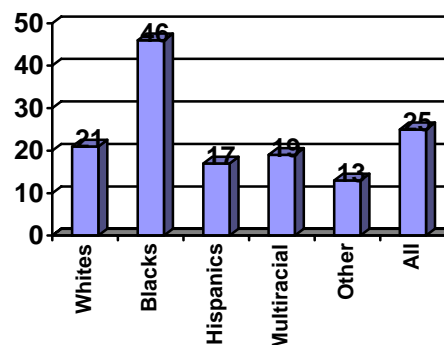
(Global HIV Prevention Working Group, 2007)

Numerous studies have detected an increase in unprotected anal intercourse among MSM coincident with advent of protease inhibitors in the mid-1990s.

(Task Force on Community Prevention Services, 2007)

Black MSM are at especially high risk of infection, with infection rates that are comparable to many of the most heavily affected developing countries. For example, a CDC-sponsored five-city survey found that 46% of Black MSM were

**HIV Prevalence Among MSM,
5-City CDC Survey, 2004-2005**



Source: CDC, 2005

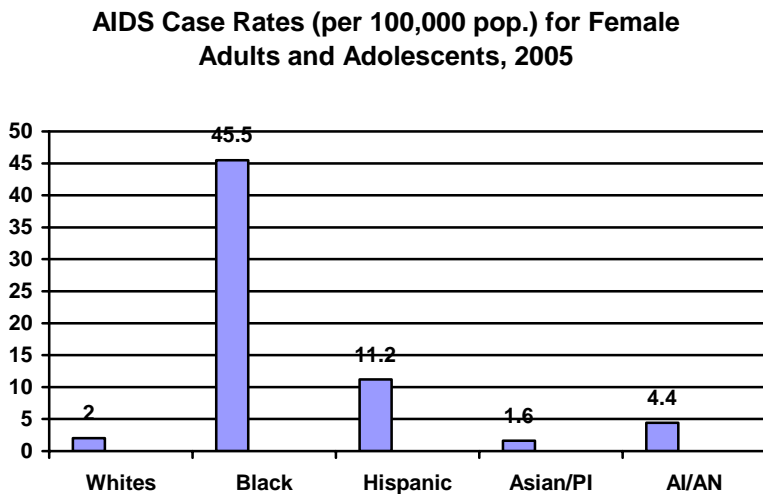
HIV-positive, with HIV incidence for all races and ethnicities ranging from 1.2% in San Francisco to 8.0% in Baltimore. (CDC, 2005a) Black MSM surveyed in six U.S. cities were eight times more likely to be unaware of their HIV infection than white MSM. (MacKellar, 2006) Recent data from New York City indicated a doubling of new diagnoses of HIV among MSM between ages of 13-19 years, with Black MSM twice as likely to have received positive diagnosis in 2006. (NYC Department of Health and Mental Hygiene, 2007)

The HPTN 015 (EXPLORE Study) has provided important insights into the transmission of HIV among MSM in the US. MSM who have symptoms of mental health disorders are at higher risk for HIV infection (Koblin, 2006), as are MSM with a history of childhood sexual abuse. (Saewyc, 2006; Kalichman, 2004) MSM also report high rates of alcohol and drug use, which is associated with unsafe sex. (Gorman et al., 2004; Stall, 2001) Especially noteworthy is the association among MSM with HIV risk and use of stimulants and club drugs. (Colfax, 2006)

As for other populations, efficacious HIV prevention interventions for MSM overwhelmingly focus on participants' skills, attitudes and norms, with little attention paid to other factors that increase vulnerability to HIV. Few validated interventions operate at a community level, and no structural intervention has been systematically assessed for its efficacy in preventing HIV infection among MSM.

Women

HIV/AIDS is the leading cause of death for Black women ages 25-34 and the third leading cause of death for Black women between ages 35-44. (CDC,



Source: CDC, 2007

2007b) While non-Hispanic Blacks represent 12% of all women in the US, they accounted for 66% of HIV/AIDS cases reported among women as of December 2005 in 33 states with mature name-based surveillance systems.

Heterosexual sex is the source of transmission in 80%

of HIV/AIDS cases among female adults and adolescents. Women in the South

have been most heavily affected; the number of Southern female adults and adolescents diagnosed with AIDS from 2001-2005 is almost twice as high as the number in the Northeast and roughly six times higher than the number diagnosed in the Midwest or the West. (CDC, 2007)

A recent review of published studies identified seven women-targeted interventions with evidence of efficacy in reducing unprotected sexual intercourse. (Lyles, 2007) None of these studies, however, used HIV as an endpoint in evaluating the behavioral intervention, although some have looked to STI incidence as an outcome. These studies followed trial participants for no more than 12 months. Participants in these intervention studies for women were required to attend as many as 16 sessions, potentially limited the feasibility of these interventions in the field. Few interventions studied have attempted to influence social networks of women or sought to change the sexual behaviors of women's sexual partners.

NIH is currently sponsoring 15 HIV prevention studies in women. These include evaluations of targeted interventions for homeless women, drug users, victims of sexual abuse, and women with mental health disorders. These studies, however, are of limited size and are focused on behavioral rather than on biological outcomes.

Several prevention research gaps exist with respect to interventions for at-risk women. Continued efforts are needed to develop HIV prevention technologies that women can control. Additional interventions are also needed to reduce the HIV-related vulnerability of women who are involved with the criminal justice system. Effective prevention programs are required that take account of the economic and social factors that increase vulnerability, including for poor, urban Black and Hispanic women as well as rural Black women in the South. Strategies that favorably influence the gender norms and behaviors of men are also needed, as are programs that use women's social networks to promote safer behaviors.

People Living with HIV

As HIV prevalence increases due to favorable impact of antiretroviral therapy on mortality and with the associated improvement in quality of life, opportunities for HIV transmission may increase at a population level. The likelihood of transmission is especially elevated with respect to HIV-infected individuals who are unaware of their infection or who have been diagnosed but are not in care. (Marks, 2006) As noted, CDC estimates that approximately one-quarter of people living with HIV are unaware of their infection (Glynn, 2005), with Blacks more likely than other groups to be HIV-infected but unaware.

Although a positive HIV test result typically motivates individuals to avoid exposing others to the virus, a substantial percentage of people living with HIV

continue to have unprotected sexual intercourse, including with non-steady partners with unknown serostatus. (Denning, 2005) According to a 16-site survey of HIV-positive MSM, 40% of sexually active MSM reported engaging in insertive anal intercourse in the prior 12 months, with one in four such men reporting that they did not use a condom. (CDC, 2004) High rates of risk behavior have also been reported among patients with an ongoing relationship with an HIV primary care provider. (Absalon, 2005)

Over the past decade, increased attention has focused on the development of HIV prevention strategies for people living with HIV. A meta-analysis of prevention programs targeting HIV-positive individuals found that such programs collectively resulted in a 43% relative reduction in unprotected sex and a decreased acquisition of STIs. (Crepaz, 2006) To facilitate the delivery of HIV prevention services for HIV-positive individuals, the Public Health Service recommends the integration of HIV prevention activities in clinical settings. (CDC, 2003) Unfortunately, studies indicate that many clinical settings have yet to take steps to incorporate HIV prevention into clinical encounters or office operations, in part because time constraints sometimes inhibit delivery of prevention messages in busy medical practices. (Yarnall, 2003)

Finally, individuals with acute HIV infection may have particularly high infectiousness and unlikely to know their new serostatus, resulting in the transmission of HIV to sexual partners in their social networks. (Pilcher, 2005) In a recent study in Quebec, approximately half of all recent HIV infections were associated with the rapid transmission of HIV among acutely infected individuals. (Brenner, 2007) (This finding has not been confirmed in other settings.) In Sections V and VI, we discuss the urgency of developing effective strategies to identify cases of acute HIV and to intervene to minimize the risk of further HIV transmission.

