The HIV Epidemic in the United States: A Time for Action

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It is not uncommon to encounter in a hospital emergency room in San Francisco, Atlanta, New York City, or Washington, DC, a young man or woman with the diagnosis of life-threatening cryptococcal meningitis or pneumonia caused by Pneumocystis jirovecii as the first manifestation of HIV infection. How could this be possible in 2010, fully 3 decades into the epidemic in the United States? How could this be possible in a country that prides itself on the widespread availability of HIV testing and treatment options? How could this be possible in a country with broad access to health messages and a plethora of communication tools? How could this be possible in one of the richest countries on earth?

The answers to these questions are sobering. HIV in the United States is currently an invisible epidemic, largely confined to vulnerable and disenfranchised populations. It has disappeared from the public discourse. The prevailing perception is that HIV is a problem of the past, with few new infections and with miracle drugs available for all those living with HIV. Yet, beside the tragic anecdotes cited above, data indicate that there are an estimated 56,000 new infections per year in the United States, with an alarming impact on men who have sex with men and African American men and women. Great disparities remain in access to care and treatment for racial/ethnic minorities with HIV. How to address these disparities is the immediate challenge.

The articles included in this supplement focus on some of the populations who have been most heavily impacted by the domestic HIV epidemic, including disenfranchised women of color, men who have sex with men, transgender persons, and substance users. Some of the articles describe specific venues, both physical and virtual, that are common in the lives of people living with, and at increased risk for, HIV, such as prisons, bathhouses, and the Internet; others discuss some of the factors that potentiate susceptibility to infection, such as substance use and depression. This supplement also features a wide array of approaches designed to slow the tide of the epidemic, ranging from culturally nuanced social, behavioral, and structural approaches to biomedical interventions, such as HIV testing, vaccines, and the use of antiretroviral drugs for prevention. Another paper describes lessons from Africa that could inform the response to the US HIV epidemic. The underlying theme is that HIV is spread in diverse communities, influenced by multiple biological, behavioral, cultural, societal, economic, and structural factors, and that curbing the epidemic will require an extensive variety of tactics carefully titrated to the needs of communities and individuals.

The newly released National HIV/AIDS Strategic Plan, the first in the history of the epidemic in the United States, offers a fitting framework for action. This supplement to the Journal of Acquired Immunodeficiency Syndrome is an attempt at articulating a path ahead. Yet, substantial progress will not be achieved unless there is a concerted effort by the breadth of stakeholders to work together tirelessly and selflessly to reach defined priority goals. From policy makers to funders, researchers, providers, community organizations, and individuals living with HIV, all must be fully engaged in a united front to confront this epidemic in our midst. The time for action is now.
Epidemiology of HIV in the United States

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Background: The United States has a comprehensive system of HIV surveillance, including case reporting and disease staging, estimates of incidence, behavioral, and clinical indicators and monitoring of HIV-related mortality. These data are used to monitor the epidemic and to better design, implement, and evaluate public health programs.

Methods: We describe HIV-related surveillance systems and review recent data.

Results: There are more than 1.1 million people living with HIV in the United States, and approximately 56,000 new HIV infections annually. Risk behavior data show that 47% of men who have sex with men engaged in unprotected anal intercourse in the past year, and 33% of injection drug users had shared syringes. One third (32%) of people diagnosed with HIV in 2008 were diagnosed with AIDS within 12 months, indicating missed opportunities for care and prevention. An estimated 72% of HIV-diagnosed persons received HIV medical care within 4 months of initial diagnosis.

Conclusions: Conducting accurate and comprehensive HIV surveillance is critical for measuring progress toward the goals of the 2010 National HIV/AIDS Strategy: reduced HIV incidence, increased access to care, and improvements in health equity.

Key Words: antiretroviral therapy, behavior, epidemiology, HIV, sexual transmission, surveillance

(INTRODUCTION The United States has a comprehensive system of HIV surveillance that includes HIV case reporting and staging of disease, monitoring of HIV-related mortality, supplemental studies of behavioral and clinical indicators, and estimates of incidence and prevalence. Additional studies, such as longitudinal cohorts of HIV-infected persons, contribute to understanding of disease over time in individuals. The data highlight substantial changes in HIV and late disease stage (AIDS) incidence, prevalence, and mortality, and profound disparities across populations related to sexual behavior, drug use, race, ethnicity, geography, and socioeconomic status.

INCIDENCE AND PREVALENCE OF HIV AND AIDS

State and local governments hold legal authority for public health surveillance, including the designation of reportable conditions and reporting methods. Reporting of HIV surveillance data to the federal government is voluntary. AIDS reporting started in 1981; by 1986, all 50 states, the District of Columbia, and several US territories had instituted AIDS case reporting. Beginning in 1985, many states implemented HIV case reporting as part of an integrated HIV and AIDS surveillance system; although recommended by the Centers for Disease Control and Prevention (CDC) since 1999, the implementation of HIV reporting across the United States occurred at different points in time. As of 2008, all states had implemented confidential, name-based HIV reporting.

CDC's HIV surveillance system tracks new diagnoses of HIV infection and stage 3 disease (AIDS). Most cases are initially reported to state or local health departments through routine laboratory reporting of confirmatory HIV antibody, viral detection, or CD4 cell count test results. Completion of case reports occurs through provider-based reporting or follow-up by health department staff.

For 2006, it was estimated that 1.1 million people were living with HIV in the United States (95% confidence limit: 1.06 to 1.16 million), with considerable geographic variation. For example, AIDS diagnosis rates vary across states, ranging from 1.8 per 100,000 in Vermont to 27.7 per 100,000 in Maryland (Fig. 1A). In addition, because of higher total population and rates of AIDS in certain states, the epidemic is concentrated in certain geographic regions; 50% of reported AIDS cases in 2008 were from 5 states: New York, California, Florida, Texas, and Georgia. Furthermore, within states, higher numbers of cases are generally reported from urban areas (Fig. 1B).

HIV disproportionately affects different populations. HIV incidence estimates indicated that there were 56,300 new HIV infections in 2006. Of these new HIV infections, 45%...
were among blacks and 17% among Latinos (Fig. 2A); the incidence among blacks was 7 times, and among Latinos 3 times, the rate among whites. More than half (53%) of new HIV infections were among men who have sex with men (MSM); 12% were among injection drug users, 4% among MSM who inject drugs, and 31% attributable to heterosexual contact (Fig. 2B). MSM are estimated to have a diagnosis of HIV infection at a rate more than 40 times the rate among other men and among women.7

HIV surveillance data are used to estimate HIV prevalence in the United States, including the estimated number of persons infected but undiagnosed. Of the estimated 1.1 million persons living with HIV in the United States, 21% were undiagnosed and presumed to be unaware of their infection.4 The National Health and Nutrition Examination Survey is a national household-based survey that conducts interviews and testing, including for HIV infection. Data from National Health and Nutrition

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Examination Survey during the period 1999–2006 indicated that 0.5% of the adult population had HIV infection, with considerable disparities. The prevalence was 2.0% among blacks and 9.4% among MSM.

MEASURES OF BEHAVIORAL AND SOCIAL RISK FOR HIV INFECTION

The National HIV Behavioral Surveillance System (NHBS) is a community-based survey that conducts interviews and HIV testing among 3 populations: MSM, injection drug users, and heterosexuals at increased risk for HIV infection. NHBS is conducted in large metropolitan statistical areas in the United States, where approximately 60% of the nation’s AIDS cases had been reported.

Risk behavior data from NHBS have shown that 47% of MSM had engaged in unprotected anal intercourse during the past year, and 33% of injection drug users reported sharing needles. Data from NHBS highlight that HIV infection is influenced by social, structural, and economic systems. In impoverished urban areas (ie, where ≥20% of residents have household incomes below the poverty level), 21% of heterosexual NHBS participants were infected with HIV. Infection was independently associated with lower household income, unemployment, lack of housing, and low education, but did not differ significantly by race or ethnicity.

HIV TESTING

Persons who do not know they are HIV infected account for a disproportionate percentage of new transmissions because they are more likely to engage in high-risk sexual behavior than persons who have learned they have HIV. To increase the number of persons who know their HIV status and who are, if positive, linked to clinical and preventive services early, CDC recommends offering universal routine opt-out voluntary HIV screening for all persons ages 13–64 years in health care settings and repeat annual testing for persons at high risk for HIV. Data from the National Health Interview Survey indicate that between 1987 and 2006, the number of persons reporting having ever been tested for HIV infection rose from 6% to 38%.

Among MSM participating in NHBS during 2008 in 21 cities, HIV prevalence was 19% among all tested men, of whom 44% were unaware of their infection, and 28% among black MSM, of whom 59% were unaware of their infection. In a study of black and Latino MSM conducted in Los Angeles, New York, and Philadelphia, 17% of black and 5% of Latino MSM who did not know they had HIV tested positive. Among young black MSM college students and black women in North Carolina, most reported that at the time of their positive HIV test they believed they were unlikely to be infected.

Late HIV diagnoses are an indicator that testing needs to reach more persons earlier. It is estimated that 32% of people diagnosed with HIV received a diagnosis of AIDS within 12 months of diagnosis. The median first CD4 cell count is low, between 167 and 175 cells/mm³, within 12 months of HIV diagnosis. However, recent reports suggest improvements may be occurring.

ACCESS TO CARE AND QUALITY OF CARE

To maximize the benefit of early HIV diagnosis and treatment, patients need to have access to high-quality medical services. Receipt of care depends on prompt linkage to services and retention in care after diagnosis. A meta-analysis of studies from the mid-1990s to 2006 found that 72% of HIV-diagnosed persons in the United States entered HIV medical care within 4 months of diagnosis. Among persons entering
Evidence from a clinical trial

Much of the morbidity and mortality benefit associated with widespread use of highly active antiretroviral therapy has been derived from the associated profound reductions in AIDS-defining opportunistic illnesses (Fig. 3). Since its advent in 1996, the timing of highly active antiretroviral therapy initiation has been an area of considerable interest and controversy. Recently revised US guidelines recommend initiating antiretroviral therapy at CD4 cell counts <500 cells per cubic millimeter with the option of initiating at higher CD4 cell counts. Evidence from a clinical trial and multiple cohort studies suggests that patients initiating antiretroviral therapy at higher CD4 cell counts experience improved survival and have reduced risk for non-AIDS–defining illnesses and complications and toxicities of treatment with antiretroviral drugs.

Initiation of antiretroviral therapy at higher CD4 cell counts does not seem to increase the risk of developing antiretroviral drug resistance or of exhausting available treatment options and failing therapy.

To evaluate the impact of these recommendations, researchers examined data from the Medical Monitoring Project, a national, population-based surveillance system of HIV-infected persons who receive clinical care. The project uses a 3-stage sampling design to obtain annual cross-sectional probability samples of adults receiving outpatient care for HIV infection in 23 jurisdictions. Data are collected by interview and medical record review. Survey data from 2007 indicated that patients with CD4 <500 cells per microliter who were not already taking antiretroviral drugs accounted for 8% of the analysis population (4% with CD4 <350 cells/μL—the previously recommended threshold—and 4% with CD4 between 350 and 499 cells/μL). Based on these data, under the current guidelines, state and local jurisdictions may need to provide treatment resources to an additional 10% of HIV-infected patients in care.

Studies continue to demonstrate that widespread use of antiretroviral therapy since 1996 has led to sustained and continually improving reductions in morbidity and mortality among HIV-infected adults and children. In the United States, life expectancy after HIV infection increased from 10.5 to 22.5 years between 1996 and 2005, respectively. With improved survival on antiretroviral therapy, HIV-infected persons are increasingly affected by chronic and often preventable illnesses and non-AIDS–defining cancers, further reductions in mortality and morbidity will require effective prevention and treatment of these conditions.

FUTURE DIRECTIONS

Throughout the 30 years of the HIV epidemic, US surveillance systems and cohort studies have tracked many changes. HIV incidence peaked in the mid-1980s with approximately 130,000 infections per year and has decreased to approximately 56,000 infections per year more recently. Confidential name-based HIV reporting in all 50 states will greatly improve our ability to monitor the epidemic nationally. The first national reports on trends of diagnoses of HIV infection will be available for 2012 data, due to methods for adjusting data for reporting delays that require 4 years of experience with reporting data. These data will provide the clearest picture of the epidemic to date; funding opportunity announcements targeting dollars by group or geography will follow suit.

With the release of the National HIV/AIDS Strategy for the United States in July 2010, epidemiologic data will take on new importance for addressing the HIV epidemic. The constellation of surveillance systems and cohort studies provides data to monitor the epidemic and better design, implement and evaluate public health programs. The successful impact of the National HIV/AIDS Strategy will be assessed using epidemiologic data collected from these systems to measure reduced incidence, increased access to care, and improvements in health equity.

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REFERENCES


Challenges of a Hidden Epidemic: HIV Prevention Among Women in the United States

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Abstract: HIV/AIDS trends in the United States depict a concentrated epidemic with hot spots that vary by location, poverty, race/ethnicity, and transmission mode. HIV/AIDS is a leading cause of death among US women of color; two-thirds of new infections among women occur in black women, despite the fact that black women account for just 14% of the US female population. The gravity of the HIV epidemic among US women is often not appreciated by those at risk and by the broader scientific community. We summarize the current epidemiology of HIV/AIDS among US women and discuss clinical, research, and public health intervention components that must be brought together in a cohesive plan to reduce new HIV infections in US women. Only by accelerating research and programmatic efforts will the hidden epidemic of HIV among US women emerge into the light and come under control.

Key Words: HIV in women, HIV prevention science, racial disparity

INTRODUCTION

HIV incidence in the United States has remained an estimated 56,000 cases annually since 1991.1 The lack of substantive progress in reducing new HIV infections for almost 20 years is noteworthy despite remarkable advances,2 including the advent of rapid HIV testing, opt-out testing, and a variety of potent once-daily antiretroviral therapies and the availability of evidence-based behavioral interventions.3

Unlike the generalized epidemic in regions of sub-Saharan Africa, the US HIV epidemic is concentrated among certain subpopulations, particularly men who have sex with men (MSM) and persons of color.4 Although the high HIV prevalence among MSM in the United States is well recognized, the impact of HIV on women is less widely appreciated. Moreover, women at risk for HIV acquisition frequently do not appreciate this risk. The HIV epidemic among US women is, in many ways, hidden from effective dialogue, both among the populations at risk and within the broader scientific community. We summarize current epidemiology of HIV/AIDS among US women and discuss critical components that must be brought together in a cohesive plan to reduce new HIV infections in US women.

DISCUSSION

Epidemiology of HIV in US Women

Prevalence and incidence trends depict a concentrated epidemic with hot spots that vary by location, poverty rate, race/ethnicity, and transmission mode. By 2003, an estimated 1.1 million US adults and adolescents were HIV infected; approximately 21% of HIV-infected individuals were unaware of their infection.5,6 Although US HIV incidence estimates peaked at 150,000 cases per year during the mid-1980s, followed by a plateau at about 56,000 cases per year since 1991,7 the annual rate of new HIV cases has been increasing in certain subgroups, particularly MSM and black and Latina women. Eighty percent of HIV cases in women occur in black women.8

The HIV epidemic among US women is concentrated in the Northeast and South, with a significantly higher proportion...
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of HIV infections occurring in areas with high poverty rates.9 Heterosexual activity has been the major mode of HIV acquisition for US women since 1995, when it surpassed injection drug use (IDU).10 Of women newly identified as HIV infected, 83% are estimated to have acquired HIV heterosexually, with most of the remaining acquiring HIV through IDU.7

Trends in AIDS rates among US women are of particular concern. Although women accounted for only 15% of AIDS cases from 1981 to 1995, they accounted for 27% of AIDS cases from 2001 to 2004.11 The Centers for Disease Control and Prevention reported a 15% increase in AIDS cases among women from 1999 to 2003, compared with a 1% increase in men.11 In addition, estimated AIDS diagnoses are 23 times greater in black women than in white women.12

Mortality trends among women with HIV are striking. Although the death rate due to HIV has decreased, HIV remains the third most common cause of death among black women aged 35–44 and the fourth most common cause of death among younger black women aged 25–34.12 The age-adjusted annual death rate due to HIV among black women during 2001–2005 was higher than that observed in every racial/ethnic group except non-Hispanic black males.13 Similarly, when compared with white women, black women with HIV have a 13-fold mortality risk ratio.14

**Why Are Women at Risk for HIV?**

Many factors contribute to HIV acquisition among women. Gender inequalities, both social and economic, hamper some women’s abilities to negotiate condom use and other safer sex behaviors.15,16 Interpersonal violence is a risk factor for HIV among women, regardless of race or ethnicity.17 Factors associated with transmission of HIV and other sexually transmitted infections (STIs) include poverty, lack of access to medical care, poor knowledge about HIV/AIDS, lower social status,18,19 financial dependence on male partners, assortative mixing within HIV prevalence communities,20 feelings of invincibility, low self-esteem, and alcohol and drug use.21

However, individual risk behaviors do not explain the dramatic racial disparities in STI and HIV rates.22,23 In one study, black men and women with “low-risk” behaviors had 25-fold higher incidence of HIV and STIs compared with their white counterparts,23 a disparity that remains unexplained. Black women may underestimate the HIV risk status of their male partners; 6% of HIV-infected black women versus 14% of HIV-infected white women reported having a bisexual male partner, despite the fact that more than twice as many black HIV-infected men as white HIV-infected men (34% vs 13%) reported sex with both men and women.24 More black men and women than white are unaware of their HIV infection.25,26 These data may reflect a number of factors, including differences in HIV testing uptake, HIV prevalence, and structural features of the social environment. Sexual networks shaped not only by individual preferences and behaviors but also by macroeconomic, political, societal, and other structural features of the environment play a critical role in HIV acquisition among women.20,27,28 Concurrent sexual partnerships can amplify HIV transmission, particularly when one partner has early HIV infection, a period with high transmissibility.27,29 The higher prevalence of concurrent partnerships observed in US black and Hispanic men may contribute to racial disparities in HIV rates among US women.30 Sexual mixing patterns connecting women at low risk for HIV with men at higher risk may increase HIV acquisition in women; such mixing patterns have been observed among black men and women in the southeastern US.20

Recent studies demonstrate strong associations between prior incarceration9 or incarceration of a partner31 with HIV infection in US women. Though correctional inmates may view themselves at low or no risk for HIV acquisition,32 HIV prevalence among prisoners is more than 2.5 times higher than the general US population with a relatively high proportion of HIV-infected persons passing through the correctional system.33–35 The racial disparity of incarceration is striking: 1 in 9 black men between the ages of 20 and 34 is incarcerated, compared with 1 in 30 US men in the same age group.36 Incarceration influences sexual networks by disrupting stable sexual partnerships and has been associated with concurrent partnerships and dissortative mixing that promote HIV transmission.20,31,37 To date, incarceration has not been consistently used as an HIV prevention opportunity; condoms and clean injection equipment are unavailable to inmates in some correctional systems. Similarly, HIV testing policies vary widely among correctional systems.

**HIV Prevention for US Women: Current Status**

Early domestic HIV prevention successes included implementation of mandatory blood product screening and effective programs for prevention of mother-to-child transmission.2 Harm reduction programs throughout the United States have contributed to sharp declines in new HIV diagnoses among IDUs.38,39

Unfortunately, although consistent male condom use is known to be efficacious in reducing HIV transmission40 and female condoms have been assumed to be similar to male condoms in preventing HIV,41 condom implementation has not been effectively realized to decrease numbers of new HIV infections. Over the past decade, multiple microbicide trials have been disappointing.42–46 However, a number of ongoing trials are assessing new vaginal microbicides and antiretroviral drugs for pre-exposure prophylaxis,7,47 and results from the CAPRISA 004 microbicide study (a double-blind randomized placebo-control study among 989 women) recently demonstrated tenofovir 1% vaginal gel to have 40% efficacy in preventing HIV acquisition.48 To date, multiple vaccine trials have failed to prevent HIV transmission.49,50 with the possible exception of a recombinant canarypox vector vaccine (ALVAC-HIV) plus 2 booster injections of recombinant gp120, which demonstrated vaccine efficacy of 31.2% (95% CI: 1.1 to 52.1; P = 0.04) in modified intent-to-treat analysis.51 Although statistically significant and perhaps useful to inform development of future vaccines, this 6-injection vaccine series did not demonstrate statistically significant efficacy in the per protocol analysis and had no effect on the level of HIV-1 viremia.

Antiretroviral treatment as a strategy to decrease HIV transmission has been the subject of recent interest.53–56 However, individuals with known HIV infection in the United States confront an array of barriers to health care access, medication adherence, and achievement of optimal
virologic outcomes needed for this approach to effectively prevent HIV transmission.\(^5\)\(^7\)

Multiple behavioral interventions to prevent HIV acquisition by women have been developed. However, a recent review of this area identified only 7 behavioral interventions demonstrating subsequent reductions in unprotected sexual intercourse\(^3\) and STIs\(^5,58,59\) and none of the studies used HIV incidence as an end point. An additional limitation of most of these studies was a requirement that participating women attend multiple sessions, limiting the feasibility of broad implementation of these interventions in at-risk communities. Furthermore, few of the interventions attempted to directly influence social networks or sexual behaviors of women’s partners—a critical component to HIV prevention in US women.\(^60\)–\(^62\) Of 11 interventions listed as effective for women of color by the Centers for Disease Control and Prevention,\(^63\) none have assessed effect on HIV acquisition.

The Way Forward

Four areas must be urgently addressed to effectively decrease new HIV infections in US women. First, an absence of rigorous HIV incidence data among at-risk women impedes design of prevention trials with HIV incidence as primary end point; sample size calculations are not feasible without reliable estimates of incidence in the target population.

Second, behavioral strategies addressing male partners of women are needed. To date, only limited research has attempted to alter the sexual attitudes and behaviors of heterosexual and bisexual men.\(^58,61,62\) Research evaluating strategies that favorably influence gender norms and behaviors of men are critically needed. Although data suggest that sexual networks may be effectively used to identify cases of undiagnosed HIV,\(^64\) few sexual or social network interventions have been evaluated in women.\(^65\)

Third, expanded HIV testing and linkage to care and effective antiretroviral treatment of individuals with HIV are critical to successful HIV prevention. Novel programs must be developed to facilitate effective virologic suppression among persons living in social chaos (ie, high poverty rates, high community violence, homelessness, and fragile social supports).

Finally, it is heartening that a national HIV/AIDS Strategy for the United States has recently been created.\(^66\) Moving forward, we must assure that HIV prevention plans include attention it is due. Research is needed to identify effective interventions that decrease US women’s risk of HIV infection and are feasible to scale up in these populations. In addition, there is an urgent need to establish programs that enable US women to protect themselves. New, innovative prevention programing must build upon knowledge gained from past HIV prevention trials. Equally critical is the effective implementation of a multidimensional HIV prevention plan incorporating community, correctional institutions, and treatment programs (including support services such as substance abuse programs). Only by accelerating both research and programmatic efforts will the hidden epidemic of HIV among US women emerge into the light and be effectively addressed.

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CONCLUSIONS

The ongoing HIV epidemic among US women, particularly black and Hispanic women, must receive the attention it is due. Research is needed to identify effective interventions that decrease US women’s risk of HIV infection and are feasible to scale up in these populations. In addition, there is an urgent need to establish programs that enable US women to protect themselves. New, innovative prevention programing must build upon knowledge gained from past HIV prevention trials. Equally critical is the effective implementation of a multidimensional HIV prevention plan incorporating community, correctional institutions, and treatment programs (including support services such as substance abuse programs). Only by accelerating both research and programmatic efforts will the hidden epidemic of HIV among US women emerge into the light and be effectively addressed.


Mental Health and HIV Risk in Men Who Have Sex With Men

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Abstract: Evidence-based HIV prevention interventions with men who have sex with men (MSM) in the United States have moderate effect sizes in reducing HIV sexual risk behavior. Mental health and psychosocial problems, which both disproportionately affect MSM populations and are implicated in HIV transmission risk behaviors, also likely interfere with the uptake of HIV behavioral interventions. Moreover, given that mental health and psychosocial problems such as depression, substance use, and violence frequently co-occur for many MSM (eg, as syndemic conditions), what is probably needed are combination prevention efforts, or prevention “cocktails,” similar to treatment “cocktails,” that address the psychological and behavioral mechanisms that interact to produce elevated risk for HIV. Such interventions should incorporate a holistic framework to address the sexual health and overall well being of MSM. Addressing co-occurring psychosocial risk factors is apt to improve effect sizes of current HIV prevention interventions and allow for more effective uptake by MSM.

Key Words: mental health, HIV, MSM

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INTRODUCTION

Evidence-based HIV prevention interventions with men who have sex with men (MSM) (because not all men identify as “gay,” we use the term “MSM” throughout this commentary) in the United States have successfully reduced HIV sexual risk behaviors.1–7 A meta-analysis of 44 HIV behavioral interventions found that randomized controlled trials of prevention interventions and model intervention programs with MSM reduced sexual risk by about one third.6 Despite these empirically grounded prevention efforts, MSM continue to be the largest group of individuals infected with HIV in the United States; they comprise more than half of all new HIV infections annually.8,9 Given that MSM are more than 44 times more likely to be newly diagnosed with HIV than other men,10 a focus on ameliorating disparities in HIV infection is essential for enhancing the health of MSM at the population level. A question that warrants immediate attention for both the science of HIV prevention and public health practice: How can we enhance current HIV behavioral interventions to improve current effect sizes and promote long-term and sustainable behavior change to reduce HIV sexual risk among MSM?

DISCUSSION

HIV Risk in MSM Occurs in the Context of Other Mental Health and Psychosocial Problems

Most research on sexual minority men’s health in the HIV era has focused on risk for sexual transmission of sexually transmitted infections, including HIV. However, increasing evidence has shown that US MSM populations also suffer from very high rates of depression, violence victimization, and substance abuse across the life course.11–21 among other health problems. Moreover, research has demonstrated that the psychosocial factors that disproportionately affect MSM—depression, for example—are related to HIV sexual risk taking.22–25

Although many studies involving MSM have shown interconnections between psychosocial factors and HIV risk, such as substance use and high-risk sex,21,26 recent studies have focused on documentation of how these diverse psychosocial issues interact to produce elevated HIV risk behavior among MSM, a phenomenon known as a syndemic.27,28 According to the Centers for Disease Control and Prevention, a syndemic is “two or more afflictions, interacting synergistically, contributing to excess burden of disease in a population.”27,29 Psychosocial health problems such as substance use, depression, and violence have a tendency to interact so that their impact on the overall health of the individual is greater than one would expect the additive effect to be.28

The “syndemic” condition has been documented in samples of adult28 and young27 MSM. Using a probability sample of MSM in four major US cities, Stall et al28 found that the more psychosocial health problems an individual endorsed, the greater their risk for both participation in sexual risk behaviors and HIV infection. Mustanski et al27 found similar results among a sample of young MSM ages 16 to 24, where endorsement of each additional psychosocial health problem...
significantly increased the odds of unprotected anal intercourse [odds ratio (OR) = 1.42, confidence interval (CI) = 1.19 to 1.68], multiple sex partners (OR = 1.24, CI = 1.05 to 1.47), and HIV seroprevalence (OR = 1.42, CI = 1.12 to 1.80). This pair of studies demonstrated that as the number of psychosocial conditions endorsed by individuals increased, their odds of engaging in HIV sexual risk behaviors also increased, as did their odds of HIV infection. It has been suggested that this set of co-occurring health problems (ie, the presence of a syndemic condition) may actually be driving the HIV epidemic among MSM.

If sexual minority men suffer from a syndemic that is working to drive HIV risk, we must question why MSM are at greater risk than other populations of men and examine what might be driving the syndemic condition among sexual minority men. Young men’s development is influenced by many contextual factors, including socioeconomics, race/ethnicity, and familial variables. However, sociocultural pressures, including the pressure to meet socially valued masculinity norms (not the least of which includes heterosexuality) also affect the development and behavioral patterns of MSM. Masculine socialization stress results from the “shaming and other punishment of gay males for failing to achieve masculine ideals.”

This gender role-related stress occurs through overt homophobia, such as hate crimes and the use of derogatory language, and in more institutionalized and subtle forms, such as the recent proliferation of so-called promarriage legislation.

Further, if homophobia is a culture-wide phenomenon, then it affects everyone, including children. Homophobic attacks directly made against or witnessed by boys who will in time grow up to be sexual minority men are thus occurring at an age when they are unlikely to be able to understand why these attacks are occurring or to find social support to fend off the attacks. To the extent that men internalize these attacks to mean that they are less worthy than other males, that their sexuality is something that is shameful and should be hidden, or that their sexuality is forbidden by religious script or contrary to “nature,” these boys will grow up to be men at higher risk for depression, substance abuse, or revictimization, which can snowball into raising levels of risk for HIV and other sexually transmitted infections. Finding ways to address multiple psychosocial health conditions so that they support HIV risk reductions may well increase the effect sizes of HIV prevention interventions.

These Mental Health and Psychosocial Problems Likely Interfere With Existing HIV Prevention Interventions

The high rates of significant and distressing psychosocial problems facing MSM are not only associated with HIV risk behavior and HIV infection rates in this population, but also likely interfere with the ability of high-risk individuals to benefit from traditional HIV prevention interventions that do not address the context of HIV risk behavior. Evidence of this can be seen in four meta-analyses of behavioral interventions for sexual risk taking among HIV-uninfected MSM conducted since 2003, which generally have shown individual-level, group-level, and community-level intervention effects in the moderate range.

Interventions for HIV risk reduction among MSM have been delivered at the individual level and generally target social psychology variables theorized to be associated with health behavior change. These variables include self-efficacy, attitudes and beliefs, motivations, perceived social norms, perceived risks and benefits of a health behavior, information, and skills building. Given the high frequency of co-occurring psychosocial problems and their association to HIV sexual risk behavior, it is necessary to know how such problems would interact with the aforementioned social psychology variables that are at the basis of existing HIV risk reduction interventions for MSM.

Clinical depression and anxiety are examples of mental health conditions that have the potential to interfere with the effect of existing behavioral interventions for HIV risk reduction in MSM: The symptoms of these conditions can be directly related to the psychological variables at their base. Symptoms of depression, for example, include persistent sadness, anhedonia, concentration problems, feelings of guilt and worthlessness, and loss of energy. In more than 30 years of research using Aaron Beck’s empirically tested cognitive theory of depression, studies have demonstrated that depression is related to excessively negative and distorted cognitions and beliefs, including thoughts and cognitions about one’s self, others, and the world; and the past, present, and future. Consider such symptoms and associated negative beliefs with respect to a social cognitive model of sexual risk taking that includes variables such as self-efficacy and perceived social norms. Self-efficacy, the variable at the core of this model, is the belief that a person feels he or she has the ability to do a certain task—in this case, use a condom in different situations. According to this theory, a sexual minority man with clinical depression who has negative thoughts about himself and the world would, therefore, likely hold distorted negative cognitions and beliefs related to his own self-efficacy, social norms about condom use, or the other cognitive variables related to sexual risk.

We recently tested the hypothesis that depression may moderate the degree to which a social cognitive theory could predict HIV transmission risk behavior in a sample of HIV-infected MSM. We found that for those who did not screen in for major depression, the model fit the data well, with negative expectancies about condom use and social norms about condom use being associated with self-efficacy, and self-efficacy in turn being associated with less HIV transmission risk behavior. For those who screened in for major depression, however, the model did not fit the data. In this case, self-efficacy, the central hypothesized mediator, was not associated with the central outcome: HIV transmission risk behavior. Although this was the first study to empirically examine the degree to which a clinically significant mental health problem (in this case, depression) would interfere with a conceptual model of unsafe sex, our belief is that such a phenomenon would extend to other syndemic conditions, such as post-traumatic stress disorder, other anxiety disorders, substance abuse, or current intense life stressors, such as domestic violence. Mental health problems moderating the effect of...
models behind behavioral interventions to reduce HIV risk behaviors would be consistent with a secondary analysis from project EXPLORE that suggested that childhood sexual abuse may have moderated the potential efficacy of the EXPLORE intervention for HIV-negative MSM.19

Currently, few interventions address mental health in the context of HIV sexual risk.3 However, a variety of cognitive-behavioral interventions are well studied and validated for the treatment of mood and anxiety disorders.37 Typically, these treatments are approximately 12–20 sessions long and involve therapy sessions and home practice with a trained therapist. Behavioral interventions for HIV risk reduction could be integrated into such treatments. For example, an intervention presented by Mimiga et al integrates behavioral activation therapy and HIV risk reduction counseling in MSM who abuse crystal methamphetamine.38 The conceptual model focuses on anhedonia (a loss of interest in previously enjoyed activities) as a consequence of continued meth use. For individuals who abuse meth, drug use becomes the central means for (or the only means for) obtaining enjoyment.39 The hypothesized mechanism of intervention action is that behavioral activation will gradually allow individuals to relearn how to engage in pleasurable, goal-directed, nondrug use activities (eg, interests or hobbies that were enjoyable before meth use). These life activities then serve as a natural reinforcement for functional behavior by increasing pleasure and mastery, and improving mood when not on meth, thereby resulting in reductions in unprotected sex and meth use. Additionally, we have an intervention in progress that addresses another highly prevalent psychosocial problem among MSM discussed above—childhood sexual abuse. This intervention involves integrating cognitive processing therapy40 with HIV risk reduction counseling for HIV-uninfected MSM with a history of childhood sexual abuse. By addressing the relevant mental health problem, individuals may be better equipped to respond to integrated HIV prevention counseling.

CONCLUSIONS

Current HIV prevention intervention approaches aimed at reducing HIV risk behavior among MSM in the United States are the metaphorical equivalent of early AZT monotherapy to treat HIV infection. Current behavioral change technologies produce modest and statistically significant effect sizes but typically only for short periods of time. Increasing the effect sizes of current intervention trials represents an important task moving forward. Integrating the treatment of mental health problems that frequently co-occur with syndemics may be one important way to do this. Other steps may improve the effect sizes of existing interventions. One possibility would be to conduct in-depth qualitative interviews with men who did not change during an HIV prevention intervention and men who did change. Interviews may allow for greater understanding of positive change and strengths-based processes, and of barriers and obstructers that impede changes in men whose levels of HIV risk stays the same. Another possibility would be to conduct mediational analyses of proven interventions, with a view toward identifying the variables that predicted the most change and disentangling these from those variables that did not account for much change at all. After this type of analysis was completed, one could examine the intervention content, augment those activities that seemed to be associated with greater change processes, cut down those intervention components that did not seem to contribute to change, and end up with a more empirically guided and tailored form of the intervention. Retesting the efficacy of the revised intervention might well yield more impressive effect sizes.

As stated above, psychosocial and mental health problems, which are disproportionally prevalent for MSM, may moderate the ability of existing prevention efforts to reduce HIV risk. In this article, we argue for conceptualizing HIV prevention efforts in MSM as prevention “cocktails” that address psychological and behavioral mechanisms that interact to produce elevated risk for HIV and that incorporate a more holistic framework to address MSM’s sexual health and overall well being. Although potentially more costly than interventions that are easier to administer, addressing co-occurring psychosocial risk factors may not only improve the mental health of those at risk for HIV but also should improve effect sizes of current HIV prevention interventions and allow for more effective uptake of risk reduction.

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Testing for HIV, Sexually Transmitted Infections, and Viral Hepatitis in Jails: Still a Missed Opportunity for Public Health and HIV Prevention

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Abstract: Jails provide an underutilized public health opportunity for screening for HIV, sexually transmitted infections (STIs), and viral hepatitis, and for such other infectious diseases as tuberculosis. Incarcerated individuals are more likely to be men, poor, persons of color, and at high risk for HIV. The vast majority of jails in the United States do not screen routinely for HIV or STIs, thereby missing an opportunity for HIV and STI diagnosis, treatment, and prevention. Nesting HIV testing within STI testing and treatment in conjunction with testing and treatment for other infectious diseases, as appropriate based on community prevalence, provides a public health opportunity and will enhance HIV prevention. HIV testing and linkage to care, both within corrections and in the community, comprise an important component of the "seek and treat" strategy to further prevent HIV infection. Jail-based screening of infectious diseases, especially for HIV and STIs, in conjunction with treatment and linkage to community care has thus far been a neglected component of HIV prevention among high-risk communities.

Key words: HIV, STI, viral hepatitis, testing, prevention, jails

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INTRODUCTION

The United States has extraordinarily high rates of incarceration. In 2008, more than 4% of the adult population passed through a jail. These individuals are primarily poor and male, have comorbid substance use disorders, and have had poor access to the health care system; collectively, these same characteristics correlate with higher risks for HIV and other infectious diseases. Individuals passing through jails are also likely to be estranged from traditional medical care systems and therefore may not have accessed HIV prevention services. Jails, therefore, provide a key opportunity to implement brief interventions that are widely accepted by the public health and medical communities and that are recommended by the Centers for Disease Control and Prevention (CDC). Yet many US jails do not adhere to these recommendations for routine screening for HIV and sexually transmitted infections linked to medical evaluation. We therefore provide an overview of potential impediments to routine testing and suggest mechanisms to mobilize and to implement infectious diseases screening as part of a comprehensive HIV prevention strategy within this correctional setting.

Epidemiology of Incarceration, Substance Use, and Infectious Diseases

In 2009, approximately 12.8 million men and women passed through jails within the United States. Jails are typically under city, county, or other local jurisdiction and house inmates for short periods. As a result, jails are often chaotic, with high turnover. For example, the average daily inmate population for the New York City Department of Corrections ranges between 13,000 and 18,000. Although the average length of stay in New York City Department of Corrections facilities is 45 days, 50% of the population is released within 10 days. Most jail stays are days to weeks, making it challenging to deliver health care services during incarceration. Furthermore, substance-use disorders, including alcohol, cocaine, methamphetamine, or opioid use, and mental illness are common comorbidities among those incarcerated. For example, the Office of National Drug Control Policy reported that 33% of prisoners were under the influence of an illegal drug at their time of arrest, and 57% reported use of any illicit substance in the month before arrest. Mental illness remains a critical comorbidity among those who interface with jails such that 38.7% of those entering jails have an Axis I disorder. Substance use and mental health disorders are both highly prevalent and play a key role in the overlap of infectious diseases and incarceration.
Minority populations, particularly African American and Hispanic men, are overrepresented within US correctional facilities. Black males are 7 times and Hispanic males are twice as likely as white males to be incarcerated. The epidemics of HIV, sexually transmitted infections (STIs), and hepatitis C virus (HCV) also disproportionately affect communities of color, particularly African Americans, who account for approximately 45% of new HIV infections annually and have an HIV prevalence 7 times that of white Americans. Similarly, gonorrhea and chlamydia rates are 8 and 19 times higher among African Americans, respectively, than among whites.

Because individuals with substance use and mental health disorders are much more likely to be both incarcerated and infected with HIV, STIs, or HCV, it is not surprising that a heavy burden of these diseases is centered behind bars. Using modeling data, it has been estimated that 14% of all those with HIV and nearly 20% of HIV-infected African Americans and Hispanics passed through a correctional facility during 2006. In a 2006 blinded seroprevalence survey of entrants to New York City jails, 5% of entrants were HIV infected; of these, 28% were not diagnosed by the jail, although it is unknown how many were previously unaware of their status. Most undiagnosed inmates denied traditional HIV risk factors, affirming the need to avoid risk-based testing.

Viral hepatitis is also prevalent among those who enter jails. Up to 40% of all Americans with chronic viral hepatitis and approximately 30% of persons with acute hepatitis B virus (HBV) infection have been incarcerated. Among patients with acute HBV reported to the CDC, 5.6% have a history of incarceration during the disease incubation period. HBV infection is known to be transmitted within a correctional setting, and incidence has ranged from 0.82% to 3.8% per year. Among HBV outbreaks in correctional settings, the source patients were found to have subclinical infection that could have been identified by routine screening; this provides support for the CDC recommendation for HBV vaccination in correctional settings.

Data from 1997 suggested that between 29% and 43% of all persons with HCV infection and 40% of all persons with tuberculosis (TB) passed through a correctional facility in that year. In the CDC’s STI surveillance report from 2007, between 2% and 19% of individuals 24 years of age in a correctional facility tested positive for gonorrhea or chlamydia, with the highest prevalence among women aged ≤20 years. Although we do not fully understand the complex interaction among the myriad social, cultural, and economic factors underlying these facts, their confluence has a significant impact on the risks for both incarceration and acquisition of HIV infection. In the United States, many communities of color confront similar social and structural disparities that contribute to both of these risks. Further, many inmates, particularly those with HIV infection, face a multitude of challenges during community reentry, including relapse to substance use or dependence, mental illness, unstable housing, unemployment, lack of health insurance. Many of these challenges, if not addressed, perpetuate the revolving door of reincarceration.

Why Jails?

Jail incarceration is a key opportunity to provide health interventions for 2 reasons. First, many more individuals pass through jails than prisons. As demonstrated by figures from the Bureau of Justice Statistics for 2008, approximately 735,000 were released from prison, while more than 12 million passed through jails. Jail-based interventions are necessary if the public health goal is to reach the majority of the incarcerated population. Second, reducing the morbidity of prevalent infections and reducing incident infections of HIV, TB, STIs, and HCV among jail detainees will likely lower the rates of these infections in the community. This is particularly true if the incarcerated individuals are rendered noninfectious (cured, in the case of STIs) or markedly less infectious (by reduction of HIV-1 RNA levels due to antiretroviral therapy), even with little or no changes in risky behavior. Reduction of infectiousness is particularly important in the case of communicable diseases such as pulmonary TB, which are spread via airborne routes of transmission. The challenge, however, is to complete the screening and implement treatment within this setting given the limited time frame of jail incarceration.

Data from several studies have suggested that screening and treatment of inmates for STIs such as syphilis and chlamydia may reduce their prevalence in the community at large. For example, routine testing and treatment of gonorrhea and chlamydia among men in a San Francisco jail was associated with declining rates of these infections among women attending an STI clinic in a part of the city that had high rates of poverty and incarceration. Additionally, a strong correlation has been established between rates of incarceration among black males and HIV risk experienced by their sexual partners. Similar correlations across races exist between the incarceration of an individual’s partner and his or her risk of HIV infection.

Is It Possible to Implement Medical Interventions Within Jails?

There is ample evidence that medical interventions can be successfully implemented in environments such as jails, which are often overcrowded and have high rates of turnover and limited health care budgets. In providing services, jails operate by creating protocols, testing them, and then implementing them with little deviation. Effective protocols in jail settings have included screening for suicide risk, mental illness, and substance use disorders (urine testing) and for HIV and STIs. Although its timing may vary among facilities, a medical evaluation is part of the intake process in most jails and provides an opportunity to integrate interventions.

In 2 controlled studies of routine HIV testing in Connecticut, male and female jail detainees were significantly more likely to be HIV tested if routine testing was offered within 24 hours of admission and linked to medical screening. This finding reinforces the need to link screening procedures with care. Although HIV prevalence was high (~4%) in these studies, only a single new HIV-infected person was identified. The process was important, however, in identifying a large number of previously identified individuals and allowing for them to be reengaged in HIV care.
The Washington, DC, jail system provides an example of successful routine HIV rapid testing among jail inmates. The program was implemented in conjunction with city-wide efforts to improve HIV detection and treatment rates. The DC correctional testing algorithm utilizes “automatic” HIV testing upon jail entrance, with a provision for opting out of HIV testing available. Among 33,162 intakes between June 2006 and May 2008, 68% (22,515) of jail inmates were tested, with a confirmed HIV seropositivity rate of 3%. Although data are not currently available to determine the effectiveness of this strategy, it does provide proof-of-concept that routine large-scale HIV testing can be implemented in a busy city jail. It is hoped that the testing and linkage to care program will lead to better treatment coverage for HIV-infected individuals in Washington, DC, resulting in better virologic control and, hence, less transmission.