Releasees and Residents of Correctional facilities

History of prior incarceration is an important risk factor for HIV infection in the US. In addition, inmates in prisons and jails have been noted to have HIV prevalence rates several times higher than the general population. Rates are especially elevated in the Northeast, where 3.9% of male inmates and 7.9 % of female inmates were found to be HIV-infected in 2004. (Bureau of Justice, 2006) Individuals entering correctional facilities have much higher HIV prevalence than similar populations in non-correctional settings. Most striking is the heavy HIV burden among women in correctional settings. For example, HIV prevalence among Black female prisoners in New York State remained stable at 14.5% between 1988 and 2003, while prevalence among all other demographic groups declined (Wang, 2006.)

In 1999, 26% of all people living with HIV in the South were released from prison or jail that year. (Hammett, 2006) There is limited evidence to support the

occurrence of HIV transmission in prison from one study (CDC, 2006g), although reliable data do not exist on HIV incidence in correctional settings in general.

Blacks are especially affected by the close linkage between HIV and time spent in a correctional setting. This is likely due to similar and overlapping risk factors for both or the possibility of increased risk due to incarceration experience. One in three Black men will be incarcerated during his lifetime, compared to 1 in 17 white men. Black women are seven times more likely than white women to be incarcerated. In the South, where overall incarceration rates are highest, substantial numbers of poor, rural Black women living with HIV are incarcerated each year in southern correctional facilities. (Hammett, 2006) Upon release, HIV-infected inmates return to their communities, potentially exposing their sexual partners to HIV infection. (Adimora, 2006) Thus, the implementation of effective prevention strategies within correctional facilities is an important priority with the availability of large populations of HIV-infected individuals. In addition, effective interventions for those without HIV-infection are also critical in order to prevent the acquisition of HIV after release. In addition, the contribution of incarceration to societal disruption and consequently on risk of HIV in specific communities, needs particular emphasis.

Basic HIV prevention tools – such as condoms and clean injection equipment – are unavailable to inmates in most correctional systems. Similarly, HIV testing policies vary widely between correctional systems. Some community-based organizations currently provide HIV prevention services in correctional settings, but the extent of such services is unclear and most such efforts have not been rigorously evaluated for effectiveness. Establishment of high quality HIV-related services within correctional facilities is also critical in order to enable access to appropriate therapeutic and preventive interventions for those with HIV infection. Few HIV prevention services are specifically targeted to individuals who have been released from correctional facilities. Linkage of HIV-infected inmates to post release organizations and facilities is critical in order to ensure continuity of their therapeutic program as well as to reinforce important prevention messages.

* * *

In summary, research to develop more effective strategies to prevent HIV infection among MSM, Black and Hispanic women can be expected to have a significant effect on incidence of new HIV/AIDS diagnoses in the US. Black MSM have HIV prevalence similar to some of the most severely affected countries in sub-Saharan Africa, with 46% of Black MSM participating in a five-city survey of MSM in the US testing HIV-positive. Incidence of HIV in MSM in the US, particularly Black MSM, rivals incidence rates in several countries in sub-Saharan Africa. Black and Hispanic women account for more than 80% of new HIV/AIDS diagnoses reported among women in the U.S., with 80% of these infections acquired through heterosexual transmission.

Interventions are urgently needed to strengthen HIV prevention in these highly vulnerable populations. In developing and evaluating new prevention approaches for these key populations, attention should be given to the localized “hot spots” in the HIV risk in the US whether based on geographic patterns or risk patterns. For Black and Hispanic women, this involves densely populated Black and Hispanic neighborhoods in urban areas and in more geographically dispersed rural areas in the South. While for MSM, it is defined by specific vulnerable populations.

V. Priority Research Focus for the HPTN Domestic Prevention Effort

While individuals with high risk behaviors remain at risk for acquisition of HIV infection, a remarkable paradox has been noted in various studies of HIV in the US. While some Black as well as Hispanic women and Black MSM report relatively low risk behaviors (Millett, 2006), they remain at substantially higher risk for HIV acquisition compared to their white counterparts who report similar low rates of risk behaviors. This central paradox must inform the development of the domestic agenda. This section describes the factors that appear to have produced the paradox of high HIV risk in the context of low risk behaviors, summarizes key factors associated with high risk behavior, and proposes high-priority research concepts to address the factors that increase HIV risk and/or risk behavior. Important issues affecting the design and conduct of HIV prevention trials under the proposed research concepts are also discussed.

Factors That Increase Risk in the Context of Low Risk Behaviors

A number of factors contribute to the paradox of high HIV risk in the context of low risk behaviors. Improving our capacity to reduce HIV incidence in the most heavily affected groups will require the development of interventions that address such factors.

Sexual Networks that Include Individuals with Chronic HIV Infection

Limited data suggest that high background HIV prevalence, nature of relevant sexual and social networks and the rapid transmission that may occur within sexual networks as a result of acute HIV infection and untreated STIs may explain the high rates of infection among Black MSM. (Millett & Peterson, 2007; Bingham, 2003) Various programs – such as the Popular Opinion Leader intervention tested with a primarily white population of MSM (Kelly, 1991) – aim to capitalize on social networks for the delivery of HIV prevention messages. Data also suggest that sexual networks may be effectively used to identify cases of undiagnosed HIV infection. (CDC, 2005) Yet few sexual or social network interventions have been evaluated in Black MSM or in other heavily affected populations, such as at-risk women. (Weeks, 2002)

Even with the availability of treatment opportunities for people living with HIV in the US, individuals with chronic infection confront an array of impediments to health care access, service utilization, and optimal medical outcomes. (Institute of Medicine, 2004) These include individual barriers (e.g., drug or alcohol abuse, mental illness, homelessness or housing instability, child care responsibilities, lack of transportation, lack of health insurance, attitudinal barriers to treatment adherence, co-morbid conditions), as well as structural impediments (e.g., waiting lists and restrictive formularies for federally-supported AIDS drug assistance, poorly developed HIV primary care and social service infrastructure, interruptions in services due to funding shortfalls, or shortage of services tailored to the specific needs of a particular population).