In 1997, the Institute of Medicine report, “The Hidden Epidemic,” recommended providing STI services in prisons, jails, and juvenile facilities as part of a comprehensive STI prevention program. New York City successfully implemented routine STI testing within city jails. When gonorrhea and chlamydia screening was added to the medical evaluation, chlamydia and gonorrhea cases increased in the jails by 1636% and 1023%, respectively, resulting in a 59% increase in total STI cases identified citywide. In the midst of a TB epidemic in Chicago, Cook County Jail instituted radiographic screening of inmates for pulmonary TB at intake. This resulted in increased case finding rates and facilitated earlier airborne isolation of infectious cases. These examples demonstrate that it is possible to implement effective routine screening and treatment procedures for a number of infectious diseases within jails. In each of the examples above, there was clear alignment in goals from the leadership within the jail and community health settings that were conjoined with political will and commitment of resources.

A number of important lessons have been learned from these experiences. Voluntary testing, in which inmates opt in, has repeatedly confirmed lower rates of testing than routine opt-out strategies. In North Carolina, although prisoners rather than jail detainees were targeted, a November 2008 change in HIV screening policy for incoming prison inmates from opt-in to opt-out resulted in an increase in testing from 61%–91% (Fig. 1). These numbers are similar to those of successful HIV testing programs among sentenced prisoners in Rhode Island. Inmates who opt-in and volunteer for HIV testing have lower HIV prevalence than those who do not get tested in the general inmate population. Indeed, among women entering jail in Connecticut, risk-based testing resulted in only 62% of HIV-infected women being identified using blinded serosurveillance, and routine HIV testing among pregnant women in jails proved cost-effective. Testing that relies on self-identified risk behaviors within corrections often misses the majority of infections. Stigma within criminal justice settings is often a significant barrier to self-identification of risk behaviors. In jails, routine HIV testing programs must be implemented in a timely fashion to maximize case identification before detainees’ release. Testing for HIV and other infectious diseases is better integrated into a medical evaluation than “exceptionalized” and requiring outside counselors and thus additional time and often additional funding.

Screening Can Be Tailored Based on Community and Correctional Prevalence

Prevalence of HIV, STIs, and HCV varies widely by state and community. The benefits of identifying HIV infections are enormous, both in preventing progression to AIDS (via antiretroviral therapy) and in preventing HIV transmission to others. Jail detainees who are newly diagnosed with HIV can be counseled and linked with care, although the process can be challenging. Continuity of care for released HIV-infected jail detainees has been dismal, at best. Among HIV-infected detainees in the San Francisco jail, as few as 15% received continuous antiretroviral therapy after their release. For many HIV-infected individuals who already know their diagnosis, another positive HIV test is an opportunity for directed counseling and reinitiation of HIV care. Even relatively low rates of HIV justify routine screening. Although HIV testing itself has not been demonstrated to reduce HIV risk behaviors among those testing negative, it does provide an opportunity to introduce brief HIV risk reduction interventions that have been proven to reduce HIV risk behaviors.

Screening for STIs in jails in higher prevalence communities is recommended but very rarely implemented. STI prevalence is highly age specific, and current guidelines recommend targeting STI testing to younger men and women. Data from the CDC and other studies, however, confirm that expanding STI testing to those younger than 30 years confers high yield in jails. Testing practices may focus on regional differences as follows: in 2007, the South had the highest gonorrhea and chlamydia rates in the country. Successful implementation of STI testing with high treatment rates in correctional facilities in high prevalence communities will necessitate coordination between the correctional facility and the local health department, not only for provision of treatment but also for contact tracing in the community.
Screening for HBV in correctional settings is not only recommended by the CDC but also has been demonstrated to be cost-effective. Unlike HIV, STIs, and HCV, HBV infection can be prevented by an effective vaccine. Yet routine HBV testing and vaccination in jails is rare. Completing the standard series of HBV vaccinations requires 6 months, but protective antibodies are present with even a single dose of vaccine (30% to 50%) or 2 doses (89%). Accelerated vaccination schedules that complete the 3-part series in 3 weeks or 2 months may hold promise for jail settings.

Much less is known regarding the feasibility, costs, and impact of HCV screening in jails. HCV screening is currently recommended by the CDC but only for inmates with identifiable HCV risk factors (ie, injection drug use, men who have sex with men, etc); this is another missed opportunity. Although jails do house a population with increased HCV, the diagnoses may not be made because many HCV-infected inmates do not admit to risk behaviors. Screening is indicated because, as shown for injection drug users with HCV and HIV, individuals who learn that they have a chronic infection tend to reduce their risk behaviors by more than 50%. Previously, HCV testing required phlebotomy; it took several days to obtain results, and it was costly. However, the availability of new HCV rapid testing technology approved by the US Food and Drug Administration, less expensive and more feasible, may tip the balance toward an expansion of routine HCV testing within correctional settings. The expected availability of new direct-acting HCV antiviral medications that are more effective and reduce the duration of treatment may stimulate additional screening and treatment. These medications hold the potential for improved outcomes, providing barriers to treatment—in the form of costs, toxicities, and the numerous challenges to implementing routine HCV testing and providing HCV treatment to this population—can be overcome.


The Way Forward

Although incarceration itself poses challenges to public health and to HIV prevention and treatment, it provides a structured setting in which a number of interventions may be effectively implemented. The concentration of infectious diseases within the criminal justice system, affecting a population that is often estranged from traditional community services, warrants reconsideration of jails as sentinel sites for screening, prevention, and treatment activities.

CONCLUSIONS

Diagnosing and treating infectious diseases such as HIV and STIs have a high cost–benefit ratio; screening and treating these infectious diseases will prevent spread in the community. Economic and logistical obstacles to testing in jails, stigma surrounding incarceration, and lack of political will need to be addressed for progress to be made in implementing HIV, STI, and HCV testing and care programs within jails. Promoting screening for infectious diseases within jails, particularly HIV, STIs, and HCV, is the first step. The next is improved treatment, both within jails and prisons, and in the community after release. Diagnosis within jails, linked with treatment, will result in improved prevention of HIV and other serious conditions.
infections within both correctional facilities and the community as a whole.

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Progress in HIV Reduction and Prevention Among Injection and Noninjection Drug Users

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Abstract: Substantial progress has been made in reducing HIV among injection drug users (IDUs) in the United States, despite political and social resistance that reduced resources and restricted access to services. The record for HIV prevention among non-injecting drug users is less developed, although they are more numerous than IDUs. Newer treatments for opiate and alcohol abuse can now be integrated into primary HIV care; treatment for stimulant abuse is less developed. All drug users present challenges for newer HIV prevention strategies (eg, “test and treat,” nonoccupational postexposure prophylaxis and preexposure prophylaxis, contingency management, and conditional cash transfer). A comprehensive HIV prevention program that includes multicomponent multilevel approaches (ie, individual, network, structural) has been effective in HIV prevention among IDUs. Expanding these approaches to noninjecting drug users, especially those at highest risk (eg, minority men who have sex with men) and incorporating these newer approaches is a public health priority.

Key Words: contingency management, epidemiology, HIV, injection drug use, noninjection drug use, prevention, treatment

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National data have consistently estimated that 20.1 million Americans use illicit drugs. Of those, roughly 1.2 million inject drugs, a practice that has been recognized for its role in HIV transmission, accounting for 11% of HIV infections. Among injection drug users (IDUs) in the United States, the HIV rate has been estimated to be 28%. Addressing the challenge of the HIV epidemic in injectors was made difficult by powerful political and social resistance (eg, zero tolerance campaigns) that dampened access to important resources for drug users. However, during this period, the US Public Health Services developed and disseminated a hierarchy of prevention. Briefly, its first tier called for abstinence, which could be facilitated through treatment for drug abuse. For those IDUs who could not or would not quit drug use, a second tier advised using sterile syringes and disposing of them safely. The third tier, a recommendation applicable when sterile injection equipment was unavailable, was disinfection with bleach. These messages have been successfully implemented by combining interventions at individual, community, and policy levels that promoted education through community outreach and HIV testing; behavioral interventions; drug abuse treatment, including opioid agonist therapies; and syringe exchange programs, which were later supplemented by providing syringe access through pharmacies. Concerns about the potential for syringe access to encourage initiation of drug use among youth and to increase drug use, needle sharing, and crime, proved unfounded. Even before the availability of antiretroviral therapy, HIV prevalence and incidence among injection drug users declined.

The purpose of this brief review is to discuss newer approaches to HIV prevention strategies and potential implementation challenges for prevention both among noninjecting drug users (NIDUs), sometimes mistakenly referred to as “recreational users,” who have received insufficient attention for HIV prevention and among IDUs—framed within consideration of hurdles encountered in the prevention hierarchy of IDUs.

NONINJECTING DRUG USERS

HIV risk, prevalence and transmission rates vary widely among NIDUs using crack, cocaine, methamphetamine, alcohol, pills and noninjected heroin, but may be relatively high because of the co-occurrence of drug use with sexual risk behaviors (eg, unprotected sex, multiple partners, and survival sex) and the overlapping of social network risk groups. These associations have been dramatic, especially among men who have sex with men (MSM).

Approaches to Screening and Prevention

Targeted interventions with outreach specialized to reach types of NIDUs according to drug of choice may be necessary given different behavioral patterns of drug use. However, in general, NIDU interventions should be comprehensive in their ability to serve multiple risk groups (eg, drug users, MSM) with multiple risk factors (eg, drug use, sex, mental health). For example, multicomponent interventions such as MP3 (Methods for Prevention Package Programs) and Screening, Brief Intervention, Referral, and Treatment need to include approaches along with wraparound services to be comprehensive in addressing drug users’ multiple complex needs (eg, relating to sex, mental health, homelessness, and...
Current efforts in the United States are focused on reaching and engaging minority MSM, who have particularly high rates of HIV infection. In this population, as in others, interventions need to go beyond “test and treat” (TNT) to assess and address drug use issues, including polydrug use. In a broader sense, incarceration and neighborhood factors that have been shown to influence availability and opportunity for drug use also need to be considered in addressing drug-related concerns.

WHERE ARE WE NOW?

Especially with the advent of antiretroviral therapies, the spectrum of HIV prevention in drug users has broadened to include TNT; nonoccupational postexposure prophylaxis (nPEP); and pre-exposure prophylaxis (PrEP). These interventions need to be tailored to ensure that they are accessible and feasible for drug users and incorporated on multiple levels (eg, individual, community, and structural).

Test and Treat

TNT aims to reach virtually everyone in the US population and treat HIV infection with antiretroviral medications, an intervention that would presumably reduce population viral loads and HIV incidence. For NIDUs and IDUs alike, the success of TNT requires the ability to reach this more elusive population at higher risk of HIV exposure and to retain them in a program of frequent testing and treatment. TNT could be expanded outside conventional hospital, clinic, and emergency room settings to include those who attend drug treatment and IDUs who have developed rapport with syringe exchange programs and pharmacies. However, among hard-to-reach groups where HIV is making inroads, the purported benefits of TNT may be suboptimal without explicit strategies to incorporate HIV testing into a broad range of facilities on a widespread basis; to reach drug users who do not access services and are likely at highest risk of HIV exposure; to train health care workers to communicate effectively with and engage this population; to optimize approaches to maintain adherence to antiretroviral treatment, especially for those outside drug-abuse treatment; and to ensure that all those at risk for HIV exposure have access to all needed services.

nPEP and PrEP for IDUs

Elsewhere in this issue, nPEP and PrEP in general have been discussed. Data are sparse on nPEP for drug users and for IDUs in particular, and results of PrEP trials in IDUs are not yet available. Should the data show effectiveness, the next challenge will be to appropriately disseminate information via street outreach strategies. Although some view nPEP and PrEP for IDUs and NIDUs with trepidation because of valid concerns over drug toxicities, drug users’ ability to adhere to treatment, and the potential for development of drug resistance that would subsequently limit potential treatment options, it is feasible to integrate provision of these drugs into drug treatment programs and pharmacies, where there is the ability to frequently perform HIV testing and creates linkages to providers to monitor patients. However, additional infrastructure is needed to attract and engage both IDUs and NIDUs.

Substance Abuse Treatment

Substance abuse treatment has been a mainstay for HIV prevention among drug users. For opioid abuse and dependence, methadone and now buprenorphine/naloxone are established treatments, which have the advantage of unchallenged integration into primary HIV care. The greater challenge has been the ability to produce effective substance abuse treatment for stimulant users. Several pharmacotherapies have been tested, and others are in the pipeline. For treatment of methamphetamine abuse, little or no benefit has been seen in trials for bupropion and modafinil, but efforts continue with newer agents such as varenicline are under investigation. The experience to date with pharmacologic treatment for cocaine and crack is similarly disappointing; the promise of antidepressants and carbamazepine has not been realized, but examination of newer drugs is ongoing.

With the slower progress on pharmacologic treatments for methamphetamines and other stimulants, the most promising approach to date has been cognitive behavioral therapy with contingency management. As has been shown for IDUs, treatment combinations on multiple levels (eg, individual pharmacotherapy and behavioral change) are needed not only to reduce drug use but also to successfully target and maintain integration of NIDUs into social services.

Alcohol, the most widely used drug, is also associated with sexual risk for HIV infection. Rapid screening tools for alcohol abuse and dependence have been developed, yet only half of HIV-infected problem drinkers discuss their predicament with their HIV care providers. Given the association of problem drinking with increased risk of HIV transmission and acquisition, screening for alcohol use needs to be more widely incorporated into HIV care and research. A number of pharmacologic treatment options for alcohol misuse are being studied, including naltrexone and disulfiram. Yet no standard pharmacologic therapies for alcohol abuse and dependence exist. Techniques of motivational interviewing (MI) could possibly be effectively provided in primary HIV care settings. But MI’s effectiveness has been demonstrated only as a multisession intervention, limiting its feasibility in many primary HIV care settings, where staff face many competing demands. This suggests that modifications are needed in the structure of MI content and its...
requirement for health care provider involvement. Telephone counseling alone (or possibly as an adjunct to MI) has shown some promise for problem drinkers.54

Contingency management and conditional cash transfer are two iterations of another approach to substance abuse treatment and HIV prevention that has been used for some time.55 There is resistance to the idea of “rewarding” drug users, but available data from prospective studies suggest that this approach improves otherwise costly follow-up without increasing drug use.56 Addressing the challenge of missed doses for treatment, a recent trial of longer-acting implantable buprenorphine implantshowed less opiate use than standard buprenorphine use.57 Likewise, naltrexone implants have shown benefit over oral dosing for improved clinical outcomes58 and recently, Vivitrol (long-acting Naltrexone) has been approved by the U.S. FDA for treating opiate dependence among those successfully detoxified from use.59

CONCLUSIONS: FROM STIGMATA TO REDEMPTION—MAKING EFFECTIVE INTERVENTIONS POSSIBLE

Multilevel, multicomponent interventions among IDUs have been successful at reducing HIV incidence and provide a model for more broadly addressing HIV prevention. Yet challenges remain—not only for IDUs but for the much larger population of noninjectors. Drug use needs to be approached comprehensively to reach and provide options for those who do not or cannot quit drugs. Further, going beyond specific programs into the policy choices that create resources to ensure access to services and support for adherence to the evidence-informed health supporting protocols that are currently available is warranted. Practical strategies to overcome problems of access and adherence include utilizing our standard tools of (1) “education,” to increase knowledge about behaviors that can prevent HIV infection at the individual and community levels; (2) “HIV testing” in nontraditional settings (eg, pharmacies) to reach drug users whose activities put them at high risk of HIV exposure; (3) “behavioral interventions” that not only address drug use–associated behaviors and health problems but also HIV risk behaviors to lure and integrate drug users who are members of other overlapping risk groups; (4) “drug treatment,” which should be expanded, especially in communities where access is now poor and in primary HIV care settings; and, for IDUs, (5) “syringe access,” to increase access to sterile equipment. It is a combination of these strategies applied simultaneously on individual, community, and policy levels that have been successful in reducing HIV incidence and prevalence among drug users to date, and it is these strategies that researchers, community members, and policy makers should work to expand for use and application of upcoming HIV interventions.

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HIV Prevention in Gay Bathhouses and Sex Clubs Across the United States

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Abstract: Gay bathhouses (including sex clubs) contributed to HIV prevention from the early days of the AIDS epidemic, but the extent to which prevention interventions are implemented in bathhouses is unknown. Using telephone survey methodology, bathhouse managers provided data about HIV prevention in their bathhouses. All the bathhouses provided free condoms, and nearly all displayed educational posters in public areas and had informational pamphlets available for patrons. A few of the bathhouses offered outreach services and counseling services. Almost all promoted testing for HIV sexually transmitted infection (which included providing information about where to get tested), and 75.5% had HIV testing programs in their venues. Most of the HIV testing programs were started during the past 5 years, initiated by the bathhouse management or a community agency, and operated by community-based agencies. About one third of the programs offered rapid HIV testing. The results of the telephone survey revealed that all the bathhouses engaged in prevention and many offered a wide range of prevention services, suggesting that managers have embraced the issue of HIV and collaborated in bringing prevention to high-risk men. The absence of studies evaluating these prevention efforts remains a concern and an obstacle for efficient use of the prevention resources.

Key Words: HIV prevention, gay bathhouse, sex clubs, sex environments, gay men, men who have sex with men

(J Acquir Immune Defic Syndr 2010;55:S88–S90)

INTRODUCTION

Gay bathhouses and sex clubs (hereafter, simply “clubs”) have contributed to and served as sites for HIV prevention from the early days of the AIDS epidemic, and they continue to do so without deleterious effects on their businesses. Although data from probability samples of men leaving clubs show that risk behavior inside the clubs themselves is atypical, clubs do attract men who engage in such behavior. High-risk men who have sex with men (MSM) are more likely than their peers to go to clubs, and more than half of all non-testing high-risk MSM go to clubs. Clubs are an ideal environment in which to target this otherwise hard-to-reach population with appropriate prevention interventions. Recent research has focused on the challenges of implementing HIV testing programs in clubs, whereas other studies have shown that men at clubs will avail themselves for testing when it is available on site and that such in-club testing has been associated with a reduced risk behavior for more than a 3-month period. The scientific literature indicates a wide range of HIV prevention programs, and services have been initiated in clubs to try to reach men at risk with important HIV prevention services and information. To determine the extent to which HIV prevention is implemented in clubs across the United States, we interviewed club managers. This article presents the findings from that study.

METHOD

The study population included all clubs operating in the United States and listed in the Damron Men’s Travel Guide 2004 (a gay resource directory for the United States) or www.cruisingforsex.com (at the time, the most comprehensive Web listing of places for men to meet men for sex). Lists of establishments in these resources were inclusive of a variety of places where men meet for sex. We operationally defined a club as any listed business that provided a space where anonymous sex was permitted between male patrons, that had a permanent location, and that operated at least 3 days a week.

Managers of these clubs served as key informants, providing data about the clubs they manage. To recruit these managers, we followed procedures used in a similar survey of clubs conducted from October 1996 to February 1997. A letter introducing the study was addressed to the general manager of each club and mailed at least a week before the initial telephone contact; attempts to complete direct contact with a club owner or manager followed and continued until a representative of the club verbally declined study participation. During the subsequent initial direct contact, the interviewer described the study, answered any questions, and determined whether the general manager or whether someone else (eg, a manager who oversees the HIV prevention activities at the club) should be the respondent. Participation was voluntary, and the participants gave verbal consent. The telephone interview lasted from 1.5 to 2.5 hours. Interviewers used a computer-assisted telephone interview system. The questionnaire was developed from the formative work on HIV prevention services in clubs in New York, Los Angeles, and San Francisco and was reviewed in advance by 3 club managers. The interview included items requesting detailed data about the specific club’s size and amenities, its...
rules and regulations, its prevention programs (including education and information, condom and lube distribution, and on-site testing programs for HIV/sexually transmitted infection), and the barriers to and facilitators for providing HIV testing services. All procedures and protocols were approved by the Institutional Review Board at the University of California, San Francisco.

RESULTS

We identified 94 gay sex establishments in the United States, of which 77 met the eligibility criteria (ie, provided space where sex was permitted, had a permanent location, and operated at least 3 days a week). We completed interviews with representatives of 53 clubs, a response rate of 70.1%.

These businesses used various terms to describe themselves, including bathhouse (43.4%), health club (34.2%), sex club (13.2%), and sauna (5.7%); the remaining respondents did not know or preferred not to say (2.8%). Clubs varied widely in their size, as indicated by the range in the number of rentable rooms (22–129; mean = 55.0, median = 55.0) and lockers (34–400; mean = 127.6, median = 100.0), although 1 club offered neither rooms nor lockers to rent. In general, clubs that offered rooms to rent were larger, and the more rooms and lockers available to rent, the larger the club.

About half the venues (50.9%) permitted sexual behavior among patrons in the public areas; 22 (81.5%) of these 27 clubs purposely kept the lighting levels lower in the public areas intended for sex. About 4 (41.5%) in 10 clubs had rules about safer sex (eg, it was the only type of sex permitted inside the club), and most of those (77.3%) asked patrons to agree in writing to follow the rules, usually at each visit (68.4%). All clubs had rules prohibiting the use of drugs (including alcohol), and a majority (60.4%) did a bag check at entry. A few clubs (6.3%) prohibited on-premise use of “poppers” (ie, alkyl nitrites, inhaled for recreational purposes), but more than half (56.6%) sold them. Methamphetamines and alcohol were most frequently reported as the substances causing the largest problem at a club (29.9% and 16.1%, respectively).

More than half of the clubs (58.5%) had a designated employee responsible for oversight of club prevention activities, with about a quarter of these employees (25.9%) dedicating 50% or more of their work time to managing prevention activities. Table 1 summarizes the range of prevention activities and the proportion of clubs engaging in each prevention activity. All the venues made free condoms available to all patrons, and nearly all displayed educational posters in public areas and had informational pamphlets available for patrons; a few clubs also offered other outreach services, but special events that focused on risk reduction and counseling services were not as prevalent. Almost all the clubs promoted HIV testing (at a minimum, providing information about where to get tested), and 40 of 53 offered HIV testing on site (ie, inside the “paid” area of the club).

Of the clubs offering on-site HIV testing, 14 had more than 1 group providing testing at the club; 7 clubs had 2 different groups offering testing, 3 clubs had 3 groups, and 4 clubs had 4 groups. Table 2 summarizes key features of the 65 testing programs implemented inside the 40 clubs that offered testing on site. Those programs had been offering testing on average for 5.6 years (median = 4.5 years; range ≤1–25 years). At the time of the study, they operated on average 3.7 days a month (median = 4.0 days, range = 1–12 days), constituting 13.6 hours of testing (median = 12.0 hours, range = 2–48 hours), serving 26.4 clients per month (median = 16.0, range = 2–100). Of the 62 programs that offered HIV testing, 37 (59.7%) delivered test results inside the club, and of those, 10 (27.0%) delivered results solely inside the club. Of the 41 programs (63.1%) that offered testing for sexually transmitted infection, 20 (48.8%) delivered results inside the club.

DISCUSSION

Clubs across the United States continue to provide a wide range of HIV prevention efforts. Rather than resist HIV

<table>
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<th>TABLE 1. Prevention in the US Clubs (n = 53)</th>
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<tr>
<td>Condoms</td>
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<td>Distributed in public areas</td>
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<td>Educational materials/activities</td>
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<td>Promote HIV/STI testing</td>
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<td>Provide HIV testing inside club</td>
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<tr>
<td>Provide STI testing inside club</td>
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<td>Special room built out for testing</td>
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*Among clubs with private rooms (n = 48).

<table>
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<th>TABLE 2. Characteristics of 65 Testing Programs at Clubs That Offered Testing on Site</th>
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<td>HIV (standard)</td>
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<td>Gonorrhea</td>
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<td>Chlamydia</td>
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<td>Hepatitis (A, B, or C)</td>
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prevention, club managers seemed to promote and engage actively in it. Our telephone survey found that most clubs have assigned a specific employee to manage prevention activities and that on-site testing programs were more likely to have been initiated by the clubs themselves than by any other single group of stakeholders. Although condom and information distribution remain the primary prevention activities, many clubs reported additional prevention efforts, including outreach programs, counseling services, and special events that focused on HIV prevention and testing. In fact, when compared with a similar study conducted in 1996–1997, the percentage of clubs offering HIV testing programs has almost doubled.

The data presented described the extent to which prevention programs were offered in clubs across the country. Further research is needed to determine the efficacy of prevention activities (such as where condoms are distributed in the club), to develop best-practices standards for service programs (such as on-site HIV testing), and to identify the facilitators that lead clubs to engage in prevention and the barriers that stifle such engagement. Providing answers to these questions can help direct future prevention efforts by focusing resources on effective programs and assisting public health officials and service providers in exploiting facilitators and minimizing barriers for clubs to engage in prevention. Although local jurisdictions have instituted many different policies to establish particular approaches to prevention in clubs, little or no research has been conducted to determine whether any of them are effective or more appropriate than other approaches.

Studies of how these policies alter club environments in ways that might decrease risk behavior (eg, always using a condom for anal sex) or increase protective behavior (eg, testing by high-risk MSM) are required to better understand how these environments can facilitate prevention efforts that will reach the highest-risk segment of the MSM population.

The following limitations should be kept in mind when interpreting the results of this study. All data were provided by 1 key informant at each site, without any observational or secondary source verification. It is possible that different information may have been provided had a different key informant been interviewed. It also is possible that we received refusals from clubs that were not providing prevention efforts. Finally, the information on HIV testing programs is limited, as the program providers were not interviewed.

In summary, nearly all the businesses engaged in HIV education and prevention. We found that free condom distribution was a universal characteristic of prevention in clubs, followed closely by such educational efforts as posters and pamphlets. Most clubs provided on-site HIV testing. The absence of studies evaluating these prevention efforts remains a concern and an obstacle for efficient use of the resources. Nevertheless, these data suggest that HIV prevention in clubs is perceived by most managers as a necessary part of doing business. The willingness of these clubs to promote HIV prevention suggests that the business aspect of venues that serve at-risk populations is not necessarily an impediment to intervening in these venues.

ACKNOWLEDGMENTS

The authors acknowledge the club owners and managers, without whose cooperation the survey could not be conducted. They also wish to recognize the efforts of the survey team, specifically Justin Bailey, Paul Cotten, Robert Siedle-Khan, Alberto Curotto, Gabriel Ortiz, and Joseph Morris.

REFERENCES

**HIV in Transgender Communities: Syndemic Dynamics and a Need for Multicomponent Interventions**

Don Operario, PhD* and Tooru Nemoto, PhD†

**Abstract:** Transgender communities are among the groups at highest risk for HIV infection in the United States. Using syndemic theory, we examine how HIV risk in transgender communities is embedded in multiple co-occurring public health problems, including poor mental health, substance use, violence and victimization, discrimination, and economic hardship. Although safer sex counseling and testing programs are essential platforms for HIV intervention, these modalities alone may be insufficient in reducing new infections. Multicomponent interventions are necessary to respond to the complex interacting syndemic factors that cumulatively determine HIV vulnerability in transgender individuals.

**Key Words:** transgender, HIV, syndemics

*J Acquir Immune Defic Syndr* 2010;55:S91–S93

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**INTRODUCTION**

Transgender is an umbrella term referring to the population of individuals whose gender identity differs from the gender assigned at birth. Researchers have described a state of emergency related to HIV in the transgender community. To date, there exist no efficacious HIV prevention interventions for transgender individuals. The lack of research reflects, in part, the challenges in studying this population. For example, no reliable estimates exist of the size of the transgender population, many transgender individuals wish to be hidden, and assessing transgender identity and gender history remains difficult. We argue that the lack of progress in HIV prevention for transgender people is also due to the complexity of the epidemic in this community, attributable to multiple co-occurring public health problems that determine their HIV risk.

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**EPIDEMIOLOGICAL STUDIES**

A systematic review by Herbst et al identified 29 studies reporting biological or behavioral HIV data in transgender communities, of which 22 reported HIV prevalence data on transgender women (or male-to-female transgenders) and 5 reported data on transgender men (or female-to-male transgenders). Meta-analysis of biological data estimated 28% HIV seroprevalence in transgender women, with extremely high seroprevalence (56%) in African Americans. Meta-analysis of self-report data estimated 12% HIV and 21% prevalence of any other sexually transmitted infection (STI) in transgender women; STIs commonly assessed include gonorrhea, chlamydia, herpes, syphilis, trichomoniasis, and hepatitis B and C. Compared with biological findings, lower self-reported HIV prevalence might reflect unknown infection or unwillingness to disclose. Two studies reported HIV incidence in transgender women: 7.8 infections per 100 person-years in a San Francisco study and 3.4 infections per 100 person-years in a Los Angeles study. Meta-analysis of data from transgender men was not conducted; only 1 study in transgender men reported HIV seroprevalence (2%), and 4 studies in transgender men found low self-reported HIV infection (0%–3%). Another study of transgender women in New York city, released after the meta-analysis by Herbst et al, found a high HIV seroprevalence in African American and Hispanic (22% and 36%) transgender women (48% and 50%, respectively) compared with white transgender women (4%). High prevalence of syphilis and hepatitis B were also detected in African American (15% and 36%) and Hispanic (36% and 22%) transgender women.

Multiple HIV behavioral risk factors have been identified, based mostly on studies of transgender women. Risk behaviors for transgender women include multiple partners, unprotected receptive anal intercourse, commercial sex, sex under the influence of alcohol and drugs, needle use for injecting drugs and gender-related hormones or silicone. In several studies, African American and Hispanic transgender women report greater risk behaviors compared with white and Asian and Pacific Islander transgender women. Few studies have examined behavioral risk factors in transgender men, but there is emerging evidence of unprotected penetrative sex between transgender men and biological men.

**HIV-Related Syndemics in Transgender Communities**

Syndemic theory has been a useful framework for understanding the determinants of HIV disparities in high-risk...
populations. Syndemic refers to the concentration within a specific population of multiple co-occurring epidemics interacting and reinforcing one another and ultimately giving rise to other health problems. Singer et al have described how epidemics of substance abuse and violence facilitated a subsequent HIV epidemic in inner city Hartford, and Stall et al have examined the epidemics of substance use, mental health, and childhood abuse in men who have sex with men as interacting drivers of the domestic HIV epidemic in men who have sex with men. Similarly, data from studies of transgender populations in the United States reveal syndemic dynamics that facilitate sexual risk behaviors and HIV transmission.

Mental health problems are frequently reported in transgender communities. Studies have shown high rates of depression, emotional distress, loneliness, and social isolation in transgender populations. Results from meta-analysis revealed that 54% of transgender individuals surveyed had suicidal thoughts and 31% had attempted suicide. Mental health problems can undermine motivations to practice safer sex behavior and can increase motivations for engaging in unprotected sex as a means for cognitive escape, emotional release, and feelings of love and intimacy.

High rates of alcohol and drug use in transgender communities, including injection drug use (IDU), are also reported. In a San Francisco study, 34% of transgender women reported lifetime IDU and 18% reported past 6-month IDU, and 18% of transgender men reported lifetime IDU and 4% reported past 6-month IDU. Other drugs commonly used include marijuana, cocaine, crack, and methamphetamine, although within-group differences are observed. For example, in San Francisco, cocaine and crack use were higher among African American transgender women than among transgender women in other ethnic groups, and methamphetamine use was higher in Asian and Pacific Islander transgender women. Substance use before or during sex compromises cognitive or behavioral abilities to use condoms and is an independent predictor of unprotected receptive anal sex in transgender women.

Transgender women and men may be at an increased risk for violence and victimization, including physical and sexual abuse. A national review of data from survey research, police reports, and social service records highlights multiple forms of violence that transgender people experience throughout their lifetimes. Abuse may begin in adolescence or childhood when transgender individuals begin to express atypical gender characteristics. Violence and victimization directly and indirectly lead to HIV risk. Forced sex confers likelihood of exposure for HIV/STI transmission, and other forms of physical violence can contribute to mental health problems and substance use, which increase the likelihood for sexual risk behaviors.

Studies have reported high levels of poverty, unemployment, and homelessness in transgender women and men. These outcomes likely stem from general stigma and job and housing discrimination against individuals whose transgender identity is exposed. Indeed, a goal for many transgender women and men is the ability to “pass” and receive affirmation as their desired gender, which manifests in the capacity to blend into mainstream society unnoticed.

Some individuals have a difficult time passing due to physical characteristics that call attention to their transgender status, and these individuals may be more prone to stigma and discrimination and to ensuing syndemics of mental health, substance use, and violence that facilitate HIV risk.

Social and Structural Conditions for Syndemics in Transgender Communities

As noted, the syndemic dynamics described here reflect social and structural conditions that govern the treatment of transgender individuals. Because sex and gender are basic organizational principals in most societies, including contemporary US society, deviation from prescribed sex and gender dichotomies is reprimanded at nearly every level of social life. Consequently, transgender individuals experience a developmental life course characterized by cumulative stigma, alienation, and internalized stress. Studies of transgender youth have documented unsupportive and frequently hostile family members and peers. This adversity extends and augments into adulthood, manifesting in explicit discrimination, denial of opportunities, exposure to violence, and frequently unresponsive legal systems. Structural inequalities for transgender individuals are particularly salient in the health care system. Multiple studies report, among transgender communities, limited access to health services, inappropriate or nonexistent care protocols and facilities for transgender clients, and untrained and often discriminatory health providers and staff.

Not Just Testing and Condoms: Need for Multicomponent Interventions

Recognition of multiple co-occurring epidemics and challenging social and structural conditions call into question the feasibility of standard HIV prevention approaches for addressing the needs of transgender women and men. Dominant paradigms in HIV prevention include testing and counseling, informational and motivational training to improve condom use and encourage partner reduction, and other approaches that focus on safer sex as the primary or sole outcome. Syndemic analysis of the determinants of HIV risk in transgender communities—particularly in transgender women, who have been the focus of most previous studies reviewed here—reveals that more complex prevention approaches are warranted. Indeed, previous research has suggested that transgender women are highly aware of their HIV-related sexual risk behaviors but that HIV prevention is simply a low priority compared with other immediate concerns.

Multicomponent interventions are necessary to mitigate the HIV syndemic dynamics in transgender communities. Several recent articles have called for the development of multicomponent HIV interventions that recognize and address interactions among, for example, substance use, mental health, poverty, and HIV risk. Ickovics has described the benefit of “bundling” HIV prevention services with other health/social services to achieve meaningful improvements in public health. In order for multiple services to form a meaningful bundle, they must be complementary, synergistic in their health benefit, cost-effective, and accepted by target audiences. HIV testing and behavioral–motivational risk reduction counseling....
offer platforms for bundling other intervention foci and modalities, which might include transgender support groups, brief substance use counseling and treatment referrals, brief mental health counseling and referrals, life skills coaching and training, and other programs that correspond to recognized transgender syndemic dynamics. Intervention components must also consider developmental trajectories in transgender identity, including the needs of adolescents and young adults, and prevention needs that might differ according to gender transformation procedures. Enhancing sensitive and appropriate channels of care and establishing linkages between care services are essential to this multicomponent approach.

The science of multicomponent HIV prevention intervention for transgender and other high-risk populations is still in its infancy. Condoms and testing alone cannot reduce the burden of HIV infection and AIDS in transgender individuals and other high-risk populations. Major efforts must be invested in developing and testing complex population-focused interventions. For transgender communities, the capacity to respond to HIV syndemic dynamics can be a matter of life and death.

REFERENCES

HIV Prevention and Care in the Digital Age

Mary Ann Chiasson, DrPH,*† Sabina Hirshfield, PhD,* and Cornelis Rietmeijer, MD, PhD‡

OBJECTIVES: To describe the technologic advances in the digital media, including computers, mobile phones, and the Internet, that have greatly expanded opportunities to deliver evidence-based HIV education, prevention, and treatment programs.

METHODS: This article examines the use of digital media in the United States and its potential role in HIV prevention and care.

RESULTS: Although the “digital divide” is shrinking, access varies by age, race/ethnicity, and education. The Internet is an important medium for delivering universal and targeted HIV prevention and education, especially for men who have sex with men, who report going online to seek health information online and for social and sexual networking. Online and off-line behavioral interventions using digital media range from computerized multimedia interventions that take into account individual behaviors to brief untailored video interventions. Numerous Web sites facilitate access to care by providing a variety of services, including location of and linkage to HIV testing and treatment sites. HIV treatment and adherence programs that use online medical records text messaging, paging, and tablet computer–based counseling tools are also being developed.

CONCLUSIONS: HIV prevention and care programs using digital media have great potential to cost-effectively meet the complex needs of diverse and often underserved populations living with or at high risk of HIV.

KEY WORDS: HIV, Internet, prevention, sexually transmitted infection, computer technology, MSM

(J Acquir Immune Defic Syndr 2010;55:S94–S97)

INTRODUCTION

Technologic advances in digital media, including computers, mobile phones, and the Internet, have revolutionized the way we communicate with each other, both personally and professionally. The transformation of the Internet from Web 1.0 as a unidirectional information source to the interactive and participatory Web 2.0 has important implications for HIV transmission, HIV education and prevention, and medical management of HIV. The Internet’s borderless geographic and demographic social networks and equally limitless possibilities for interventions have the potential to change both community norms and individual behavior cost-effectively.

DISCUSSION

Who’s Online

In 2010, most adults (77%) and nearly all teenagers (93%) in the United States are online.1-2 Overall, 41% of Americans use social networking sites with the greatest use (75%) reported by those between 18 and 29 years of age.3 This group also leads in the use of mobile phones (94%) and texting: 88% text, and of these, 80% texted a median of 20 times during the past 24 hours.1 Yet even within this group, there are variations by race/ethnicity and education, despite the high usage levels. Whites are more likely to use the Internet (95%) than blacks (91%) or Hispanics (73%), and those with some college (96%) are more likely to be online than those without (83%),1 suggesting that the digital divide is closing. However, disparities are still seen among 18–29 year olds who create profiles on a social networking site: whites (83%), blacks (71%), Hispanics (52%), and those with some college (86%), compared with only 59% of those with no college.1 The limited data available on Internet access among those living with HIV show similar disparities by race/ethnicity and education but far lower overall rates. Only about the half report ever using the Internet (P. Messeri, MD, personal communication, June 21, 2010).3 Not surprisingly, active drug use, poverty, and homelessness are associated with very low rates of Internet access4; text messaging may be an effective way to contact such difficult-to-reach populations.5

Seeking Sex Online and HIV Risk

Most studies of the relationship between Internet use and sexual behavior have focused on gay, bisexual, and other men who have sex with men (MSM) because they account for the majority of newly reported HIV-infected population in the United States6 and frequently seek sexual partners online.7 Most population-based studies do not compare the prevalence of seeking sex online by gender and sexual orientation.8 Community-based studies have found that MSM are more likely to seek sex partners online than gay women and heterosexual men and women.9-12 High-risk sexual behavior observed in online studies largely reflects the risk-taking profile of individuals who choose to seek sex partners both online and...
off-line and is not associated with the Internet per se.\textsuperscript{10,12–17} Manhunt (www.manhunt.net) and Adam4Adam (www.adam4adam.com) are 2 of the largest Web sites for MSM seeking sex partners in the United States and abroad. Manhunt members can send e-mails, text messages, and instant video messages to potential partners. Adam4Adam members can locate potential partners through “Plan-a-Trip” before they reach their destination. MSM who meet sex partners online report more sex partners,\textsuperscript{18–21} sex with casual partners,\textsuperscript{18–21} and more unprotected anal intercourse,\textsuperscript{22} although their behavior is similarly risky with partners met off-line.\textsuperscript{14–16,23} Thus, those meeting partners online can expand their sexual networks, thereby increasing the potential for transmission of HIV and other sexually transmitted infections (STIs).\textsuperscript{7,24,25}

Health Education Online

Many Americans search for health information online, with 75% of all adults and 28% of all teens online reporting this activity.\textsuperscript{2} At best, the Internet may provide access to the most current and most scientifically accurate information available on all aspects of HIV/AIDS, from risk factors for transmission and acquisition to early signs and symptoms to HIV testing and treatment. There are numerous sites targeting both professional and lay audiences. Two recently published studies provide comprehensive assessments of national and international HIV/AIDS resources online for clinicians and researchers that include sources for treatment guidelines, disease management, and continuing medical education.\textsuperscript{26,27}

Web sites such as The Body (www.thebody.com) and POZ (www.poz.com) are dedicated to education and clinical information on HIV/AIDS testing, diagnosis, treatment, and prevention for consumers and include access to experts, forums, blogs, and other digital media. In addition to traditional informational Web sites, a number of interactive safer sex educational Web sites, many targeted to teens,\textsuperscript{28} and non-traditional sites, such as “Kicesie’s Sex Ed—What They Don’t Teach You In School” on YouTube,\textsuperscript{29} have been developed. For young gay men, the Internet fills an important unmet need for sexual health education and support during the coming out process, although it can also expose them to homophobic messages.\textsuperscript{30} Despite this ready access to information, separating disinformation from scientific fact can be difficult even for the most experienced searcher. Unsurprisingly, therefore, the Internet is also a fertile field for AIDS denialists (those who deny that HIV causes AIDS) and proponents of proven treatments for HIV.