Partners of Women at Risk

Studies have found that Black women who themselves report low rates of risk behavior may often be exposed to HIV by men who have been previously incarcerated, secretly engage in sexual activity with other men, or have a history of drug use. (Adimora, 2006) Such findings, as well as various conclusions that have been drawn from available data in the popular media, have sometimes proven controversial. (Roberts, 2003) Some may also be unaware of their sexual partners' HIV seropositivity (due to their failure to disclose) or their partners may truly be unaware of HIV status. In view of the absence of women-controlled HIV prevention methods and the generally low levels of risk behavior reported by at-risk women, effective HIV prevention for women requires influencing the behaviors of their male sexual partners. Only limited research to date has focused on strategies to alter the sexual attitudes and behaviors of heterosexual men. Likewise, prevention programs for men who are bisexually active have primarily focused on reducing unprotected anal intercourse with another man.

Lack of Knowledge of HIV Serostatus

Another factor that may influence the higher rates of HIV infection in Blacks is the large proportion of individuals who may be HIV-infected but are unaware of their HIV status among Blacks. Research is needed on effective strategies to promote knowledge of serostatus among the estimated one-quarter of HIV-infected individuals who are unaware of their infection. The longer a case of HIV infection remains undiagnosed, the greater the likelihood that the individual will unknowingly transmit the virus. In New York City, 28% of AIDS cases in 2004-2005 received their AIDS diagnosis within 31 days of first testing HIV-positive (New York City Department of Health and Mental Hygiene, 2006b), a finding that highlights the need for interventions to encourage more timely diagnosis of HIV.

Studies of HIV-infected individuals have associated a positive HIV test result with adoption of safer behaviors (CDC, 2006d; Hays, 1997), but clear evidence is lacking that interventions to increase testing uptake (e.g., routine testing in health care settings, mandatory testing in correctional settings, laws to streamline

informed consent process) have an impact on HIV incidence. Research to evaluate the effectiveness of testing as a component of an intervention to decrease the risk to members of the community or sexual network is needed. In addition, HIV counseling and testing may not currently be effective as a primary HIV prevention strategy for individuals who test negative. (Weinhardt, 1999) Research is needed on strategies to improve the impact of HIV testing as a meaningful HIV prevention intervention for uninfected individuals.

Acute HIV Infection

As the magnitude of plasma viral load is closely associated with the likelihood that an individual will transmit HIV to others, it has been increasingly recognized that the high-grade viremia associated with acute infection may be responsible for a substantial number of new HIV infections. (Wawer, 2005) Recent mathematical modeling has estimated that individuals in the acute infection phase are the source for 8.6% of all new sexually transmitted HIV infections in the U.S. – a smaller number than has generally been assumed (Pinkerton, 2007) – although a recent phylogenetic analysis of recent HIV infections in Quebec suggested that half of all new HIV infections could be tied to individuals with acute infection. (Brenner, 2007) As the Quebec study underscored, introduction of one or more cases of acute HIV infection into social networks can result in the rapid spread of infection throughout the network.

Effective interventions to address acute infection face considerable obstacles. Many individuals may fail to present with signs and symptoms suggestive of such infection to their primary care provider, while many providers may not be alert to the possibility of HIV infection, especially in primary care settings and emergency departments where some clinicians may have only limited experience with HIV/AIDS. In addition, the lack of specificity associated with the signs and symptoms of acute infection has also limited the ability to target those most likely to have such an infection. Moreover, while intensive efforts are needed to ensure appropriate preventive behaviors by individuals with acute infection, no consensus exists on the therapeutic benefits of antiretroviral treatment during acute infection. The many scientific and operational questions associated with acute infection warrant additional research.

Factors Associated with High Risk Behaviors

In addition to the paradox of high rates of transmission in the context of low risk behaviors, significant HIV transmission continues to occur as a result of high risk behavior. Especially in populations where background prevalence is elevated, these behaviors, some of which have only clearly emerged over the last several years, help accelerate the spread of HIV.

Stimulant Use Among MSM

Heavy use of crystal methamphetamine and other stimulants appears to be fueling a resurgence of the epidemic in urban MSM communities. MSM tend to use methamphetamines more frequently than other populations at high risk of HIV infection. (Stall, 2005) According to results of a 2004 Countywide Risk Assessment Survey in Los Angeles, 18.4% of MSM used methamphetamines in the prior six months. (Rohde, 2005)

Curbing the use of methamphetamines among MSM represents an HIV prevention priority. For individuals who are dependent on crystal methamphetamine, treatment appears to reduce drug use and associated depressive symptoms. (Shoptaw, 2005; Peck, 2005) However, treatment drop-out rates and frequency of relapse are higher among individuals addicted to methamphetamines and other stimulants than with users of other drugs. (Levounis, 2006) No validated pharmacological method currently exists to treat addiction to methamphetamines. Most studies that have been undertaken to date regarding prevention of crystal methamphetamine abuse have primarily focused on white MSM; relatively few data are available on the extent of methamphetamines use among non-white MSM and on its relationship to HIV infection in such populations. Clearly, there is urgent need for research to develop effective, evidence-based interventions to treat methamphetamine addiction.

To date, a number of approaches have been tried to reduce stimulant use among MSM, including cognitive behavior therapy, contingency management, and tailored cognitive behavioral therapy, all of which have been associated with a decrease in drug use and unprotected anal intercourse among MSM. (Shoptaw, 2005) However, none of these studies have focused on HIV incidence as the endpoint.

Other Forms of Non-Injection Substance Use and Alcohol Use

HIV prevention for drug users has historically focused on reducing the harms associated with injection drug use. Recently, however, studies have found that HIV prevalence among non-injection drug users may be as high and sometimes even higher than among injectors. (Des Jarlais, 2007; Friedman, 2003) While injection drugs pose a risk of HIV transmission through the use of unsterile injecting equipment, non-injection drugs may also facilitate HIV transmission by reducing inhibitions associated with risky sexual activities or by encouraging the exchange of sex for drugs. On the other hand, heroin, the most commonly injected drug in the US, has been shown to reduce libido, potentially curbing risky sexual behaviors among active users but raising the possibility of an increase in sexual activity upon cessation. (Daniell, 2002; De, 1973)

Among a cohort of at-risk women, no association was found between HIV infection and recent or lifetime use of injection drugs, but an association was detected with both recent and lifetime use of non-injection heroin, crack or cocaine. (Macalino, 2003) Among poor Black women living in the rural South, a strong correlation exists between crack use and HIV infection. (Adimora, 2006)

Studies in the US and internationally have found a strong association between alcohol abuse and HIV infection risk. (Chaisson, 2007; Koblin, 2006; Catania, 2001; Mbulaiteye, 2000) Among MSM, studies have consistently found that one of the factors with the strongest association with HIV infection is use of amyl nitrites during sex. (Schwartz, 2007b; Plankley, 2007)

As noted above in the discussion regarding crystal methamphetamine, validated pharmacological methods to prevent or treat dependence on non-opiate drugs do not presently exist. Studies have demonstrated that naltrexone, an opioid receptor antagonist, is effective in reducing the frequency and severity of alcohol relapse. (Latt, 2002) Episodic abusers of alcohol do not perceive a need for the use of naltrexone and other pharmacologic agents for treatment for alcohol dependence. For most non-injection substances, behavioral interventions can help reduce harmful substance abuse, but such interventions tend to be labor-intensive, time-consuming, and often not covered by private health insurance and none have shown an effect on HIV incidence.

Prioritization of Domestic Studies

In prioritizing domestic prevention interventions, the HPTN proposes that this be guided by an assessment of their potential impact on reduction of annual incidence in the US, recognizing the limitations of available data. In order to maximize this impact, the following characteristics of each intervention will be evaluated:

1. *Potential impact*, measured by the attributable risk of the transmission pathway to be addressed by the proposed intervention. The greatest unmet need likely would be defined by the pathways that provide an appreciable fraction of the US incidence.
2. *Plausibility to achieve the potential impact*, as measured by how persuasive are the proof of concept data that the intervention will affect the targeted transmission pathway.
3. *Feasibility, Affordability and Practicality* of implementing the intervention widely enough to realize a substantial effect.
4. *Strength of scientific proposal*, including availability of appropriate evidence from earlier phase of study.

5. *Efficiency of the research proposal*, such as use of factorial designs to assess multiple interventions in a single trial.
6. *For studies to be conducted by HPTN, consistency with HPTN strengths*, including uniqueness of HPTN scientific and site resources for trial design, conduct and analysis.

Key Design and Operational Issues

The HPTN proposes key design and operational issues that need to be taken in planning of a domestic prevention agenda. The following are elements that need to be incorporated in proposed studies:

Focus on HIV-Infected individuals

As noted, HIV prevention efforts have historically focused on HIV-uninfected individuals. The self-protective motivations that have animated traditional prevention efforts are unlikely to be effective with HIV-infected individuals, necessitating the development of new prevention models that address the unique needs and perspectives of people who are already infected. Although early studies have identified promising approaches to encouraging safer behaviors among people living with HIV, substantial additional research is needed to develop a broad array of prevention options for the population of HIV-infected people in the US.

Focus on Key Risk Factors

Existing prevention models primarily aim to build knowledge, motivation and skills for individual risk reduction. Few, however, focus on specific factors that increase HIV risk. No validated behavioral intervention address the use of stimulants among MSM, and best evidence prevention models for women fail to take account of the role of partner risk, crack use or the effects of severe poverty. Similarly, no proven prevention strategy exists for addressing individuals with acute HIV infection; available models do not target social networks of people at risk; and existing best evidence interventions typically do not take account of prior victimization, mental illness, or substance abuse.

Conduct of Multi-Site Studies

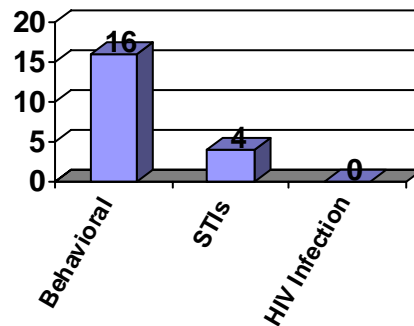
The nature of the epidemic in the U.S. is quite distinct from generalized epidemics in resource-limited settings. While the epidemic in the US is heavily concentrated in particular populations, such groups are often geographically disparate. Due to these factors, studies that evaluate the effect of prevention interventions on biological endpoints must be multi-site in nature and conducted in settings where pockets of the at-risk population exist. This factor lends itself

to the strength of the HPTN as a network with multiple sites situated in some of the severely impact communities in the US.

Biological Endpoints (e.g., HIV seroconversion, STI incidence)

The vast majority of efficacy studies on HIV behavioral interventions rely on self-reported behaviors of study participants as the outcome. Similar to other self-reported behaviors, self-reported sexual as well as drug using behaviors are subject to recall bias and to participants' desire to report information that is socially favored.

Endpoints in Best Evidence HIV Prevention Intervention Studies



Source: Lyles, 2007

(Weinhardt, 1998) Given that the goal of HIV prevention is to prevent HIV infection, measuring an intervention's impact on infection rates clearly represents the best way to assess prevention efficacy.

However, few prevention trials have used biological endpoints. (Herbst, 2007) Four of 18 HIV prevention efficacy trials deemed to meet criteria for scientific rigor developed by CDC's HIV/AIDS Prevention Research Synthesis Team assessed the intervention's impact on newly acquired sexually transmitted infections. Only one of the 18 studies supported by the CDC attempted to measure the intervention's effect on HIV incidence, with no significant effect noted. (Lyles, 2007)

The lack of behavioral intervention studies demonstrating an impact on the rate of new HIV infections (or, at a minimum, on other STIs) complicates efforts to ensure evidence based planning and resource allocation. Prevention trials are needed that utilize biological measurements as endpoints in order to demonstrate the impact of the experimental intervention(s) on the epidemic. Such trials will inevitably be more complex and costly than trials that rely solely on participants' self-reported behaviors, although use of STI incidence as a surrogate for HIV may help contain costs associated with essential prevention trials.

Longer Duration of Follow-up

Efficacy studies of prevention interventions in the US have typically followed study participants no more than 12-18 months, with many reporting the effect of the intervention immediately upon its completion. (Lyles, 2007; Herbst, 2007) Multi-year studies are needed to assess the sustainability of the behavioral gains identified to date in studies of behavioral interventions. The conduct of longer-term studies requires attention to participant retention and adherence with follow-up assessments. Due to the importance of determining the durability of the interventions, studies should have a minimum duration of 18-24 months.

Evaluation of Combined Interventions

Most prevention trials study a single intervention to determine its efficacy. (Lyles, 2007, Herbst, 2007) In the field, however, prevention programs often bundle multiple interventions. For example, a common approach might combine a media campaign to influence community norms, small-group educational and skills-building sessions, individual counseling, access to HIV testing, and condom distribution. To better inform prevention practice, studies that combine multiple interventions are needed. Experience has also demonstrated that biomedical interventions require behavioral components in order to optimize outcomes. In a recent clinical trial of female diaphragms for HIV prevention, study participants' limited adherence with device use may have influenced study results. (Padian, 2007) In addition, it is possible that behavioral interventions that have demonstrated limited efficacy on their own might achieve more robust effect when delivered in conjunction with a biomedical intervention or if combined with another behavioral intervention

Use of Community, As Well As Individual, Randomization

While virtually all best evidence intervention studies have randomized individuals between experimental and control groups, the concentration of HIV infection in particular communities offers the opportunity to use community randomization to evaluate the public health impact of experimental interventions. On the other hand, the use of such an approach adds various complexities, including the need to define communities with specific characteristics, outcome of interest and how to measure such an outcome. Two approaches that have been used to date include assessment of the outcome in cohorts recruited from the experimental and control communities, as well as tracking changes in the community over time. Successful conduct of trials on community-based interventions requires a partnership between researchers and leaders in the targeted communities.

Use of Interventions That If Proven Effective Can Be Easily Implemented

HIV behavioral interventions meeting best evidence criteria range in their duration from 1 to 32 hours to administer, with the number of sessions varying from one to eight. (Lyles, 2007) In general, trials have associated intensity and time required of an intervention in terms of sessions with the magnitude of the behavioral impact. In the real world, however, client retention is affected by the number of sessions and the total hours required for recipients of a prevention intervention. In selection of the interventions of interest, particular attention is needed to achieving this optimal balance between intervention dose, participant burden, and outcome of the intervention.