Expanding Access to Care

The Internet can facilitate the diagnosis and treatment of HIV and other STIs through Web sites that provide education and information about the location of community-based testing and clinic-based HIV and STI services (eg, www.hivtest.org). Web-based,\textsuperscript{31–33} text,\textsuperscript{34} and instant messaging\textsuperscript{35} programs have also been developed to educate and encourage testing through clinic referrals, preprinted laboratory requisition slips, and provision of online access to STI test results.\textsuperscript{36} In addition, Internet sex partner notification for STI exposure is proving to be acceptable to MSM,\textsuperscript{37} and Internet-based partner notification programs have been developed\textsuperscript{38} although the effectiveness of the latter has not been demonstrated.\textsuperscript{39,40}

Self-collection kits for mail-in testing for HIV\textsuperscript{41} and a number of other STIs and home test kits can be purchased online, although the cost of kits from commercial sites can be high.\textsuperscript{42} Self-collection kits for mail-in STI testing are also available from public health Web sites in some geographic areas.\textsuperscript{43} HIV and STI self-collection kits for mail-in testing and home testing are appealing to many for reasons of both privacy and convenience.\textsuperscript{44,45} However, a recent study found that consumer services available from commercial Web sites may be poor and testing accuracy may be variable: Although mail-in specimen test results were highly accurate, home tests were often inaccurate.\textsuperscript{42}

Improving HIV Treatment and Adherence

The Internet and development of Web-based applications have had a major impact on medical record keeping and access to medical records by patients. Web-based electronic records can be shared easily by all who need access, including medical care providers and the patient. Using industry-standard software to protect the confidentiality of information, Web-based electronic medical records offer the timely and active sharing of test results. The sharing of STI test results online is a promising development that not only enhances patients’ access to their test results but also may improve treatment outcomes.\textsuperscript{31,36} Likewise, the provision of HIV viral load and CD4 test results online, including trends over time, could provide the patients with important tools in managing their illness. Because adherence to antiretroviral treatment is critically important in adequately suppressing HIV in infected individuals and preventing the emergence of resistant HIV strains, there has been considerable interest in developing adherence interventions. One such intervention used an Internet-based paging system to improve adherence among patients who had failed more traditional off-line adherence systems\textsuperscript{46}; another piloted the use of a tablet computer–based counseling tool to improve adherence and to reduce secondary transmission of HIV in an HIV-infected population with mixed computer use experience.\textsuperscript{47}

Behavioral Interventions Off-line and Online Using Digital Media

HIV/STI behavioral interventions using digital media have been developed in many forms, ranging from complex computer-tailored multimedia interventions that take into account individual behaviors and stages of change to brief untailored video interventions.\textsuperscript{28,48–50} Interventions using digital media are appealing because they can be delivered consistently either alone or in combination with more traditional counseling modalities and in a variety of settings, either in person via computer or video in clinics, social service agencies, and schools\textsuperscript{51–57} or electronically via text messaging,\textsuperscript{58} handheld computers,\textsuperscript{2} or online.\textsuperscript{59–68} Effective HIV prevention interventions that use digital media are likely to be highly cost-effective because they are easily replicated after development, require minimal staffing, and have unlimited geographic reach.\textsuperscript{69}

The development of online HIV prevention interventions of proven efficacy is an area of intensive research,
although it lags far behind online interventions for smoking, obesity, and mental health problems. Of the 7 published randomized trials of intensive individual-level online HIV behavioral interventions primarily targeted to MSM, 5 have demonstrated some reduction in 1 or more HIV risk behaviors, an increase in HIV testing, or short-term increases in knowledge, self-efficacy, and outcome expectancies. Two trials reported no changes in behavior attributable to a variety of factors, including loss to follow-up, participant fatigue, technical problems, Internet connection speed, single-session intervention, and content not tailored to all outcomes or study populations. Preliminary efficacy studies using soap opera video delivery to handheld computers, online dramatic video, chat room, and mobile phone texting interventions have also been published in addition to findings from a brief physician e-mail intervention to reduce at-risk adolescents’ display of risk behavior on a social networking Web site.

**FUTURE DIRECTIONS**

A new generation of HIV prevention interventions is needed to stem the tide of infections in the United States. Digital media are increasingly being used in all aspects of HIV prevention and care to meet the complex needs of diverse and often underserved, vulnerable populations worldwide. Effective evidence-based approaches using digital media have the potential to play an important role in achieving the goals of the National HIV/AIDS Strategy for the United States in the future; translation of existing evidence-based interventions into digital media formats and development of new effective interventions that capitalize on the technologic advances in digital media are both a priority.

**REFERENCES**


Couple-Based HIV Prevention in the United States: Advantages, Gaps, and Future Directions

Nabila El-Bassel, DSW,* Louisa Gilbert, PhD,* Susan Witte, PhD,* Elwin Wu, PhD,* Tim Hunt, MSW,* and Robert H. Remien, PhD†

Abstract: This article presents an overview of couple-based HIV prevention research to date, advantages of using and core components of couple-based interventions, gaps in the current understanding of couple-based HIV prevention, status of dissemination research and the transportability of effective couple-based HIV prevention and treatment to real-world settings, and recommendations for future directions in couple-based prevention and treatment. Couple-based studies conducted among several populations—heterosexuals, men who have sex with men, and drug users—reported in the research literature were reviewed. Commonalities and limitations were noted in customary focus areas of the couple-based approaches: sexual and drug risk reduction, HIV testing behaviors, adherence to HIV treatment, and prevention of mother-to-child transmission. Couple-based intervention strategies have been rigorously tested and are a valuable addition to the arsenal of HIV prevention strategies. Immediate needs and opportunities include couple-based prevention strategies for prevention of HIV and other sexually transmitted infections among serodiscordant couples, couples who do not know their HIV status, and couples in whom both partners are HIV negative but at risk of HIV infection. There is a particular need to develop couple-based intervention strategies for men who have sex with men and for drug-involved couples.

Key Words: HIV/AIDS, couples, prevention

(J Acquir Immune Defic Syndr 2010;55:S98–S101)

INTRODUCTION

Although a 2008 surveillance report by the Centers for Disease Control and Prevention indicates that 86% of new HIV cases in the United States were attributed to sexual transmission, either through men who have sex with men (MSM; 54%) or heterosexual contact (32%), and although the proportion of new HIV cases attributed to sexual transmission has steadily increased since 2005,1 most HIV prevention efforts in the United States have continued to focus on individual or group interventions, neglecting the critical role partners may play in transmission.2–4 Among both heterosexuals and MSM, sexual transmission of HIV occurs most frequently in the context of intimate relationships,5,6 a fact that underscores the need for couple-based HIV prevention (ie, involving both intimate sex partners in the HIV intervention).

A systematic review of couple-based HIV studies found that couple-based approaches are generally efficacious in promoting safer sex behaviors.7 Compared with individual-level approaches, couple-based interventions are more efficacious in promoting HIV counseling and testing,7,8 supporting medication adherence among HIV-infected individuals in serodiscordant relationships,9 and improving adherence to treatment regimens for preventing mother-to-child transmission.10,11

The few couple-based HIV interventions conducted in the United States have mostly focused on reducing unsafe sex or improving adherence to HIV medication. Most studies conducted internationally have focused on voluntary counseling and testing or prevention of mother-to-child transmission of HIV.7 All but 2 couple-based studies in the United States have been conducted with heterosexual men and women.7 This article presents the advantages and challenges of couple-based approaches, describes core components included in the couple-based studies, highlights the state of science of couple-based HIV research in the United States and the state of dissemination of these approaches to real-world settings, and discusses future directions that may improve couple-based HIV research in the United States.

DISCUSSION

Advantages and Challenges of Couple-Based HIV Prevention

The literature identifies several advantages of couple-based approaches. They provide an opportunity for the 2 members of the couple to recognize their mutual responsibility for protecting each other from HIV transmission and to work together to stay healthy.12–14 Couple-based approaches accentuate the relationship’s context (ie, commitment, love, trust) and its connection to HIV acquisition, and then, they redirect attention to the value of the couple’s relationship and the power of the dyad in behavior change.12–14 A safe environment is created that fosters discussion of sensitive or taboo topics (eg, sexual concurrency, power imbalances in the relationship, couple’s sexual preferences, and sexual coercion). A couple-based modality allows the pair to learn together,
in vivo with a third party (a facilitator), skills in couple communication, negotiation, problem solving, and couple goal setting as well as technical skills in condom use. Joint processing with the facilitator promotes accountability and increases commitment to change.\textsuperscript{12–15}

**Core Components of Couple-Based HIV Prevention in the United States**

There is a notable heterogeneity in HIV intervention content in couple-based studies.\textsuperscript{7} Most studies explore the knowledge of HIV and sexually transmitted infections (STIs), technical skills in condom use, couple skills in communication and negotiation as well as problem solving and goal setting; couple power imbalances associated with sexual decision making\textsuperscript{8}, and ways to promote and maintain a healthy relationship. Other content of HIV interventions addresses couple HIV counseling and testing, family planning, a review of cultural values to reinforce commitment to protect one’s partner and community, and changing couples’ peer norms regarding safer sex practices.\textsuperscript{7,12–15} This combination of couple-based skills and intervention content are illustrated in 3 studies conducted in the United States by the authors of this article.

The project Connect, with 217 heterosexual couples, was the first study funded by the National Institute of Mental Health of the National Institutes of Health to test a relationship-based HIV/STI risk reduction intervention. The intervention, a series of 6 once-weekly sessions (delivered to couples in a study arm and to women alone in another), was found to be efficacious in increasing condom use, compared with the third study arm, the control—a single HIV/STI information session.\textsuperscript{12,13,15} The weekly sessions targeted the relationship context, and all exercises and homework assignments were geared toward the couple; all participants attending these sessions were asked to practice the communication, negotiation, and condom skills that they learned in the weekly sessions with their partners. Connect is currently being disseminated by the Centers for Disease Control and Prevention as a DEBI (diffusion of effective behavioral interventions) and tested for adoption by 80 New York State agencies.\textsuperscript{16}

The project Eban, with 535 African American serodiscordant couples in 4 US cities, was recently completed.\textsuperscript{14,17} Couples assigned to the Eban couples risk reduction intervention compared with a health promotion comparison condition were more likely to increase condom use over the 12-month period.\textsuperscript{17}

The project Connect with Pride, an adaptation of Connect that was targeted to African American MSM couples composed of at least 1 methamphetamine user, was recently piloted with 34 MSM dyads with promising results.\textsuperscript{18}

Couple-based prevention research on drug-related HIV risks is emerging. Specific core components of drug-related interventions include syringe disinfection skills, triggers for drug use, gender imbalances in HIV risks associated with a couple’s drug-using contexts, and improved access to harm reduction programs.\textsuperscript{19}

Addressing treatment adherence within a couple has the potential advantage of not only improving the health of persons living with HIV but also reducing the risk of transmission within the pair by reducing the viral load of the infected partner and thus the risk of HIV transmission.\textsuperscript{9,20} Core components of interventions to promote adherence include enhancing a couple’s commitment to maintain a steady supply of medications, helping to identify and resolve ongoing barriers to adherence, improving communication and mutual caretaking, promoting sexual risk reduction skills, and encouraging regular HIV testing for uninfected partners. In prevention of mother-to-child transmission interventions, couple sessions also focus on HIV testing for the male partner.\textsuperscript{16}

**Gaps in the Science of Couple-Based Research**

Since the HIV epidemic began, only 6 couple-based studies have been conducted in the United States.\textsuperscript{9,15,17,18,21,22} Six of these focused on sexual risk reduction; 1 included both sexual risk reduction and adherence to antiretroviral therapy, where HIV prevention was incorporated into treatment and care.\textsuperscript{9} Two included MSM,\textsuperscript{9,18} and of these, 1 was conducted with MSM who use drugs.\textsuperscript{18} None was conducted solely with drug-using non-MSM populations. None has focused on primary prevention among HIV-uninfected couples who engage in HIV risks or among HIV-infected seroconcordant couples.\textsuperscript{9}

Existing models vary in their definition of a “couple.” In studies conducted by the authors, couples include ongoing dyadic heterosexual or same-sex relationships, which may include but are not limited to relationships between spouses, common-law spouses, intimate partners, lovers, and casual sexual partners. Most couple intervention models allow the index participant to identify his or her partner. Several have more stringent criteria, such as length of the relationship, level of commitment, and sexual orientation.\textsuperscript{9,17} Thus, key questions remain unanswered: To what extent are the findings generalizable? For whom are the interventions particularly efficacious?

Most couple-based studies are limited by 1 or more methodological drawbacks, including relatively small sample sizes, lack of a randomized control design, and/or the lack of biologically confirmed STIs as an outcome variable.\textsuperscript{7} None of the couple-based studies to date have been sufficiently powered to examine new STI and HIV infections as outcomes.

To date, few studies have examined whether couple-level interventions are effective in reducing extradyadic sexual relationships among partners. This is an important outcome to consider, as partner concurrency has been found to increase HIV risk within a partner’s sexual network and within the dyad.\textsuperscript{23} It is unclear whether existing couple-based HIV prevention approaches reduce HIV risk with extradyadic partners.

Couple-based HIV prevention approaches have used different modalities to deliver their intervention. The science of couple-based HIV prevention has yet to tell us which modality works better. Are interventions more effective when sessions are delivered to each couple individually, when the sessions bring a group of couples together, or when some sessions are delivered in small, single-gender groups? Future research should address the question of which is the most efficacious and/or cost-effective modality.

The particular mechanisms that lead to behavior change remain unspecified. To advance the science of HIV prevention intervention with couples, there is a need to identify mediators responsible for behavioral change. Moreover, greater attention
must be given to the use of relationship-based theories that move beyond social cognitive theory, which has guided most couple-based studies. Statistical techniques using data collected from couples also need to be developed more thoroughly. Examples of areas to be targeted for development include the following: Is the unit of analysis the individual or the couple? What is a conservative way to handle discrepant reports from partners on conjoint behaviors?

A number of challenges need to be highlighted in the couple-based interventions. Although some evidence suggests that couple-based HIV prevention interventions may not work as well for couples experiencing severe conflict or intimate partner violence, research has yet to identify whether the effects of couple-based interventions are moderated by certain relationship characteristics (eg, length and type of relationship, relationship satisfaction level, history of intimate partner violence). Another challenge is that couple-based interventions require more clinical training and skills than individual-based interventions. Agency clinical staffs also tend to be more comfortable conducting individual interventions and may take more time to feel comfortable delivering couple-based sessions.

Dissemination of Couple-Based Prevention Interventions

Despite their demonstrated value in reducing risk behaviors and improving adherence to HIV medication, couple-based approaches are rarely employed in HIV service settings. Even partners who present and want to be treated together will likely not find such services. Most DEBI approaches that have been disseminated are delivered using individual or group modalities. Reasons for the limited dissemination and scaling up of couple-based HIV interventions to date may include common ideological preferences of staff and administrators for individual or group services, lack of structure to provide couple services within agencies, lack of access to evidence-based HIV interventions for couples, and lack of funding and staff training in couple-based modalities. Expanding the scope of dissemination and scaling up couple-based HIV interventions will require commitment on the part of government and donors to fund research on dissemination and implementation as well as training for providers in couple-based approaches.

CONCLUSIONS

Couple-based HIV interventions are in the early stages of development in the United States, compared with individual and group-level HIV interventions. Yet the advantages of couple-based approaches are evident. They can reduce drug and sexual behaviors that drive transmission of HIV and improve adherence to antiretroviral therapy and can, in turn, decrease risk of transmission. However, there remains a need for more research on couple-based approaches, especially for drug users and MSM and for seroconcordant couples.

The science of couple-based research can be advanced by addressing the gaps and challenges discussed in this article, particular assessing the impact of couple-based interventions on concurrent sexual relationships and biological outcomes of STIs and HIV. More attention and resources must be given to the dissemination of evidence-based, couple-based prevention and treatment research into real-world settings. Advancing the science of couple-based research (eg, efficacy, effectiveness, and dissemination) has the potential to reduce HIV acquisition and transmission among vulnerable populations.

REFERENCES


The Future of HIV Testing

Bernard M. Branson, MD

Abstract: HIV testing is the essential entry point for both treatment and prevention. The need to identify acute HIV infection (the period immediately after HIV acquisition, when persons are most infectious) and HIV-2 infection, which does not respond to many first-line antiretroviral agents, poses challenges for the traditional algorithm of Western blot confirmation after a repeatedly reactive antibody screening test. Immunoassays that detect antibodies earlier, tests for HIV RNA, and combination assays that screen simultaneously for both p24 antigen and HIV antibody are now approved for HIV diagnosis by the Food and Drug Administration. A revised testing algorithm can address the challenges posed by acute infection, HIV-2 infection, and the shortcomings of the Western blot. These new diagnostic strategies will allow earlier more accurate identification of infected persons so that they can benefit from effective treatment and also enhance abilities to focus prevention efforts where HIV transmission is most active.

Key Words: HIV antibody tests, acute HIV Infection, HIV diagnosis, HIV confirmatory tests

EVOLUTION IN HIV TEST TECHNOLOGY

Figure 1 depicts the appearance of laboratory markers at different stages of HIV infection. As recently as 2006, nearly 70% of public health laboratories employed first-generation or second-generation assays that detect only immunoglobulin G antibodies to HIV-1, and only on average 45–60 days after infection.4,5 Thus, infection went undetected in many persons who were tested during the infectious seroconversion “window period.” During the 1990s, third-generation assays were developed that also detected immunoglobulin M (the first antibodies generated in the immune response) and did so an average 20–25 days after infection (Fig. 2).6 These tests also incorporated specific antigens to detect both HIV-1 and HIV-2. Because they were more expensive, third-generation assays were not widely adopted until the remaining first-generation HIV-1 assay was withdrawn from the market in 2007.7 The third-generation assays also complicate confirmatory testing because they become reactive before any bands appear on the Western blot.8 Although some clinicians order RNA viral load assays to diagnose early HIV infection, the first qualitative RNA assay was not approved by the Food and Drug Administration (FDA) for HIV diagnosis until 2006.9

EIAs are best suited for batch processing of large volumes of specimens in centralized laboratories. Because typical turnaround times for results range from a few days to more than a week, many infected persons failed to receive conventional test results.10 Since 2002, the FDA approved 6 rapid HIV antibody tests with sensitivities and specificities similar to those of first or second generation conventional EIAs.11 Because these rapid assays can be performed in 30 minutes or less, their use allows many more patients to receive their test results.12 Several factors, however, have begun to temper the initial enthusiasm for rapid tests. First, many persons who receive preliminary positive rapid test results do not return for their confirmatory test results and thus might not access necessary medical care.13 Second, reduced sensitivity during the early stages of infection contributes to false-negative results in some high-risk frequently tested populations in which rapid tests are often used. In one clinic, rapid tests detected infection in only 91% of antibody-positive men who have sex with men and in only 80% of those whose infection was documented by a combination of conventional antibody and RNA assays.14 Finally, rapid tests are impractical for large-scale screening programs in health care settings. Single-use rapid tests are time consuming to perform, and their cost remains persistently higher than that of conventional tests or the $1–$3 charged for identical tests outside the United States.

Since 2006, 2 random-access third-generation chemiluminescent immunoassays have received FDA approval.15,16 These run on automated platforms for a variety of tests in
addition to HIV, can test specimens individually or in batches, and generate test results in 1 hour or less. Random-access platforms are already widely available in many hospital and clinical laboratories and are well suited for screening programs that include HIV as one of the battery of tests ordered routinely for patients being seen in the emergency department or admitted to the hospital. Combination p24 antigen-HIV antibody (Ag/Ab) fourth-generation assays that identify ≥80% of HIV infections otherwise detectable only by RNA have been used extensively worldwide for several years. The first fourth-generation Ag/Ab combination assay recently received FDA approval, and others are expected soon to become commercially available.\(^\text{17}\)

CHALLENGES FOR HIV TESTING

Acute HIV infection (AHI) is defined as the interval between the appearance of HIV RNA and that of detectable antibodies (Fig. 1).\(^\text{18}\) Beginning with AHI, extremely high levels of infectious virus are detectable in serum and genital secretions and persist for 10–12 weeks.\(^\text{19}\) Cohort studies suggest that the rate of transmission during AHI is 26 times as high as that during established HIV infection.\(^\text{20}\) Mathematical models indicate that AHI, despite its short duration, can account for 10%–50% of all new HIV infections, especially in the context of high sexual partner concurrency or high rates of partner change.\(^\text{21–23}\) AHI screening programs that applied RNA assays to pooled antibody-negative specimens (to reduce per-patient costs) found that AHI generally represents only a small proportion (0.02% to 0.3%) of persons with negative HIV antibody tests but constitutes a substantial proportion (10%–25%) of new HIV diagnoses, especially among men who have sex with men.\(^\text{14,24–26}\) Until now, the high cost of RNA assays made routine screening for AHI impractical. Once they are commercially available, Ag/Ab assays that detect AHI 4–5 days later than RNA assays (Fig. 2) will allow widespread screening for AHI with an initial screening test.\(^\text{27}\) Because most do not distinguish antigen from antibody reactivity, new testing algorithms will be required to distinguish AHI from established HIV infection.

Differentiating HIV-1 from HIV-2 poses another challenge. The number of HIV-2 diagnoses in the United States is believed to be low, but definitive diagnosis is difficult and surveillance is incomplete. Persons and partners of persons who acquired HIV-2 in West Africa have been diagnosed in Western Europe and the United States.\(^\text{28}\) Because of cross-reactivity between HIV-1 and HIV-2 antigens, the HIV-1 Western blot may be interpreted as positive in patients with HIV-2.\(^\text{29}\) “Cryptic” HIV-2 infection is thus often identified only after patients with an HIV-1 diagnosis manifest clinical deterioration despite a repeatedly undetectable HIV-1 viral load. HIV-2 has important implications for prognosis and treatment because HIV-2 does not respond to nonnucleoside reverse transcriptase inhibitors or to several protease inhibitors.\(^\text{30}\)
NEW STRATEGIES FOR HIV TESTING

Contemporary HIV testing strategies need to emphasize sensitivity, especially for the highly contagious phase immediately after infection. Despite longstanding concerns about false-positive test results, false-positive tests will be discovered and resolved promptly as part of subsequent testing for clinical evaluation. False-negative results, however, might not be detected for years, until HIV disease has advanced, after early effective treatment has been delayed, and after partners might have been unknowingly infected.

A revised testing algorithm has been proposed to address not only the challenges posed by AHI and HIV-2 but also the shortcomings of the Western blot.1 Testing begins with the most sensitive test possible, optimally a fourth-generation combination Ag/Ab test (Fig. 3). Repeatedly reactive specimens are then tested with an assay that differentiates HIV-1 from HIV-2 antibodies. Specimens that are repeatedly reactive on the Ag/Ab screening test but negative for antibodies are then tested for HIV-1 RNA. Detectable RNA establishes the diagnosis of AHI, which requires, in addition to linkage to medical care, urgent intervention to prevent further transmission and elicitation and evaluation of recent sex partners. In one study, persons with AHI named 2.5 times as many partners and nearly twice as many partners with undiagnosed HIV infection as did persons with longstanding HIV infection.25 However, the majority of HIV-infected persons will be antibody positive and can be immediately linked to medical care, where the recommended baseline clinical evaluation includes plasma HIV RNA (viral load).23 If RNA is undetectable, further antibody testing (eg, Western blot) is indicated to determine whether HIV infection is present.