Cost-Effectiveness of Various HIV Prevention Strategies

In planning HIV prevention services, health departments and other providers inevitably work with finite resources. To maximize public health impact with limited resources, planners would benefit from reliable data on relative cost-effectiveness for various prevention approaches. Unfortunately, few data exist on the cost-effectiveness of different HIV prevention strategies. (Bertozzi, 2006)

Development of Feasibility Studies

Feasibility studies may be needed in order to determine key data in specific populations at risk (e.g. seroincidence, feasibility of specific recruitment strategy) and to evaluate the practicalities of implementing proposed experimental interventions. Community ownership and guidance are critical to the successful implementation of the proposed studies.

* * *

In summary, the current epidemiologic data in the US support the need for multi-site studies that capitalize on a deeper understanding of HIV transmission in specific populations. This research must focus on geographic communities with ongoing high rates of HIV transmission (“hot spots”) as well as other groups at high risk i.e., MSM. The HPTN proposes that research endeavors must also focus strategically on those who are HIV-infected but unaware of status or not in care, use of efficacious, multi-component interventions, utilization of social and sexual networks, and reliance on biological measures as the primary endpoints of interest.

VI. Other Key Prevention Research Questions

In addition to the areas of research described above and populations prioritized in previous section, other prevention research questions are important to delineate. Below is a list of research questions about behavioral, biomedical,

structural prevention interventions, categorized by population. This section also identifies gaps in epidemiological knowledge that are critical to understanding the US epidemic and informing the development and implementation of effective HIV prevention strategies.

Focus on MSM

What is the effectiveness of Internet-based interventions in reducing the risk of HIV among MSM?

Forty percent of MSM report using the Internet to locate sexual partners. (Liau, 2006) Studies have shown that MSM who use the Internet to find sex partners engage in high rates of risk behavior and often have more STIs and more partners than non-users. (Chaisson, 2007; Liau, 2006) The degree to which Internet use contributes to new HIV infections is not known, although various sexually-oriented websites have been implicated in syphilis outbreaks among MSM.

Certain MSM-oriented Internet sites have implemented various HIV prevention-related structural changes, such as expressly permitting men to indicate that they do not use crystal methamphetamines. In addition, some community-based organizations have created websites specifically designed to promote safer sexual behaviors. These interventions have not been rigorously evaluated to date. In addition to assessing the effectiveness of existing Internet interventions, research is required to evaluate new approaches, such as real-time prevention messages on sex-oriented websites and community-based programs that assist heavy users of such sites to explore their personal behavior and to develop individualized prevention plans to reduce risky behavior.

Can adult male circumcision be effective in reducing HIV infection risk for uninfected MSM?

As noted, adult male circumcision, validated as an effective prevention intervention in Africa, has not been studied in the US, where rates of circumcision are much higher. Blacks and Hispanics in the US are significantly less likely to be circumcised than whites (Laumann, 1997), suggesting that even if circumcision lacked broad applicability as a prevention strategy in the US, it might be a meaningful prevention tool for certain heavily affected populations. In the absence of US studies, few public health agencies and community groups are likely to promote the intervention in this country. It is also unclear whether anal intercourse poses a comparable risk to the insertive partner as occurs during vaginal intercourse, although recent epidemiological studies in Latin America suggest that circumcised MSM who engage only in insertive anal intercourse are less likely to become HIV-infected than uncircumcised MSM with comparable risk behavior. (Sanchez, personal communication 2007) Formative research may be needed prior to embarking on research in this area.

Does legal recognition of same-sex partnerships reduce HIV risk among MSM?

Feelings of shame and internalized homophobia are associated with HIV-related risk behavior among MSM. (Huebner, 2002) It has been suggested that public recognition of the civil rights of MSM, such as legal recognition of same-sex unions, might reduce risk behavior by alleviating stigma and internalized homophobia. (Stall, 2007) As the number of jurisdictions recognizing same-sex unions is on the rise, it might be feasible to assess whether such a legal change is associated with reduced levels of risk behavior among MSM. Alternatively, risk behaviors among MSM living in states that recognize same-sex unions could be compared with those in MSM living in states where such a civil right is not recognized.

What is the prevalence and public health impact of sero-sorting among MSM?

Limited evidence suggests that many MSM are selecting sexual partners who report having a concordant HIV serostatus. (Osmond, 2007) Widespread use of the Internet among MSM for selection of partners is believed to facilitate sero-sorting. Data on the prevalence of serosorting by MSM are presently available only from certain metropolitan areas, and no reliable evidence is currently available on the public health impact of serosorting. While the San Francisco Department of Public Health and some community organizations have promoted serosorting as an HIV prevention strategy, others caution that the preventive effectiveness of sero-sorting depends on the accuracy of individual disclosures. (Butler & Smith, 2007) A CDC-supported multi-site study found that 7% of MSM who told their sexual partners they were HIV-negative were actually infected with HIV, including 24% of Black MSM. (MacKeller et al., 2006) Additional research is needed to clarify the prevalence of serosorting among subpopulations of MSM and to assess the impact of such behavior on overall HIV incidence.

Focus on Young People

What interventions are most effective in reducing HIV infections among young Black MSM?

Although Black MSM generally face a disproportionate risk of HIV infection, vulnerability to infection is especially acute for young (under 30 years of age) Black MSM. Recent data from New York City indicate that in 2006 among adolescents, more than 90% of MSM populations under 20 years of age who were diagnosed with HIV were Black or Hispanic. (NYC Department of Health, 2007) According to CDC-sponsored surveys of young MSM in seven US cities in the 1990s, HIV prevalence was four and a half times higher among Blacks than in whites, and HIV incidence among young Black MSM was nearly six times higher. (CDC, 2001) As previously noted, Black MSM confront substantially greater risk of infection even though they are less likely to engage in unprotected anal intercourse than white MSM. Research priorities for young Black MSM

include ethnographic research to improve understanding of the social networks in which young Black MSM live, intervention strategies that take account of key factors that may increase risk (e.g., untreated STIs, depression and other mental illness, history of victimization, intergenerational sex, etc.). Structural interventions that increase the self-esteem, empowerment and acceptance of Black MSM in their communities and social networks should also be explored.

What additional non-school-based interventions are available to prevent new infections among young people?

While school-based HIV prevention and education programs may play a role in preventing new infections among young people (Kirby, 2004), they frequently confront major obstacles. Applicable regulations in many jurisdictions mandate exclusive use of abstinence-oriented programs, even though evidence reveals that such approaches are not effective in reducing STI incidence among young people. (Underhill, 2007) School-based programs may fail to address the unique needs of gay and bisexual youth and also cannot reach homeless or runaway youth. While a limited number of community-based prevention models have been validated for young people (Lyles, 2007; CDC, 2001), such studies suffer from methodological weaknesses outlined above, including short follow-up, reliance on non-biological endpoints, and a general failure to use community-level or social network approaches.

Focus on HIV-infected individuals

Are brief, clinician-delivered HIV prevention messages effective in reducing HIV risk behaviors among HIV-infected individuals in care? Are other effective approaches available to reduce sexual and drug-using risk behaviors by integrating HIV prevention and treatment services?

Brief clinician-delivered prevention interventions have proven effective for a variety of health conditions, including smoking, obesity, alcohol abuse, depression and physical inactivity. (CDC, 2003) The Public Health Service recommends that HIV prevention activities be integrated into clinical settings (CDC, 2003), although little guidance regarding the optimal content, dose and mode of delivery is available in published HIV-related studies. Early studies suggest that clinician-delivered prevention interventions may reduce the frequency of patients' unprotected sex. (Fisher, 2006) Additional research is needed to confirm the effectiveness of clinician-delivered HIV prevention messages and to inform the development and implementation of optimally effective approaches.

What is the impact of effective antiretroviral treatment of chronically infected patients on the risk of HIV transmission?

Although there is biologic plausibility to the hypothesis that antiretroviral therapy can prevent new HIV infections by reducing the infectivity of HIV-positive individuals, this hypothesis has been evaluated only in observational studies but has not been confirmed by clinical trials. (An ongoing study (HPTN 052) is evaluating the effect of antiretroviral therapy on HIV transmission in sero-discordant couples in international settings.) The degree to which improvements in HIV treatments result in risk compensation among at-risk groups is also a matter of continuing scientific discourse.

To reduce viral load and to sustain this effect, antiretroviral therapy must be effective. In this regard, a high level of treatment adherence is essential to prevent the development of drug resistance. (Paterson, 2000) In particular, depression and other mental illnesses, current substance abuse, and housing instability have been demonstrated to pose major impediments to HIV treatment adherence. (Gordillo, 1999) Although a number of interventions have proven effective in increasing treatment adherence among HIV-infected individuals (Simoni, 2003), studies of HIV-infected patients have noted that as few as 6% adhere to treatment at optimal levels (Golin, 2002), underscoring the importance of developing more effective strategies to improve treatment adherence.

What are possible effective interventions for prevention of HIV transmission from individuals with acute infection?

As noted, estimates vary widely regarding the proportion of new HIV infections that are attributable to acute HIV infection. (Brenner, 2007; Pinkerton, 2007) Additional epidemiological research is required to better define the actual role of acute infection in the transmission of HIV and to investigate possible interventions to prevent such transmission, including whether use of antiretroviral drugs soon after seroconversion can reduce infectivity while conferring a clinical benefit to the individual with HIV. Improvements in HIV testing technologies, combined with a better understanding of the manifestations and potential importance of acute infection, have improved the ability to diagnose recent infections, but only at population-level, (Patel, 2006), further highlighting the potential to develop and evaluate preventive and therapeutic interventions for individuals with acute infection. Research is also needed to determine the extent to which counseling of acutely infected individuals might lead to favorable behavioral changes, as early studies of small cohorts of MSM indicate a sharp drop in sexual risk behavior following diagnosis with acute infection. (Remien, 2007)

Focus on drug and alcohol users

How can sexual and drug-using risk behaviors be reduced among injection drug users?

In the 33 states with HIV reporting systems, nearly 120,000 individuals who contracted HIV infection through injection drug use were living with HIV at the end of 2005 (including MSM who inject drugs). (CDC, 2007) When undiagnosed individuals and those living in the 17 states without HIV reporting systems are taken into account, it is clear that the actual population of HIV-infected current or former injection drug users is substantially larger. Primarily through their sexual partners, HIV-infected IDUs serve as a potential epidemiological bridge to other populations, particularly to women.

Behavioral interventions have been shown to reduce drug-using and sexual risk behaviors among injection drug users. (CDC, 2001; DesJarlais, 1992) In general, however, the scientific literature on effective behavioral interventions to reduce drug injection is much scarcer than on structural interventions, such as programs that provide access to clean injecting equipment. While effective substitution therapeutic interventions exist for addiction to opiates (e.g., methadone, buprenorphine), no pharmacological intervention has been validated for the treatment of other substances that are often injected, such as cocaine or methamphetamine, underscoring the need for additional biomedical research to complement studies on new behavioral intervention strategies to reduce drug use.

What are the most effective strategies for preventing HIV infection as an indirect result of non-injection drug use?

The disproportionate use of crystal methamphetamines among MSM exemplifies a broader prevention challenge – how to reduce abuse of non-injection substances and how to reduce the contribution of such behavior to sexual exposures that result in HIV transmission. Studies have also demonstrated the association between crack use and HIV seroconversion. (Adimora, 2006) As with the evidence regarding prevention and treatment of crystal methamphetamines above, the evidence base for the prevention and treatment of dependence on non-injection drugs is limited. Similarly, validated interventions to reduce sexual risk in the context of drug use do not currently exist.

What are the most effective strategies for reducing alcohol abuse among specific populations, such as MSM, urban minority groups, and persons living with HIV?

Alcohol abuse is strongly associated with higher levels of HIV risk behaviors, including unprotected sex and injection drug use. (NIAAA, 2002) This association has been observed in a number of populations, including MSM,

urban minority groups, adolescents and people living with HIV. Due to the likelihood that individual-level interventions will be insufficient to produce the broad-based, sustained changes in alcohol consumption needed to sever the link between alcohol and HIV/AIDS, there is a need for research to study the effectiveness of particular structural interventions to reduce risk behaviors associated with alcohol abuse (e.g., restrictions on alcohol advertising, zoning changes for alcohol-oriented establishments, taxes to increase the price of alcoholic beverages, etc.). Such research should be supplemented by efforts to develop community-level interventions tailored to specific at-risk populations.

Focus on incarcerated men and women

How can the risk of HIV infection be reduced among women with potential, current or prior involvement with the correctional system?

Women who become involved in the criminal justice system have high rates of HIV infection, with infection rates that are often twice as high as for male correctional inmates and several times greater than among non-incarcerated women. At the same time, Black and Hispanic women of low socioeconomic status are at disproportionate risk of being incarcerated, and in the South large numbers of women from rural areas reside in correctional facilities. (Hammett, 2006)

One study of HIV-infected inmates at Connecticut's sole correctional facility for women found that HIV infection was strongly associated with a history of syphilis or genital herpes, minority race/ethnicity, and injection drug use. (Altice, 2005) In the South, incarcerated women living with HIV tend to be poor, Black and rural dwellers. (Hammett, 2006) Thus, research is needed to identify shared characteristics of women at high risk of incarceration, with the aim of informing the development of effective interventions that prevent incarceration and reduce HIV risk behaviors.

With respect to HIV-infected women in correctional settings, few prevention models have been developed and evaluated, despite the pressing prevention needs of this population prior to their release. Among HIV-infected women recently released from correctional settings, 26% report having engaged in unprotected sexual intercourse with their regular partners upon release. One-third of HIV-infected female correctional releasees having a regular partner report having engaged in unprotected sex with HIV-seronegative partners upon release. (Stephenson, 2006) Whether during their incarceration or upon release, such women require effective therapeutic as well as prevention interventions.

What is the behavioral impact of integrated HIV prevention and service/care linkage for correctional inmates/releasees?