The frequency of AHI should be monitored to guide retesting recommendations. Both RNA and Ag/Ab tests reduce the window period after infection—they don’t eliminate it. The 10-day duration of the eclipse period during which infection is undetectable (Fig. 1) is approximately the same as the interval during which AHI can be identified in antibody-negative persons. Therefore, the number of AHI cases might roughly approximate the number of infected persons whose infection is undetectable. This suggests that persons seeking an HIV test after 1 or more recent risky exposures, especially in populations with an increased frequency of AHI, should be encouraged to retest in 3–4 weeks, even if their Ag/Ab test was negative. Evaluating factors associated with AHI can also be used to develop prediction models for persons at higher risk for HIV acquisition who need more frequent retesting and more intensive prevention interventions. If it is not possible to screen with Ag/Ab tests (for example, in outreach settings when rapid HIV tests are used), retesting recommendations deserve particular attention. Individuals whose activities put them at higher risk of HIV acquisition and those from high-prevalence populations should be asked about recent potential exposures, multiple or concurrent sex partners, and other behaviors associated with increased HIV incidence (eg, methamphetamine use), and those with a higher likelihood of recent exposure should be encouraged to retest in 4–6 weeks.

HIV testing is the entry point for both care and prevention, and progress continues at a rapid pace. Rapid Ag/Ab combination tests and point-of-care tests for HIV RNA are in clinical trials. Promising techniques to determine whether antibody-positive persons were infected recently will soon help guide case finding and prevention and inform efforts to measure incidence. Because effective HIV treatment is available, doing everything possible to find infected persons and link them to care is more important than ever.

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Secondary Prevention of HIV in the United States: Past, Current, and Future Perspectives

Jeffrey D. Fisher, PhD, Laramie R. Smith, BA, and Erin M. Lenz, BA

Abstract: To provide a synopsis of past, current, and potential next-generation approaches to prevention for positives (PnP) interventions in the United States. For a variety of reasons, PnP interventions, with the goals of limiting HIV transmission from people living with HIV/AIDS (PLWHA) to others and protecting the health of PLWHA, did not appear with any frequency in the United States until about 2000. Even today, the number and breadth of evidence-based PnP interventions is very limited. Nevertheless, meta-analytic evidence demonstrates that such interventions can be effective, perhaps even more so than interventions targeting HIV-uninfected individuals. We review early and more recent PnP interventions and suggest that next-generation PnP interventions must involve behavioral and biologic components and target any element that affects HIV risk behavior and/or infectivity. Next-generation PnP interventions should include increased HIV testing to identify additional PLWHA, components to initiate and maintain HIV care, to initiate antiretroviral therapy and promote adherence, and to reduce sexual and injection drug use risk behavior, as well as ancillary treatments and referrals to services. Comprehensive next-generation PnP interventions, including all of these elements and effective linkages among them, are discussed.

Key Words: positive prevention, secondary prevention of HIV, prevention for positives interventions, HIV prevention, people living with HIV, behavioral-biologic interventions

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INTRODUCTION

Prevention for positive (PnP) interventions are supportive prevention efforts administered to people living with HIV/AIDS (PLWHA) and tailored to their needs. They involve behavioral and biologic strategies (Fig. 1., components B-G) that can benefit the public health by limiting HIV transmission to others and, at the same time, can protect the health of PLWHA by lowering their likelihood of acquiring other pathogens.1–4 The rationale for PnP interventions as a critical element of HIV prevention involves the fact that all “new” HIV infections must begin with an HIV-positive individual, and the finding that some PLWHA who are aware of their antibody status continue to practice risky behavior.5–9 For these reasons, from an HIV prevention perspective, it can be highly efficient to intervene with PLWHA3,10 and highly effective.1,11,12 Strengthening this argument is that because large numbers of PLWHA are on antiretroviral therapy (ART), HIV prevalence in the United States will continue to rise,3,13 along with the number of individuals capable of transmitting HIV, and even drug resistant HIV, through risky behavior.1,3

About 1.1 million Americans are living with HIV,13,14 75% to 80% of whom are aware of their antibody status.13,15,16 About one third of these PLWHA continue to practice risky behavior.6–9 Reasons vary widely and include dynamics such as lack of critical information, motivation, and behavioral skills needed to practice safer behaviors, alcohol and drug use, mental health issues, extreme poverty, and intimate partner violence, among others. These have been reviewed elsewhere.1,17–20

Despite a critical need, PnP interventions were rare until 2 decades into the US epidemic.21 The delay in funding and addressing the prevention needs of PLWHA likely occurred because US policy was late in prioritizing this issue. For reasons synthesized in a recent article,21 policies and programmatic approaches highlighting the importance of PnP emerged only circa 2000.22–24

A review article in 2000 described PnP as a “new issue.”25,26 In fact, to date, the vast majority of HIV prevention interventions in the United States have not focused on the HIV prevention needs of PLWHA. Literally, hundreds of HIV prevention intervention studies and many meta-analytic reviews of this work have been published, and almost all the populations targeted in this work were selected for characteristics other than serostatus.11,21,27 As reported in study by W. Fisher et al,21 of 898 HIV prevention interventions between 1988 and 2006 identified in a research synthesis project database of the US Centers for Disease Control, only 6.6% were directed at PLWHA, most occurring after 2000. The overall dearth of evidence-based PnP interventions is also manifest in the very small number of such interventions identified by the US Centers for Disease Control as “best” or “promising evidence” and targeted for widespread dissemination.21 This is the case despite strong arguments that PnP
Our own program of PfP research, the Options Project, was funded by the National Institute of Mental Health in 1999 to develop, implement, and rigorously evaluate a PfP intervention delivered by HIV-care providers with PLWHA in a clinical care setting. It was based on the information–motivation–behavioral (IMB) skills model of HIV risk and prevention. In terms of the model, HIV risk behavior in PLWHA, and others, is often associated with weaknesses in individuals’ levels of HIV prevention IMB. Individual-level PfP interventions, which address these elements, should lead to sustained increases in HIV prevention. Options involved having providers assess the IMB dynamics of patients’ HIV risk behavior and intervene to remediate any weaknesses. Some US studies revealed that these brief interventions, embedded in regular patient care, led to significant and sustained changes in patient risk behavior.

MORE RECENT PfP INTERVENTIONS

Since the two 2006 meta-analyses, additional PfP intervention trials have been published. Two descriptive reviews published in 2009 identified 7 new intervention outcome studies and 14 characterizations of interventions under development or investigation. Across both reviews, PfP interventions continued to be effective across a variety of intervention design and delivery processes.

Table 1 summarizes all US PfP interventions with behavioral or biologic outcomes conducted, evaluated, and published between January 1, 2005 (the approximate cutoff for the two 2006 meta-analyses), and July 13, 2010. We utilized all search terms [Search terms were combined as follows, Group 1 (OR between each term): HIV positive, prevention with positives, prevention for positives, positive prevention, behavioral, biologic].

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<tr>
<th>Study: Setting(s); Target Population; Project Name (Date)</th>
<th>Intervention Design: Level of Intervention; Intervention Delivery: Intensity–Duration</th>
<th>Intervention Description: Intervention Goal; Theory; IG and CG Brief Descriptions</th>
<th>Outcomes: Direction and Significance of outcomes in IG vs CG; (Behavioral, Biomedical), and Psychosocial Variables</th>
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<td>Coleman et al\textsuperscript{14}\textsuperscript{†}, Setting: classroom-like setting; Population*: African American MSM; CLN, COMM; Project: no name (2006–2007)</td>
<td>RCT (2 arm), feasibility pilot test; Level: group; Delivery: by group facilitators, Cog–Behavioral techniques; Intensity–Duration: 4 sessions (120 min ea); 1-mo duration; last FU 3 mo</td>
<td>Goal: increase proportion of consistent condom use for each anal sex act; Theory: SCT, TRA, TPB; IG (n = 30): taught condom negotiation skills with role-play and contextual risk negotiation, provided health-focused information; CG (n = 30): time-and attention-matched health-focused control arm</td>
<td>Sex outcomes:</td>
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<td>Fisher et al\textsuperscript{10}, Setting: 2 HIV clinics; Population*: PLWHA, CLN; Project: Options/Opciones (2000–2003)</td>
<td>Quasi-experimental (2 arms): Level: individual; Delivery: by HIV providers during routine care visits; MI approach; Intensity–Duration: 6 sessions (5–10 min ea); 18 mo duration; last FU 18 mo</td>
<td>Goal: reduce UVA/O through brief, ongoing risk reduction counseling; Theory: IMB; IG (n = 232): patient-centered conversations around sex or drug use behaviors; assess readiness to address risk behaviors, provide risk reduction strategy options, develop tailored risk reduction goal; CG (n = 245): standard of care, risk counseling at providers’ discretion</td>
<td>Sex outcomes:</td>
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<td>Gardner et al\textsuperscript{15}, Setting: 7 HIV clinics; Population*: PLWHA, CLN; Project: Positive Steps (2005–2006)</td>
<td>Prepost (1 arm); demonstration project; Level: individual; Delivery: by HIV providers during routine care visits; Intensity–Duration: 3 sessions (~ 3 min ea); 12-mo duration; last FU 12 mo</td>
<td>Goal: evaluate reduced risk of transmission in multiclinic study; Theory: N/A; IG (n = 767): screen for risk, deliver risk reduction messages, and create risk reduction plan with providers; provide supplemental brochures and posters; CG: N/A; longitudinal cohort, with only participants who had data at all time points included in analysis</td>
<td>Sex outcomes:</td>
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<td>Gilbert et al\textsuperscript{16}, Setting: 5 HIV clinics; Population*: PLWHA, CLN; Project: Positive Choice (2003–2006)</td>
<td>RCT (2 arms): Level: individual; Delivery: by computers during routine care visits; MI approach; Intensity–Duration: 2 sessions (~ 24 min ea); 3-mo duration; last FU 6 mo</td>
<td>Goal: reduce illicit drug use, risky alcohol consumption, and UVA; Theory: N/A; IG (n = 243): computer-based risk assessment preceding a tailored “Video Doctor” risk reduction counseling session; printout of behavioral assignment and referrals for substance use and harm-reduction services; CG (n = 233): computer-based risk assessment, followed by standard of care, risk counseling at providers’ discretion</td>
<td>Sex outcomes:</td>
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<td>The Healthy Living Project\textsuperscript{17}, Setting: 4 sites (HIV clinic, research, and community service sites); Population*: PLWHA, CLN, COMM; Project: the Healthy Living Project (2000–2004)</td>
<td>RCT (2 arms): Level: individual; Delivery: by facilitators; Cog–Behavioral techniques; Intensity–Duration: 15 sessions (90 min ea); 5-mo duration; last FU 25 mo</td>
<td>Goal: reduce number of sex-related risk acts with HIV-? partners, execute effective coping responses, enhance adherence with PLWHA ≥ 85% adherent at BL; Theory: social action theory; IG (n = 467): 3 modules focused on stress, coping, and adjustment; reducing transmission risk behaviors; enhancing health promotion via adherence to medical care and ART; CG (n = 469): wait-list control comparison group</td>
<td>Sex outcomes:</td>
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</table>
### Table 1. (continued) US PIP Interventions Published in English, Reporting Behavioral or Biologic Transmission Risk Outcomes Between January 1, 2005, and June 13, 2010

<table>
<thead>
<tr>
<th>Study: Setting(s); Target Population; Project Name (Date)</th>
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<tr>
<td>Illa et al(^{39}); Setting: 1 HIV clinic; Population*: PLWHA (age ≥ 45); CLN; Project: Project ROADMAP (2004–2006)</td>
<td>RCT: (2 arms); Level: group; Delivery: based on project INSPIRE(^{45}); Intensity–Duration: 4 sessions (1–2.5 hr ea); intervention duration NR; last FU 6 mo</td>
<td>Goal: target sexual risk reduction in older PLWHA; Theory: IMB, self-efficacy theory; IG (n = 149): tailored psychoeducational group sessions to address HIV, its effects on sexual behaviors, and harm reduction approaches; safer-sex negotiation skills and strategies for older PLWHA; CG (n = 92): received educational brochure, followed by standard of care</td>
<td>Sex outcomes: ↓ UVA all partners: SIG; ↓ UVA HIV-* partners: SIG; ↓ UVA HIV+ partners: NS; Psychosocial outcomes: ↑ HIV knowledge: observed in both arms, no difference between arms; ↑ sexual self-efficacy: NS</td>
</tr>
<tr>
<td>Lightfoot et al(^{39}); Setting: 6 HIV clinics; Population: PLWHA, CLN; Project: no name (2001–2004)</td>
<td>Quasi-experimental (3 arms): Level: Individual; Delivery: By computer or HIV provider/staff during routine care visits; FRAMES; Intensity–Duration: ≤ 11 sessions (10 min ea computer, 5–15 min ea providers); 30-mo duration; last FU 30 mo</td>
<td>Goal: provide brief risk reduction intervention to enhance motivation and encourage PLWHA to act in accordance with their values; Theory: N/A; IGs 2 intervention conditions: computer-delivered arm (IG-1, n = 325); provider-delivered arm (IG-2, n = 209); assess/provide feedback on behavior and personal values; enhance self-efficacy and behavior change; CG (n = 229): standard of care provided in control comparison clinics</td>
<td>Sex outcomes: ↓ no. HIV-* partners: SIG (IG-1 compared with IG-2 and CG arms); ↓ UVA HIV-* partners: SIG (IG-1 compared with CG arm)</td>
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<tr>
<td>Margolin et al(^{40}); Setting: 1 methadone clinic; Population: PLWHA, methadone-maintained drug users, COMM; Project: 3-S(^{+}) therapy (dates NR)</td>
<td>Quasi-experimental, prepost (2 arm): Level: individual; Delivery: therapist-led; Cog–Behavioral and Buddhist psychologies; Intensity–Duration: 12 sessions (session time NR); 3-mo duration; last FU 3 mo</td>
<td>Goal: increase motivation for abstinence, HIV prevention, and medication adherence; decrease impulsivity in HIV-positive drug-using population; Theory: cognitive self-schema theory, Buddhist principles; IG (n = 21): weekly therapy focused on replacing addict self-schema with a spiritual self-schema; and on increasing awareness of addiction and its impact on adherence, risk, and HIV care behaviors; CG (n = 17): standard-of-care methadone-maintenance therapy; nonrandomized; participants elected to complete preassessments and postassessments only</td>
<td>HIV risk outcomes (low response rate): ↓ HIV transmission risk behaviors: NS; Drug outcomes: ↓ intoxicant use: trend; ↑ motivation for drug abstinence: SIG; Psychosocial outcomes: ↑ impulsivity: SIG; ↑ mean influence of spirituality on motivation for health-promoting behaviors: SIG</td>
</tr>
<tr>
<td>Mausbach et al(^{41}); Setting: NR; Population*: PLWHA, MSM who use methamphetamines, CLN, COMM; Project: EDGE (1999–2004)</td>
<td>RCT (2 arms); Level: individual; Delivery: therapist-led; MI approach; Intensity–Duration: 8 sessions (90 min ea); 3-mo duration; last FU 12 mo</td>
<td>Goal: increase safer sexual behaviors in presence of methamphetamine use; Theory: SCT, TRA; IG (n = 170): targeted skills training and problem solving to enhance knowledge and self-efficacy with condom use/negotiation; serostatus disclosure to partners in context of ongoing substance use; CG (n = 171): time–attention control diet and exercise sessions</td>
<td>Sex outcomes: ↓ total UVA over time: NS; ↑ proportion protected sex acts: SIG; ↑ no. protected sex acts over time: SIG; Psychosocial outcomes: ↑ self-efficacy condom use: SIG; ↑ self-efficacy condom negotiation: observed in both arms, no difference between arms</td>
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<tr>
<td>Mitchell et al(^4); Setting: 1 HIV clinic; Population(^\ast): PLWHA, marginally housed, substance-using, CLN; Project: DAART+ (2003–2006)</td>
<td>Prepost (1 arm), feasibility pilot: Level: individual; Delivery: by case managers; strengths-based approach; Intensity–Duration: daily mDOT sessions tapered to biweekly, then monthly; 12-mo duration; last FU 3–6 mo</td>
<td>Goal: support adoption and maintenance of medication adherence and HIV risk reduction behaviors; Theory: TTM stages of change, IMB; IG (n = 30): integrated discussions on adherence barriers and current drug and substance-use behaviors in the context of mDOT; CG: N/A; longitudinal cohort, with no comparison group available</td>
<td>Sex and drug outcomes (low response rate): sexual and substance-using-risk behaviors: NS; Viral load outcomes: viral load data for participants with final assessment (n = 18), 83% achieved viral suppression</td>
</tr>
<tr>
<td>Naar-King et al(^4); Setting: 5 HIV clinics; Population(^\ast): PLWHA (aged 16–24 years), multiple risk factors, CLN; Project: Healthy Choices (2005–2007)</td>
<td>RCT (2 arm): Level: Individual; Delivery: therapist-led; MI approach; Intensity–Duration: 4 sessions (60 min ea); 2.5-mo duration; last FU 9 mo</td>
<td>Goal: enhance viral response in young PLWHA with multiple transmission-related risk behaviors; Theory: N/A; IG (n = 94): MI sessions to address 2 risk factors (eg, nonadherence; sex or drug risk) and access to enhanced support services for sexual risk, drug use, mental health, and medication adherence; CG (n = 92): standard of care, access to enhanced support services</td>
<td>Viral load outcomes: viral load: SIG(^\ast)</td>
</tr>
<tr>
<td>Petry et al(^4); Setting: HIV drop-in center; Population(^\ast): PLWHA, cocaine- or opioid-dependent diagnosis, COMM; Project: no name (2003–2007)</td>
<td>RCT (2 arm): Level: Group; Delivery: therapist delivered; Intensity–Duration: 24 sessions (60 min ea); 6-mo duration; last FU 12 mo</td>
<td>Goal: assess efficacy of contingency-based rewards on supporting and sustaining both health and substance use reduction behaviors: Theory: N/A; IG (n = 89): support group with contingency-based rewards provided for substance use abstinence and completion of health enhancement components; integrated support and substance use reduction messages; CG (n = 81): 12 step-based group support, abstinence messages</td>
<td>Sex outcomes: Sexual risk scores: SIG; Drug outcomes: drug risk scores: NS; no. consecutive drug-free urine tests: SIG; proportion drug-free urine tests: NS; Viral load outcomes: viral load: SIG(^\ast)</td>
</tr>
<tr>
<td>Purcell et al(^4); Setting: 4 community health centers; Population(^\ast): PLWHA, IDU, COMM; Project: INSPIRE (2001–2005)</td>
<td>RCT (2 arm): Level: Individual, group; Delivery: by paraprofessionals; Intensity–Duration: 10 sessions (session time NR); 1.25-mo duration; last FU 12 mo</td>
<td>Goal: reduce sexual and injection risk behaviors, increase utilization of HIV care and adherence to ART; Theory: SLT, social identity theory, IMB; IG (n = 486): focus on motivation/skills for increasing use of HIV care, for adherence, and for reducing sex and drug risk behaviors through developing new social role as a peer-mentor; CG (n = 480): discuss videos focusing on information for HIV-infected IDU</td>
<td>Sex and injection-drug outcomes: sexual and injection risk observed in both arms, no difference between arms; Health care utilization outcomes: care utilization: NS; Adherence outcomes: adherence: NS</td>
</tr>
<tr>
<td>Rosser et al(^4); Setting: 6 community sites; Population(^\ast): PLWHA, MSM, CLN, COMM; Project: Positive Connections (2005–2008)</td>
<td>RCT (3 arms): Level: Group; Delivery: by HIV+ MSM-identified or MSM-identified health professional facilitators (matched to intervention arm); Intensity–Duration: 1 session (14–16 hr); 1 weekend long; last FU 18 mo</td>
<td>Goal: reduce frequency of serodiscordant UAI; Theory: sexual health model; IGs across 2 arms: health seminars identified and address sexual health and HIV risk concerns from an HIV+ MSM (IG-1, n = 248): or general, serostatus-neutral, MSM (IG-2, n = 237): perspective; CG (n = 190): viewed and evaluated MSM HIV prevention–focused DVDs</td>
<td>Sex outcomes: frequency of serodiscordant UAI: observed in all 3 arms, no difference between arms; Psychosocial outcomes: intentions to avoid high-risk behaviors: SIG; (IG-1 and IG-2 arms)</td>
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**TABLE 1. (continued) US PfP Interventions Published in English, Reporting Behavioral or Biologic Transmission Risk Outcomes Between January 1, 2005, and June 13, 2010**