Discharge planning for HIV-infected individuals being released from correctional facilities has, in the HIV arena, focused primarily on ensuring continuity of health care and promoting treatment adherence. As studies indicate that HIV-infected correctional releasees are likely to engage in sexual risk behaviors, research is warranted to determine whether integration of HIV prevention services (such as prevention case management) into discharge planning reduces risk behaviors among HIV-infected releasees. Early research suggests that HIV prevention case management may help promote healthier sexual behaviors among individuals released from correctional settings (Myers, 2005), highlighting the potential value of more extensive research in this area. Investigation is also warranted regarding potential structural interventions – such as housing assistance, job training, drug treatment and health care access – on HIV risk behaviors of correctional releasees. (Freudenberg, 2005)

Does condom programming reduce HIV incidence among male correctional inmates?

An epidemiological and behavioral study of male inmates in Georgia correctional settings demonstrates that unprotected sex among inmates is common, sometimes resulting in HIV transmission. (CDC, 2006) Such data has not been available from other settings. However, most prison systems consider condoms to be contraband, asserting that distribution of condoms may contribute to illegal sexual contact among inmates. While studies have found that condom programs would be acceptable to inmates and correctional staff, existing correctional condom programs have not been rigorously evaluated to determine their impact on HIV risk behaviors or incidence. (CDC, 2006) To assist in the development of evidence-based public policies on HIV in prisons and jails, research is needed to determine the actual public health impact of condom access in correctional settings.

Focus on victims of violence and/or sexual abuse

How can the risk of HIV infection be reduced among victims of violence and/or sexual abuse?

Experience of sexual or physical violence is strongly associated with HIV-related risk-taking, substance abuse, and mental health disorders. (Saewyc, 2006; Whetten, 2006; El-Bassel et al., 1998; Vlahov et al., 1998; Zierler et al., 1991) Among MSM in Los Angeles County, for example, users of crystal methamphetamine are three times more likely than non-users to report a history of domestic violence and 2.5 times more likely to have experienced sexual abuse. (Rohde, 2007) Despite the clear correlation between HIV risk and prior experience of violence or sexual abuse, few validated HIV prevention

interventions exist for individuals who have been victimized by such acts. In one of the few intervention studies to address sexual or physical violence, Black female adolescents who reported a history of gender-based violence and who participated in a four-session HIV prevention intervention were significantly less likely than non-participants to engage in risky sexual behavior at six- and 12-month follow-up. (Wingood, 2006) Research is needed to better understand the relationship of victimization and HIV risk behavior, to identify various avenues for intervention, and to develop other effective interventions to reduce HIV risk in this population.

Focus on transgender individuals

What is the nature and frequency of risk behaviors for HIV among transgender individuals? How might a better understanding of the behaviors and social networks of transgender individuals inform the development of effective interventions for this population?

In comparison to non-transgender MSM who participate in New York City's house ball network, transgender females are more likely to have multiple sex partners, to exchange sex for money or drugs, and to report being depressed or experiencing a traumatic life event. (Murrill, 2005) In addition to high-risk sexual behavior, transgender individuals may also be at risk for infection through the use of unsterile equipment for hormone injections. To inform the development of effective prevention strategies for transgender individuals and communities, better understanding of HIV prevalence and incidence in this population is needed, as well as behavioral research on relevant behaviors and ethnographic research on factors that increase risk among transgender individuals and on the nature and functioning of diverse transgender networks.

Cross-Cutting research questions applicable to all/many populations at risk

Is pre-exposure prophylaxis (PrEP) with antiretroviral therapy effective in preventing new HIV infections?

As noted, while international studies are ongoing to assess the effectiveness of antiretroviral drugs as pre-exposure prophylaxis, no such studies are currently underway that evaluate PrEP in women in the US. Moreover, additional research is merited on other possible antiretroviral regimens as pre-exposure prophylaxis, including combination regimens.

Is post-exposure prophylaxis (PEP) with antiretroviral therapy effective in preventing sexual transmission of HIV?

Although the prevention of HIV through initiation of an abbreviated course of antiretroviral therapy following sexual exposure is biologically plausible (Schreibman, 2003), trials have yet to demonstrate the effectiveness of this approach. CDC has recommended use of PEP where the risk of transmission is

significant, but use of the intervention is not widespread, potentially due to their limited dissemination, ambiguity of recommendations, lack of clear evidence of the effectiveness of PEP for sexual exposure, and questions regarding cost-effectiveness. The feasibility of an efficacy trial for PEP has been questioned, given the relative inefficiency of HIV transmission after a single high-risk exposure. Individuals who engage in repeated risk behavior may be more likely to benefit from PREP.

Are STI control interventions effective in reducing the risk of sexual HIV transmission?

Untreated STIs significantly increase the efficiency of HIV transmission and acquisition. In one household survey, cocaine use and the presence of HSV-2 antibody were the only factors significantly associated with HIV infection among African Americans. (McQuillan, 2006) Similarly, a comparison of HIV-infected and uninfected women in North Carolina found that HIV infection was strongly associated with a lifetime history of genital herpes. (CDC, 2005) HSV-2 infection was associated with HIV seroconversion among 4,295 MSM recruited in one behavioral intervention study. (Brown, 2006) Among MSM who received a syphilis diagnosis in San Francisco in 2002-2003, annualized HIV incidence was estimated to be 13.9%. (CDC, 2004) In addition, high rates of Chlamydia and gonorrhea have been reported in New York City neighborhoods with high HIV prevalence. (New York City Department of Health and Mental Hygiene, 2006)

Notwithstanding the strong correlation between untreated STIs and HIV transmission risk, studies of STI control as an HIV prevention strategy have produced conflicting results. (Hitchcock, 1999, Cochrane Review) Moreover, these studies have been conducted in resource-limited countries that have higher rates and a different spectrum of STIs and thus offer limited guidance for public health practice in the U.S. MSM in the US were enrolled in a placebo-controlled trial of oral acyclovir suppression of HSV-2 to prevent HIV seroconversion (HPTN 039) which did not demonstrate effectiveness of that intervention, but further study is warranted on the role of various STI control strategies as a component of HIV prevention in diverse populations.

Can prevention interventions be developed that address economic and social factors that increase HIV-related vulnerability?

Although poverty itself does not increase the biological risk for HIV, unfavorable socioeconomic factors appear to increase HIV-related vulnerability. In a survey of HIV-infected and HIV-uninfected women in North Carolina, infected women were significantly more likely than uninfected women to be on public assistance, to be unemployed, to use crack cocaine, and to exchange sex for money, shelter or drugs. (Adimora, 2006) Financial dependence on male partners was the most commonly cited reasons reported by HIV-infected women in North Carolina for engaging in risk behaviors. (CDC, 2005)

Crack-using African-American women who received an HIV prevention intervention that specifically took into account the social, economic and legal context of their daily lives reported significant decreases in sexual risk behavior, crack use, and the number of paying partners, as well as increases in condom use by their male partners. (Sterk, 2003) Additional research is needed to identify optimal strategies to build the skills of heavily disadvantaged populations to avoid HIV exposure while coping with chaotic life circumstances.