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<tr>
<td>Serovich et al47; Setting: NR; Population: PLWHA, MSM, COMM; Project: no name (dates NR)</td>
<td>Randomized controlled, crossover design (3 arms); pilot study; Level: individual; Delivery: by facilitator, or computer and facilitator; Intensity–Duration: 4 sessions (session time NR); 1-mo duration; last FU 3 mo</td>
<td>Goal: reduce UAI and enhance disclosure to casual partners in MSM: Theory: consequences theory of disclosure; IGs 2 intervention conditions: one with facilitator risk assessment and facilitator delivery (IG-1, n = 40); the other with computer risk assessment and facilitator delivery (IG-2, n = 37); both assessed cost and benefits of disclosure and disclosure triggers and strategies; CG (n = 21); wait-list control condition</td>
<td>Sex outcomes (small sample size, low response rate CG): ↓ mean frequency of UAI all partners: NS; increased odds of UAI observed in both IG-1 and IG-2 compared with CG arm, despite a reduction in UAI over time in IG-1 arm; Disclosure outcomes: ↑ favorable disclosure attitudes: SIG (IG-1 arm); ↑ favorable disclosure behaviors: trend (IG-1 arm); ↑ favorable intentions to disclose: NS</td>
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<tr>
<td>Sikkema et al48; Setting: 1 community health center; Population: PLWHA, childhood sexual abuse–related trauma, CLN, COMM; Project: LIFT (2002–2004)</td>
<td>RCT (2 arms); Level: Group; Delivery: By cotherapists; Cog–Behavioral and coping strategies; Intensity–Duration: 15 sessions (90 min ea); 3.75-mo duration; last FU 12 mo</td>
<td>Goal: improve coping and reduce sexual risk behavior in PLWHA with childhood sexual abuse history; Theory: cognitive theory of stress and coping; IG (n = 124);↑ taught adaptive coping and problem-solving strategies to identify individual triggers and select goals; skills building for dealing with sexual abuse–related trauma and risk reduction; CG (n = 123);↑ time-matched HIV support group comparison condition</td>
<td>Sex outcomes: ↓ condom use during vaginal/anal intercourse: trend; Disclosure outcomes: ↑ proportion of partners disclosed serostatus to: SIG‡, total no. partners disclosed serostatus to: NS</td>
</tr>
<tr>
<td>Teti et al49; Setting: 1 HIV clinic; Population: PLWHA, women, CLN; Project: Protect and Respect (2004–NR)</td>
<td>RCT (2 arms); Level: individual, group; Delivery: 3 components (by HIV providers during routine care visits, health educators, HIV+ peers); Intensity–Duration: provider sessions (3–5 min ea), health education group 5 sessions (1.5 hr/wk), optional peer support group (1 hr/wk); 1.25-mo duration; last FU 18 mo</td>
<td>Goal: support HIV+ women in decreasing UVA and other sexual risks; increase serostatus disclosure to partners; Theory: TTM stages of change, modified AIDS risk reduction model, theory of gender and power; IG (n = 92);↑ brief risk reduction conversation with HIV providers; health educator–led group sessions for sexual risk reduction education and skills building; weekly HIV+ peer-led support group to discuss skills; CG (n = 92);↑ standard of care; brief provider risk-reduction messages</td>
<td>Sex and drinking outcomes: ↓ no. days with both UAI and heavy drinking: SIG‡; Drinking outcomes: ↓ no. drinks in past 30 days: SIG‡; ↓ no. heavy drinking days in past 30 days: SIG‡</td>
</tr>
<tr>
<td>Velasquez et al50; Setting: NR; Population*: PLWHA, MSM with diagnosed alcohol use disorder, COMM; Project: Positive Choices (1999–2003)</td>
<td>RCT (2 arms); Level: individual, group; Delivery: by therapist and HIV+ MSM group facilitators; MI approach; Intensity–Duration: 8 sessions (session time NR); 2-mo duration; last FU 12 mo</td>
<td>Goal: reduce both alcohol use and unprotected sexual behaviors: Theory: TTM stages of change and processes of change; IG (n = 118);↑ individual therapy sessions enhanced motivation and skills to change alcohol, sexual behavior; peer support group–sessions focused on HIV risk reduction and safer sexual behaviors; CG (n = 135);↑ resource referral control condition</td>
<td>Sex outcomes: ↓ condom use during vaginal sexual intercourse: trend; Disclosure outcomes: ↑ proportion of partners disclosed serostatus to: SIG‡, total no. partners disclosed serostatus to: NS</td>
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* Participants were screened for recent history of risk behaviors and/or sexual activity.
† Attrition rates >20% as reported or calculated based on sample size reported at BL and last FU.
‡ Significant difference between IG and CG shows some decay over time.
§ Sufficient information to calculate attrition was not provided.
BL, baseline assessment; CG, comparison group; CLN, HIV medical clinic–based sample; Cog–Behavioral, cognitive–behavioral intervention delivery techniques; COMM, community-based sample; ea, each; FRAMES, Feedback–Responsibility–Advise–Menu of Options–Empathy–Self-Efficacy; FU, follow-up; IDU, injection drug users; IG, intervention group; IMB, information–motivation–behavioral skills model; mDOT, modified directly observed therapy; MI, motivational interviewing intervention delivery techniques; NR, information not reported in manuscript; NS, nonsignificant; P, proportion; RCT, randomized controlled trial; DVD, digital video disc; INSPIRE, Investigating New Standards for Prophylaxis in Reduction of Exacerbation; LIFT, Living In the Face of Trauma.

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HIV prevention with positives, HIV/AIDS prevention with positives, secondary HIV prevention. Group 2 (OR between each term): prevention, HIV prevention, HIV counseling, transmission, risk behavior, risk reduction, harm reduction. Combine Group 1 AND Group 2 AND intervention.] provided in all previous reviews.1,11,12,33 Eighteen PIP interventions reporting behavioral or biologic outcomes10,34–50 are depicted in Table 1. Twenty-seven additional studies were identified reporting intermediate prebehavioral outcomes (eg, information, self-efficacy51–53 or characterizing intervention development and implementation processes.29,54–76 All were identified through searches in PubMed, PsyInfo, Cumulative Index to Nursing and Allied Health (CINAHL), and the previous reviews.

Across the 18 studies with behavioral or biologic outcomes, PIP interventions continue to be effective, with all but 3 reducing targeted sexual and/or drug-related risk behaviors; Table 1 provides specifics of relevant studies. Most of the interventions contained elements consistent with those identified earlier as contributing to effective outcomes.11,12 For example, most were developed using1 one1 0.05, 37, 38, 40, 42, 45, 49 or more1 0.03, 37, 46, 48, 50 health-behavior theories and were delivered in either an HIV clinic30,55, 36, 38, 39, 42, 43, 45, 48, 49 or another HIV service venue60,44 and by professional counselors/therapists30,41, 43, 44, 48, 50 or HIV care providers/other medical staff.30,15, 39, 49 A relatively small number of interventions targeted multiple HIV risk–related behaviors (eg, increasing disclosure, reducing heavy drinking or drug use, or enhancing coping skills36, 37, 40, 43, 48, 50) and targeted biologic transmission risk factors (eg, increased adherence to ART, reduced viral load87, 40, 42, 45). Compared with previous reviews,1,11,33 we note an increase in the number of PIP interventions tailored to risk dynamics unique to specific subpopulations of PLWHA (eg, decreasing sexual risk in substance-using seropositive MSM).34, 40, 41, 45, 47, 50, 76 Future meta-analysis should evaluate the effectiveness of emerging efforts to use multicomponent and more tailored intervention approaches to reduce overall transmission risk.

**NEXT-GENERATION PIPs**

We believe that a synergistic package of PIP interventions at the intersection of behavior and biology will have optimal impact on limiting HIV transmission and maintaining PLWHA health.1–4,77 In Figure 1, we identify vital components and linkages of a comprehensive behavioral–biomedical conceptualization of next-generation PIP interventions (with an alphanumeric system denoting the various components and paths as well as “movement” within the model, eg, to component C from component B via path i). All components and linkages need to be copresent and integrated in such an approach. To date, these elements remain separate unintegrated components of HIV prevention and of treatment science for PLWHA. Finally, we emphasize that the model must be evaluated and supported over the disease course of PLWHA (component A), understanding that what is needed to optimize the effect of each component and path may vary by disease stages72 and subpopulations (eg, PLWHA who are MSM vs injection drug user; young vs older PLWHA; incarcerated vs unincarcerated PLWHA; PLWHA with different comorbid conditions38, 39, 43, 48, 57, 77, 79–81).

**CRITICAL COMPONENTS OF NEXT-GENERATION PIPs**

Increased HIV testing (component B) is a critical element in next-generation PIP. This will identify PLWHA who were previously unaware of their serostatus. When individuals learn that they are HIV infected, substantial, self-initiated, postdiagnosis reductions in risk behavior often follow.82,83 Testing may also help reduce the number of PLWHA unaware of their status during periods of increased infectiousness (ie, acute, symptomatic, and late stages), which can affect transmission.4,75 Achieving postdiagnosis linkages to HIV care (component C, path i) to reduce biologic risk of transmission (eg, through identification and treatment of STIs and access to ART medications), as well as ensuring linkages to ancillary services (component G, path x) to address behavioral risk–related contextual factors, are essential.

**Initiating and maintaining HIV care (component C) aims** to facilitate routine primary care visits and continued monitoring of patients’ overall health.84 Routine appointments have been related to lower levels of behavioral79,85,86 and biologic risk (eg, treatment of existing STIs, increased viral suppression, decreased resistance).87–89 whereas prolonged absences from care relate to poorer health outcomes.80,91 Routine care provides ongoing opportunities to reduce biologic transmission through ART initiation (component D, path ii), sustained ART monitoring, and adherence support (component E, path iii). Behavioral risk reduction ideally integrates PIP support (component F, path iv) and referral to ancillary services (component G, path v), addressing contextual risk factors such as social isolation or depression4,86,92,93.

**Initiation of ART (component D) rapidly curbs viral replication and reduces** the number of viral load present in plasma or genital tracts, reducing biologic risk of transmission and facilitating overall health.94–97 The relationship between risk behaviors and being on ART or achieving viral suppression is complex. Any increases in risk behavior are likely a result of treatment-related beliefs98 and underlying contextual risk factors,2,87,96,97 not individuals’ receipt of ART or a suppressed viral load, per se.98 As biologic risk reduction requires sustaining health and high levels of adherence, support in both continuing routine HIV care (component C, path ii) and initial96 and ongoing access to ART adherence support (component E, path vi) are needed.96,100

**ART adherence behavioral interventions (component E)** sustain viral suppression through enhancing adherence behaviors. Optimal adherence decreases biologic risk by controlling both viral replication and the potential to develop treatment resistance.94,96,101 Meta-analyses report that adherence interventions significantly improve adherence behavior96,101 and support viral suppression.101 Co-occurrence of both nonadherence and HIV risk behaviors are often identified, likely resulting from common underlying barriers (eg, substance use, social isolation, psychological distress/depression).2,18,92 Integration with ongoing PIP behavioral support (component F, path vii) and referral to ancillary services (component G, path viii) to address root contextual risks4,18,92 can strengthen adherence.

**PIPs behavioral interventions (component F)** support safer sex and drug use behaviors, and overall health of
PLWHA. Meta-analyses of PfP interventions discussed earlier demonstrate their efficacy in reducing behavioral\textsuperscript{11,12} and potentially biologic risk (ie, STIs\textsuperscript{11}). In the context of existing ART, future PfP interventions need to address ART-related beliefs\textsuperscript{98} and integrate ART adherence support (component E, path vii). Referrals to or incorporation of ancillary services to address root contextual risks (component G, path ix) are also critical.\textsuperscript{1,3,48,80,102}

Ancillary treatments and referrals to services (component G) address contextual factors and vulnerabilities that may undermine necessary health behaviors (eg, ability to maintain care, medication adherence, or risk reduction) through referrals to treatment and support services (see a sample list of services in box for component G in Fig. 1). These referrals may emanate from HIV testing (component B, path x), HIV care (component C, path v), adherence interventions (component E, path viii), and PfP behavioral interventions (component F, path ix), among other sources. Simultaneously, PLWHA receiving ancillary treatments or services and who are in need of testing, medical care, and behavioral support for existing adherence and risk reduction issues should be identified and connected to other components, as appropriate. For example, HIV testing for high-risk individuals (component B, path x), reengaging PLWHA not in HIV care or who never initiated care postdiagnosis (component C, path v), and providing access to existing adherence (component E, path viii) and risk reduction (component F, path ix) behavioral interventions are critical.

Due to space limitations, our discussion of a comprehensive behavioral–biomedical approach to PfP addresses model components and their links in a somewhat arbitrary linear fashion. We recognize that the need for any component and relevant linkages could occur along paths not discussed. The next generation of PfP interventions must attend to reducing both behavioral and biologic risk factors across the components in Figure 1 and ensure the linkages among them. Fortunately, some emerging PfP interventions are beginning to incorporate elements of behavioral and biologic risk reduction, but they are not comprehensive and the links are not always fleshed out.\textsuperscript{37,43,45} Future PfP intervention development needs to ensure that the linkages among these components are maintained, enhanced, and evaluated.

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Antiretroviral Therapy: A Promising HIV Prevention Strategy?

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Abstract: The use of antiretroviral therapy (ART) has been associated with significant improvement in morbidity and survival of persons living with HIV. In addition, recently, there has been intense interest in the potential impact of ART on HIV transmission and consequently on the trajectory of the HIV epidemic globally. Evidence from mathematical modeling analyses and observational and ecological studies supports the potential for ART as prevention. However, definitive data from clinical trials are awaited. In the United States, the feasibility and potential of using ART as a prevention strategy presents particular challenges: the large number of individuals with undiagnosed HIV; the predominance of disenfranchised individuals affected by the epidemic; evidence of delay in engagement in HIV care after diagnosis with attendant late initiation of ART; and difficulties with consistent long-term adherence to ART and concerns regarding long-term risk-behavior change. Thus, for this novel effort to succeed, a multidimensional approach is necessary that must include policy changes, social mobilization, and improved access to clinical and supportive services for persons living with HIV, with a particular focus on the unique needs of at-risk populations, combined with engagement of all cadres of health care providers and community constituencies.

Key Words: antiretroviral therapy, HIV treatment, prevention, transmission

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Findings from a mathematical modeling study of the effect of antiretroviral therapy (ART) on HIV incidence and prevalence, reported by Granich et al in early 2009, were met with a mix of excitement and disbelief.1 Using data from the HIV epidemic in South Africa, this model suggested that with expanded HIV testing and prompt initiation of ART by all those found to be HIV infected, a substantial decrease in incidence of HIV could be achieved in that country.2 Skeptics derided the model’s optimistic assumptions, which included annual HIV testing for all adults older than 15 years, immediate ART initiation for the vast numbers of individuals found to be HIV infected, and achievement of high rates of adherence with treatment.3 Further, many questioned the feasibility of achieving such goals in low-income and middle-income countries, settings already struggling with efforts to expand HIV testing to their populations and to provide access to antiretroviral drugs for those with advanced HIV disease who are in urgent need of this life-saving treatment. Nevertheless, the findings from the model generated great interest in exploring the feasibility of this “test and treat” strategy, particularly in view of the limited effectiveness demonstrated by other prevention interventions to date and the lack of progress in controlling the global HIV epidemic.3–5 At the core of the rationale for use of ART for prevention are findings that demonstrate that antiretroviral drugs can lead to suppression of viral replication in the bloodstream and in genital tract secretions, with the potential consequence of a decrease in infectiousness.6–8 However, the concurrence of suppressed virus in plasma and genital secretions has not been consistently demonstrated, and HIV detection in the genital secretions may be influenced by the presence of concurrent sexually transmitted infections, the genital sampling method, and the timing of specimen collection, particularly in relation to the menstrual cycle.9–12 The use of ART in HIV-infected patients as a strategy for HIV prevention is not a novel idea. Several publications from as early as 2000 have suggested this possibility.8,12 In addition, other mathematical models have examined the issue, some using less optimistic assumptions than those used by Granich et al, resulting in a less dramatic effect on HIV incidence.14–16 Accumulating evidence from observational and ecological studies provides additional support for possible effectiveness of treatment for prevention. A study in Uganda found that the risk of HIV transmission was 0.9 per 1000 person-years with the use of ART compared with 45.7 per 1000 person-years without.17 An analysis of linked HIV transmission in HIV discordant heterosexual couples from sub-Saharan Africa demonstrated that use of ART by the HIV-infected partners was associated with a 92% decrease in HIV transmission.18 However, conflicting findings were reported from a study of discordant couples in China, where use of ART was not associated with a statistically significant decrease in HIV transmission to the HIV-uninfected partner, raising concerns that suboptimal long-term adherence could compromise ART’s benefit in decreasing infectiousness.19

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In terms of ecological evidence in support of the potential effect of ART on HIV transmission, in one study, a decrease in median community viral load in San Francisco was reported to be associated with a decrease in new HIV infections.\(^2\) Similarly, data from British Columbia, Canada, indicated that an increase in the proportion of HIV-infected individuals with undetectable viral loads was associated with a decrease in number of new HIV infections.\(^2\) Similarly, in a study from Taiwan, a decrease in HIV transmission by 53% was noted after establishment of a national program for provision of free ART to all HIV-infected individuals in that country.\(^2\)

Findings from such observational and ecological data, however, must be interpreted with caution due to possible selection biases. For example, individuals who initiate ART versus those who do not may differ in certain characteristics (eg, sexual risk taking). Moreover, ecological studies cannot account for viral load levels among individuals unaware of their HIV diagnosis in any given community; this will affect the imputations used to take into account missing viral load measurements. Thus, it is important to appreciate that definitive data supporting the long-term impact of ART on HIV incidence are not yet available and to await the results of randomized clinical trials, including HIV Prevention Trials Network (HPTN 052), an ongoing study evaluating the effect of immediate versus deferred ART on transmission of HIV to the uninfected member of the discordant couple.\(^2\)

The HIV epidemic in the United States is an entrenched one, with about 56,000 new infections occurring per year over the past decade, and no evidence to date of a decrease in the annual number of new infections.\(^2\) Although screening the blood supply, promoting the use of condoms and the expansion of syringe access and exchange, limiting the number of partners, and serosorting, and interventions for prevention of mother-to-child transmission, have shown positive effects in reducing transmission in the United States, particularly in the early years of the epidemic, the unchanged magnitude of new infections in the past decade clearly motivates the need for innovative prevention strategies, including an exploration of the test and treat approach. However, certain characteristics of the HIV epidemic need to be taken into account when such a strategy is considered, and several challenges must be confronted if the promise of ART for prevention can be realized in the United States. These characteristics include the large numbers of individuals who (1) are unaware of their HIV infection; (2) are diagnosed late with HIV infection; (3) delay or face barriers to accessing care and initiate ART at late-stage HIV disease; (4) have suboptimal adherence to ART over time; and (5) continue to engage in HIV transmission risk behaviors. Figure 1 illustrates these challenges and highlights many of the behavioral, economic, societal, and policy issues that impede individuals from achieving milestones that are critical to the success of the ART-for-prevention approach.

**LACK OF AWARENESS OF HIV STATUS**

Identifying all individuals with HIV infection in a community is the foundation of effective use of ART for prevention. However, US data indicate that of the estimated 1 million individuals living with HIV, 21% are unaware of their HIV status.\(^2\) Evidence suggests that these individuals are responsible for more than 50% of new sexually transmitted infections and are 2.5 times more likely to transmit HIV than individuals who are aware of their HIV infection.\(^2\) Of further concern is the fact that the proportion of individuals unaware of their HIV infection is even higher among blacks, a group at particular risk for HIV in the United States. In a study conducted among men who have sex with men (MSM), 77% of those found to be HIV infected were unaware of their HIV status; of this group, 91% were black and 60% white.\(^2\)

A further challenge to identification of individuals with HIV in the United States is the localized nature of the HIV epidemic, disproportionately targeting vulnerable and disenfranchised populations, particularly MSM and blacks within specific geographic regions.\(^2\) For example, in Washington, DC, the city with the highest HIV seroprevalence in the United States, HIV prevalence is highest among black males (6.5%); among MSM in that city, blacks account for 58% of all HIV/AIDS cases.\(^2\) In New York City, the US city with the largest number of people living with HIV, 1 in 10 MSM are estimated to be infected with HIV.\(^2\) Additionally, recently...
published data found that black men comprise the city’s largest demographic group of new HIV diagnoses (33%) and persons living with HIV/AIDS (29%) and have the city’s highest HIV prevalence (3.7%). Special efforts are needed to effectively reach these populations in a culturally appropriate manner that avoids further stigmatization.

Although the Centers for Disease Control and Prevention recommended almost 4 years ago that all Americans aged 13–64 be tested for HIV at least once, only 10% indicate that they were HIV tested during the past year. Many factors impede expansion of HIV screening, including health care providers’ continued reliance on risk-based testing rather than on routine screening. It is more common for health care providers to offer testing when HIV is suspected clinically or based on their perception of an individual’s risk. This approach is fraught with limitations since HIV risk in the United States is often related more to an individual’s sexual network than to his or her risk behaviors—information that many persons do not share with their health care providers.

Despite the challenges, successful initiatives have expanded HIV testing in some geographic regions. A recent scale-up effort led by the New York City Department of Health, called “The Bronx Knows,” has coincided with a statistically significant increase in the percent of Bronx residents between the ages of 18–64 reporting that they have ever been tested for HIV.

**DIAGNOSIS AT LATE STAGE OF DISEASE**

Evidence indicates that many individuals in the United States are being tested late in the course of their HIV infection: Approximately 40% of individuals receiving their first HIV-positive test result are diagnosed with AIDS within a year. In New York City in 2008, 25% of those tested had a concurrent HIV/AIDS diagnosis. In a study that examined surveillance data from New York City, concurrent diagnosis of AIDS and HIV infection was substantially more common among blacks and Latinos than among whites. The frequency of late diagnosis is of concern both to the individual and the community. Those testing late in the course of HIV infection miss out on the clinical benefits of HIV care and treatment and may also unknowingly contribute to the spread of HIV to others within their communities because their higher plasma HIV RNA levels are also correlated with increased infectiousness. Alone, expanded HIV testing could have a substantial impact on HIV transmission in the United States, as it has the potential to lead to earlier diagnosis of HIV and earlier adoption of safer behaviors and allows for earlier access to care and treatment, with its demonstrated benefits in terms of immunological response and better outcomes and survival.