Unstable housing is strongly associated with higher rates of drug use and sexual risk behavior. People with HIV are at high risk of homelessness or unstable housing. In New York City, for example, surveys of people living with HIV between 1994 and 2004 have consistently found that 30-40% experience homelessness or housing instability. (Aidala, 2006) It has been hypothesized that the provision of stable, supportive housing for people with HIV would not only health care utilization and medication adherence, but might also help prevent new infections by reducing risky behaviors by people living with HIV. (Holtgrave, 2007) Research should assess the effectiveness of housing placement as an HIV prevention intervention.

Do initiatives to address underlying mental health issues help reduce HIV risk behaviors?

Studies among African-American adolescents (Brown, 2006), urban MSM (Stall, 2003) and other populations have identified a close correlation between sexual risk behavior and various psychosocial issues, such as depression, trauma and poor self-esteem. Proposals to address the underlying psychosocial issues that contribute to sexual risk behavior include the integration of routine depression screening in clinical settings that treat large numbers of at-risk individuals (Medius Institute, 2006) and the training of service providers for at-risk populations to increase professional competence to cross-treat interacting health and psychosocial issues. (Stall, 2007) Studies should assess the HIV prevention effectiveness of such interventions.

Are HIV prevention interventions with proven efficacy actually effective when they are translated in the field?

HIV behavioral interventions are evaluated under the carefully controlled conditions of clinical trials, which may not mirror the conditions under which they are delivered by clinical providers, community-based organizations, public health agencies, or other entities. Few efficacious behavioral interventions have been evaluated for their effectiveness on behaviors with broader implementation. (Lyles, 2007) Thus, rigorous studies are needed to determine whether the behavioral interventions that have been endorsed by CDC and other agencies are effective as translated into practice, and to identify the factors that influence the effectiveness of prevention programs in the non-research setting. (Hallett,

2007) The advent of new behavioral surveillance systems and the availability of new technologies for population-based estimates of incidence and early infection make testing of large scale, community and structural interventions more feasible than in the past. (DesJarlais, 2005) In addition, as most interventions studies carefully define the population eligible for participation, research is needed to assess the effectiveness of such programs for different populations and to identify the degree to which HIV prevention practice is tailoring interventions to specific social and cultural circumstances.

Is it possible to improve the design, implementation and evaluation of HIV prevention interventions through improved understanding and characterization of high-prevalence counties, zip codes and census tracts?

A CDC comparison of the 20 U.S. counties reporting the most rapid increases in AIDS incidence with the 20 counties with the smallest increases found that areas with rapidly increasing rates of new AIDS cases scored lower on various socioeconomic measures and on standardized health and mortality indices. (Peterman, 2005) Additional research is needed to further elucidate the common characteristics and patterns that contribute to risk-taking in heavily affected communities and to develop prevention interventions tailored to these disadvantaged populations.

* * *

In summary, a broad array of unanswered questions remains as to how to prevent HIV transmission in the US. These require focused, domestically-conducted research studies with the goal of decreasing the number of new HIV infections in the US. Some of these questions and issues may benefit from ongoing and planned international studies. Challenges posed by the current status of the US epidemic are amenable to behavioral, biomedical, structural or policy interventions, and informative epidemiological studies. Some of the questions outlined above may lend themselves to smaller studies that rely on behavior change as an endpoint, while others require concerted efforts with HIV or other STIs as the endpoint.

The HPTN will remain poised to address these unanswered questions through monitoring of new scientific findings, ongoing assessment and expansion of its domestic prevention research portfolio, development of relevant bridging studies, and through enhanced collaboration with other research groups and with public health agencies.

VII. The Way Forward

Based on detailed analysis of the status of the HIV epidemic in the US, the characteristics and needs of the most heavily affected communities, and review of interventions that have been shown to be effective in terms of behavior change, a clear need emerges for research that benefits key populations with major prevention gaps, that results in interventions that move beyond a simple focus on individual risk behavior, that supplements the traditional focus on HIV-uninfected individuals with new models that address the unique needs of people living with HIV, and that responds to the specific factors that increase risk.

Within the broad array of urgent prevention research priorities, the HPTN proposes to focus its research efforts in the immediate future on MSM and women at risk through heterosexual contact, particularly Black and Hispanic women. Together, MSM and these women make up almost 75% of new HIV/AIDS diagnoses in the US, and Blacks face infection rates that are several times higher than other racial/ethnic groups. These populations exhibit many of the factors that increase risk for HIV infection, such as sex with partners at high risk, use of stimulants or other non-injection substances, and living within social and sexual networks with high prevalence of risk behaviors and chronic or acute HIV infection. Clearly, little if any progress will be made in reducing the annual number of new HIV infections in the US unless there is substantially greater success in curbing transmission among MSM and women, especially Blacks.

The characteristics of these high-priority populations and the unique geographic distribution of the communities where these individuals reside underscore the critical need for multi-site, randomized clinical trials. Greater use of biological endpoints is needed to strengthen the evidence base on HIV prevention, as are studies that assess the effectiveness of prevention models with demonstrated efficacy under controlled trial conditions. Other smaller studies are needed identify key characteristics of risk in these populations and to determine the feasibility of implementing the proposed large-scale prevention studies. These latter studies should serve as vanguard research that accelerates the development of comprehensive community interventions. To the extent possible, intervention evaluations studies should rely on biological endpoints and should permit assessment of the sustainability of the evaluation's efficacy over time.

As the research network specifically charged with the task of identifying the most promising, non-vaccine and non-microbicide interventions to prevent HIV infection, the HPTN is poised to address the urgent research needs outlined above. HPTN includes a large network of U.S. research sites, many situated within or in close proximity to HIV "hotspots" in the US, with strong linkages to the communities they service and with histories of recruitment and retention of high-risk populations. HPTN also possesses the needed experience and knowledge, diversity of research leadership, and statistical, data management and

operational expertise to design, conduct and analyze the range of needed research in a timely and successful manner. These factors position the HPTN well to embark on the proposed domestic studies as a component of its overarching global prevention agenda.

In addition to undertaking research on the three high-priority concepts described here, the HPTN is eager to play a collaborative role in developing and implementing a strategic national HIV prevention research agenda that addresses the many questions outlined in Section VI (Other Key Prevention Research Questions). Such a collaborative effort is needed to ensure the development of evidence-based prevention models for underserved populations (such as incarcerated men and women, victims of violence or sexual abuse, and transgender individuals) and to develop effective community-level and structural interventions for diverse populations and risk behaviors. For example, development of effective strategies to limit the contribution of acute infection to the further spread of HIV is an urgent priority that should be addressed through a multi-disciplinary research effort; with its strong linkages to the HIV Vaccine Trials Network and other researchers who are following HIV-negative cohorts, the HPTN is poised to play a critical role in advancing research in this cross-cutting area.

Throughout the range of future prevention research, collaborative efforts should ensure attention to the many design and operational issues discussed above, including the use of biological endpoints, use of multiple study sites, longer follow-up to assess the sustainability of the intervention, evaluation of combined interventions, and assessment of the cost-effectiveness and feasibility of implementation for experimental interventions. With its ongoing review and analysis of the state of prevention research, remaining research gaps, and emerging developments, the HPTN is ideally suited to contribute to the development and implementation of a comprehensive national prevention research plan to address the unmet challenges posed by the HIV epidemic in the US.

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