**DELAY IN LINKAGE TO HIV CARE AFTER HIV DIAGNOSIS**

The promise of treatment as a prevention strategy also depends on individuals promptly linking to care, initiating treatment when recommended, and achieving sustained viral suppression and decreasing risk-taking behavior. In terms of linkage to care, findings from New York City indicate that of 1928 newly diagnosed individuals, only 63.7% were linked to HIV care within 3 months, and 17.2% never initiated care. Studies demonstrate that not only is HIV care initiated late or not at all in some cases but also there are racial, ethnic, gender, and other disparities related to when and whether care is started. Multiple studies demonstrate that nonwhite race, foreign birth, and female sex predict delayed initiation of care. Studies have also shown that injection drug users delay care and are particularly likely to be homeless and incarcerated and to have untreated psychiatric illness that may hinder or complicate ART delivery and adherence. Injection drug users also experience more rapid HIV disease progression. The personal and societal benefits of timely HIV diagnosis can be realized only when it is combined with timely initiation of clinical care. Earlier linkage to care results in greater opportunities for virological and immunologic monitoring and initiation of ART, once eligibility is established, and greater access to interventions for prevention for positives.

**INITIATION OF ART AT LOW CD4+ CELL COUNTS**

Studies have shown that many HIV-infected individuals in the United States initiate ART at low CD4+ cell counts, substantially below the thresholds currently recommended by US guidelines for use of ART. In a study, among 35,009 patients followed from 1996 to 2007, although the median CD4+ cell count at first presentation slightly increased from 234 to 327 cells per cubic millimeter, 53% of patients still had CD4+ cell counts at presentation below the prevailing guideline threshold for ART initiation. In another study, treatment-eligible injection drug users from Baltimore who were observed from 1996 to 2007 initiated therapy, after lengthy delays, with advanced immunosuppression. Nearly one third of individuals who became eligible for treatment had not initiated ART when guidelines would suggest optimal benefit.

In addition to late diagnoses of HIV, a number of other factors contribute to delays in ART initiation, including limited treatment literacy; patient refusal to begin ART for fear of side effects; and reluctance by some providers to prescribe ART due to real or perceived barriers to adherence. Resource constraints among state AIDS drug assistance programs, which provide support for ART to approximately one quarter of all patients enrolled in HIV/AIDS care in the United States, also account for some delays in ART initiation. Some AIDS drug assistance programs already have waiting lists for patients in need of ART, a situation that may be exacerbated in view of the revised ART guidelines released in 2009, which recommend initiation of ART at higher CD4+ cell count thresholds, combined with limited public health resources in the setting of a severe economic recession.

**DIFFICULTY IN ACHIEVING AND MAINTAINING HIGH RATES OF ADHERENCE WITH ART**

Achievement of viral suppression on ART is dependent on correct and consistent use of effective antiretroviral
regimens. Results from a meta-analysis of 31 adherence studies showed that only 55% of HIV-infected patients achieved adequate ART adherence in North America. However, research suggests that high levels of adherence, between 80% and 95% depending on regimen type, may be necessary to maintain viral suppression. Various complex factors have been shown to contribute to suboptimal adherence, including active substance use (including the use of alcohol), young age, and depression—all issues that highlight the importance of providing HIV-infected patients with access to supportive services. Indeed, retaining patients in care is a prerequisite for achievement of the high rates of ART utilization and adherence required for garnering the potential benefits of the ART for prevention strategy. A recently published modeling study in which the effectiveness of a comprehensive approach to test and treat that included enhanced linkage to care after diagnosis and high retention in care was compared with solely universal test and treat demonstrated that the former package of interventions was associated with substantially increased benefits. It is also important to note that even with optimal adherence, suppression of viral replication is not always achievable and the possibility of discordance between HIV viral load in the plasma and genital secretions remains, issues that underscore the need for other interventions for prevention for positives. Several positive prevention interventions have been shown to be associated with a decrease in high-risk behaviors (eg, unprotected anal sex), a decrease in substance use, and an increase in condom use. Ultimately, the use of such interventions will be critical to complement the effects of ART for prevention.

**THE WAY FORWARD**

Continued HIV transmission in the United States has generated interest in the potential use of ART for prevention. A recent report of the results of a mathematical model utilizing data from Washington, DC, demonstrated only a modest effect on HIV transmission with expanded HIV screening and ART. Nonetheless, momentum has been generated to test this concept by embarking on feasibility studies of such an approach. From a conceptual perspective, taking into account the unique characteristics of the HIV epidemic in the United States is critical to the design of such studies and to the design of the types of interventions to include as part of the test and treat strategy. One study to address these issues is in development by the HIV Prevention Trials Network (HPTN 065), the Test, Link to Care, Plus Treat study, a collaboration between the National Institutes of Health, the Centers for Disease Control and Prevention, local health departments, and a broad array of stakeholders. The study will focus on specific interventions to optimize testing, linkage to care, and suppression of viral replication in the Bronx and Washington, DC, and may inform other large-scale domestic initiatives in the future. Based on the issues delineated above, embarking on such an effort will require addressing the factors that influence a cascade of events: individuals’ access to and acceptance of HIV testing and the impediments to engagement in HIV care, adherence to ART and positive prevention behaviors. Barriers such as stigma, mistrust of health systems, misperceptions of HIV risk, access to services, support for comorbid conditions, and psychosocial impediments need to be addressed if the test and treat approach is to succeed. In a parallel manner, interventions will be needed to address provider skills and attitudes regarding HIV testing, perceptions of eligibility for ART initiation, skills in support of adherence, and attitudes regarding the balance of patient versus societal benefits of ART. Indeed, beyond a focus on test and treat as the 2 elements of a successful ART-for-prevention strategy, the United States epidemic compels a much more comprehensive perspective that entails a seek, test, link, treat, and support approach, necessitating an unprecedented partnership involving communities, providers, support organizations, and persons living with HIV themselves.

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Chemoprophylaxis for HIV Prevention: New Opportunities and New Questions

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Abstract: Growing data suggest that antiretrovirals can be used as an effective means of HIV prevention. This article reviews the current status and future clinical prospects of utilizing antiretroviral chemoprophylaxis before and after high-risk HIV exposure to prevent HIV transmission. The discussion about using antiretrovirals as a means of primary HIV prevention has moved to the forefront of public health discourse because of a growing evidence base, the increased tolerability of the medications, the decreased cost, the ever-expanding formulary, and the limitations of other approaches.

Key Words: AIDS, ART, HIV, primary prevention, preexposure prophylaxis, postexposure prophylaxis, topical microbicides

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WHY ANTIRETROVIRALS FOR PRIMARY HIV PREVENTION?

With more than 2.5 million new HIV infections annually,1 HIV prevention is at a crucial juncture because most biomedical interventions have failed to effectively decrease HIV acquisition,2 an effective HIV preventive vaccine remains years away,3 and many behavioral strategies have not led to durable reductions in the number of new HIV infections.4 Growing observational and modeling data suggest that antiretrovirals (ARVs) can be used as an effective means of HIV prevention.5 Antiretroviral therapy (ART) for prevention includes not only prompt initiation of HIV-infected individuals on treatment to decrease the risk of transmission6,7,8 but also ART prophylaxis for at-risk uninfected individuals.5 Numerous animal model studies have demonstrated that ART administered parenterally, orally, or topically before or just after retroviral challenge was protective against HIV acquisition.9,10 Historically, treatment as prevention, or chemoprophylaxis, has been routinely used for other infectious diseases, including malaria, tuberculosis, and sexually transmitted infections (STIs).11,12 but the duration of administration is generally days to months rather than many years as may be the case with HIV medications.

Antiretroviral postexposure prophylaxis (PEP) to prevent HIV acquisition was first recommended for use in occupational settings more than a decade ago.13 Subsequent studies have led to recommendations for its use in non-occupational settings, and research is underway to examine whether ART preexposure prophylaxis (PrEP) could be an effective method of primary prevention for individuals who have ongoing risks for becoming HIV infected.9,14 This article reviews the current status and future clinical prospects of utilizing antiretroviral chemoprophylaxis before and after high-risk HIV exposure to prevent HIV transmission.

POSTEXPOSURE PROPHYLAXIS

The best proof of concept for the relationship between ARVs and HIV transmission comes from studies of the prevention of mother-to-child transmission15,16 and a case–control study of PEP after needle stick injury in health care settings.17 The Centers for Disease Control and Prevention registry documented that health care workers who took zidovudine (AZT) monotherapy after occupational exposure were one fifth as likely to become HIV infected as those who did not take treatment.18,19 The rhesus macaque simian immunodeficiency virus challenge model has suggested that 28 days of ART is needed for optimally effective PEP15 and has been the basis for the recommendation of a 4-week course for humans exposed to HIV. In the past, a major impediment to wider implementation of PEP utilization was the relative intolerability of first-line agents, such as azidothymidine and protease inhibitors.19 A study examining PEP uptake in several European emergency departments found that almost half of the individuals did not complete the full 28-day PEP course because of decreased tolerability of regimens, including AZT/lamivudine and either ritonavir-boosted lopinavir or atazanavir.20 A subsequent case–control study of nonoccupational PEP found that men who took tenofovir–emtricitabine were more likely to complete a 28-day course of PEP than historical controls taking 2-drug AZT-based regimens.21 Other newer drugs may also offer opportunities for novel PEP
strategies due to improved tolerability and novel mechanisms of action (eg, raltegravir) and/or high genital tract concentrations (eg, maraviroc). It remains to be fully elucidated whether 2 would be preferable to 3 for PEP. A 2-drug regimen would decrease regimen complexity (eg, 1–3 coformulated pills a day), increasing tolerability and completion rates, but alternatively, if the individual has been exposed to a treatment-experienced HIV-infected source, more drugs could provide extra protection against the selection for drug-resistant virus.

Though PEP has not been widely utilized outside occupational health care settings, concerns have been raised by some that wider utilization may be counterproductive among individuals at increased risk for HIV by decreasing their protective behaviors. A study of men who have sex with men (MSM) in Brazil did not demonstrate increases in risk-taking behaviors after PEP and HIV incidence was significantly lower in PEP users. Because this was not a randomized controlled trial, unintended biases could have been present (eg, PEP users being generally less risky, etc). Other studies have included prevention counseling to increase the intervention’s long-term efficacy to optimize the educable moment when at-risk individuals are seeking to protect themselves from infection. Despite efforts to use the PEP clinical encounter as a means to help people decrease risk-taking behavior, the San Francisco Health Department STD Clinic found that 1.3% of PEP users became HIV infected within 6 months after completing their medication course, underscoring the need for sustained behavioral interventions for those at increased risk in addition to the provision of drugs.

PREEXPOSURE PROPHYLAXIS

In situations where the likelihood of HIV exposure can be anticipated ahead of time, ARVs delivered in either oral or topical formulations could be a logical mode of primary prevention. The groundwork for current clinical PrEP research has been provided by animal studies over the past decade. The most widely studied antiretroviral for PrEP, tenofovir, has many features that are desirable in a chemoprophylactic agent, including long intracellular half-life, activity in monocyte/macrophages and other cells that may transmit HIV in genital secretions, and high concentrations in genital tissues. Preclinical nonhuman primate studies that evaluated the efficacy of tenofovir-based PrEP found that the drug could protect against HIV acquisition when used topically or systemically. Subsequent macaque studies suggested possibility of intermittent dosing, given the high rates of protection found as long as animals received at least one dose preexposure, and another about 2 hours after the viral challenge.

The ideal PrEP agent would have a long half-life, achieve high concentrations in target tissues, have a high barrier to the development of drug resistance, and be safe and inexpensive (Fig. 1). Although all current clinical trials of PrEP involve tenofovir plus or minus emtricitabine, concerns have been raised about reliance on these drugs for chemoprophylaxis because they are mainstays of treatment. In the worst case scenario, individuals might use chemoprophylaxis intermittently, and if they did not undergo frequent HIV screening, they could select for and then transmit drug-resistant strains. Thus, other ARVs have been suggested as promising candidates for a multidrug PrEP regimen. Lamivudine and emtricitabine may be optimal for use as PrEP because of their great tolerability and long safety record, and strains that become resistant to these drugs almost invariably develop the M184V mutation, conferring decreased viral fitness, minimizing the risk of onward transmission to sex partners. Other well-studied antiretroviral agents may not be optimal for PrEP because they do not penetrate genital tissues in adequate concentrations, which is a function of relative protein binding and other pharmacodynamic properties. Protease inhibitors are highly protein bound, achieving lower concentrations in the genital tract, compared with nucleoside analogues and nonnucleoside reverse transcriptase inhibitors. The oral CCR5 coreceptor antagonist maraviroc achieves high genital tract and rectal concentrations and could be as effective as PrEP. If the initial tenofovir-based PrEP trials demonstrate efficacy, future studies may focus on the evaluation of other drugs with novel mechanisms of action and/or different pathways of resistance.

CURRENT STATUS OF PrEP CLINICAL TRIALS

Multiple clinical PrEP trials are underway among different communities globally to examine the impact of oral and/or vaginal tenofovir or emtricitabine/tenofovir on HIV acquisition (Table 1). These trials will enroll more than 20,000 HIV-uninfected men and women to address a variety of questions, including proof of concept, and if effective, then whether intermittent PrEP can be used, whether topical or oral PrEP is more effective, and whether drug resistance emerges as a clinical problem because of extensive use of these medications for chemoprophylaxis. All of these studies are examining the influence of PrEP on risk-taking behaviors. These studies are occurring among MSM in the Americas, Thailand, and South Africa; among at-risk women in sub-Saharan Africa; among HIV-discordant couples in Africa; and among Thai injection drug users. Most of these trials are evaluating daily dosing; a few will also include intermittent dosing strategies. A community-based organization, the AIDS Vaccine Advocacy Coalition (www.avac.org), has developed a PrEPWatch feature that provides continuously updated information about the status of clinical trials currently underway.

The results of the first human PrEP study, a phase II randomized double-blinded placebo controlled trial, was completed in 2007 and demonstrated the safety of daily oral tenofovir compared with a placebo for HIV prevention among high-risk West African women who received HIV testing, counseling, and condoms. Women in the intervention arm had fewer seroconversions than women in the control arm (8 versus 2), but this difference was not statistically significant. Importantly, both groups of women reduced their behavioral risk during the course of the study. Initial data suggests that efficient recruitment and implementation of large-scale phase III PrEP trials is possible with motivated participants and community engagement. One earlier planned PrEP study among Cambodian female sex workers never began enrollment because of community concerns, which led to extensive discussions among researchers, public
officials, and other key stakeholders to anticipate concerns that might be raised in different communities—for example, regarding access to medication after trial completion. Over the next few years, data will become available to address whether oral tenofovir by itself, oral tenofovir coformulated with emtricitabine, or topical tenofovir gel (ie, a microbicide) will be more effective relative to placebo.

An area of concern has been the development of drug resistance through the continued use of PrEP if participants unknowingly become HIV infected, either by exposure to a drug-resistant virus, suboptimal adherence, or failure of the regimen (eg, inadequate tissue penetration). Individuals who had 2 weeks of tenofovir monotherapy (as a run-in to a study of a 3-drug-regimen) did not develop tenofovir resistance. In monkeys who were challenged with tenofovir-resistant SHIV, the use of tenofovir as PEP prevented HIV infection. Mathematical models of HIV prophylaxis have suggested that less than 1% of the predicted serconversions would develop a tenofovir-resistant strain. Due to the increasing use of tenofovir as part of first-line treatment regimens, continued monitoring to assess the effects of PrEP is warranted.

Data from oral and topical PrEP studies were presented at the International AIDS Society meetings in Vienna in July 2010. A study of 400 at-risk MSM, recruited in 3 US cities, compared the use of oral tenofovir with a placebo and found no evidence of increased clinical toxicities (particularly no increased renal insufficiency, bone demineralization, or other side effects) or increased sexual risk taking among the men assigned to tenofovir compared with those who received the placebo. Although this safety study was not powered to demonstrate drug efficacy, no new HIV infections were detected among the men who received the tenofovir. Another very important study, CAPRISA 004, studied tenofovir gel in high-risk women in KwaZulu-Natal, South Africa, and found that the women assigned to the tenofovir gel were significantly less likely to become HIV infected than those who used placebo gel. Although the route of administration is different than oral chemoprophylaxis, the finding of a significant level of protection by a topical antiretroviral medication is a key observation, raising the hope that oral PrEP studies will also demonstrate a protective effect. Ultimately, it will be important to determine which route of administration is most effective for each specific population because local anatomy (eg, vaginal versus rectal mucosa) and tissue pharmacology may determine the relative advantages of one approach over another. The VOICE trial being conducted by the National Institutes of Health–funded Microbicide Trials Network (www.mtnstophiv.org) will be the first to evaluate an antiretroviral gel compared with oral medication and may be a harbinger of future studies to determine the optimal chemoprophylactic strategies.

The success of the CAPRISA 004 study is important to prevention science, as the first demonstration of the ability of chemoprophylaxis to decrease HIV incidence and as the first proof of the protective effects of a topical microbicide. Future microbicide trials will evaluate other topical antiretroviral drugs, including dapivirine, a nonnucleoside reverse transcriptase agent, and other targets of the HIV life cycle, such as entry and integrase inhibitors. Future human studies will also assess whether other delivery mechanisms, ranging from vaginal rings to injectable compounds, might enhance product efficacy by decreasing the challenges of daily or coitally dependent adherence. More current information can be found on the Microbicide Trials Network website (www.mtnstophiv.org) and the AIDS Vaccine Advocacy Coalition website (www.avac.org).

IMPLEMENTATION OF ANTIRETROVIRAL CHEMOPROPHYLAXIS

If PrEP is found to be an effective mode for HIV prevention, concerns about wider utilization include risk compensation, cost (ie, who will pay?), acquisition of resistant virus, adherence, and drug-related toxicities. The Centers for Disease Control and Prevention and the World Health Organization have begun to meet regularly to anticipate community responses and to work with clinicians, national governments, and representatives of at-risk communities as efficacy data become available. Providing ART to uninfected individuals will also need to be balanced with the imperative to provide prompt treatment access to HIV-infected individuals meeting guidelines for treatment initiation. However, it is possible that PrEP could be a cost-effective means of HIV prevention for younger and high-risk populations in the United States, Europe, and elsewhere.
States given the high cost of treating new HIV infections over the life course.

If PrEP is found to be effective, questions will arise as to who should prescribe these drugs and how best to train providers. ART as PrEP will require researchers and clinicians to optimally utilize these agents in a focused manner to reduce the number of new HIV infections. Identifying individuals at high risk for HIV infection and then initiating them on PrEP could be a major challenge, given continued stigma associated with behaviors that put individuals at increased risk of acquiring HIV. Major areas that will require further clinical research include monitoring long-term safety, development of adherence strategies, assessing methods of optimal drug delivery and dosing, and minimizing selection of resistant viruses. Addressing these questions will require expanded safety and effectiveness trials and the development of public surveillance systems to monitor HIV incidence, risk compensation, and resistant virus evolution. Patients in clinical settings will require ongoing and regular HIV testing to avoid substandard therapy in the case of becoming HIV infected. Individuals with tenofovir-resistant virus could compromise their own treatment options and could spread resistant virus to their sex partners or offspring.

Potential risk compensation among individuals using PrEP may also compromise its effectiveness. It is possible that individuals could obtain off-label access to drugs in advance of efficacy data becoming available. Reports of ART being sold at clubs and of self-administration prior to high-risk

### TABLE 1. Current Trials of Tenofovir-based PrEP

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Population</th>
<th>Location</th>
<th>Drug</th>
<th>Means of Administration</th>
<th>Sample Size</th>
<th>Expected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Extended Safety Trial (CDC 4323)</td>
<td>Gay men; MSM</td>
<td>United States</td>
<td>TDF</td>
<td>Daily oral</td>
<td>400</td>
<td>TDF is safe and well-tolerated as PrEP for MSM</td>
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<tr>
<td>iPrEX</td>
<td>Gay men; MSM</td>
<td>Brazil, Ecuador, Peru, South Africa, Thailand, United States</td>
<td>TDF/FTC</td>
<td>Daily oral</td>
<td>2500</td>
<td>Fully enrolled 2009; results probable by late 2010</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study (CDC 4370)</td>
<td>Injecting drug users</td>
<td>Thailand</td>
<td>TDF</td>
<td>Daily oral</td>
<td>2400</td>
<td>Completed enrollment 2010; possible results 2010/early 2011</td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td>Heterosexual women</td>
<td>South Africa</td>
<td>TDF</td>
<td>Coitally dependent topical vaginal gel</td>
<td>1000</td>
<td>First demonstration of the efficacy of tenofovir gel</td>
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<td>TDF2 (CDC 4940)</td>
<td>Heterosexual men and women</td>
<td>Botswana</td>
<td>TDF/FTC</td>
<td>Daily oral</td>
<td>1200</td>
<td>Enrollment stopped 2009; safety data likely 2010</td>
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<tr>
<td>Partners PrEP</td>
<td>Serodiscordant heterosexual couples</td>
<td>Kenya, Uganda</td>
<td>TDF and TDF/FTC</td>
<td>Daily oral</td>
<td>3900</td>
<td>Enrolling; data expected 2012</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Heterosexual women</td>
<td>Kenya, Malawi, South Africa, Tanzania, Zambia</td>
<td>TDF/FTC</td>
<td>Daily oral</td>
<td>3900</td>
<td>Enrolling; data expected 2013</td>
</tr>
<tr>
<td>VOICE (MTN 003)</td>
<td>Heterosexual women</td>
<td>South Africa, Uganda, Zambia, Zimbabwe; additional sites to be determined</td>
<td>TDF; TDF/FTC</td>
<td>Daily oral (TDF, TDF/FTC); Daily topical vaginal gel (TDF)</td>
<td>5000</td>
<td>Enrolling; data expected 2013</td>
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<td>High-risk young MSM</td>
<td>United States</td>
<td>TDF/FTC</td>
<td>Daily dosing with or without a behavioral intervention</td>
<td>100</td>
<td>Enrolling; results in 2011 or 2012</td>
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Studies Involving Intermittent PrEP (i-PrEP)

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Population</th>
<th>Location</th>
<th>Drug</th>
<th>Means of Administration</th>
<th>Sample Size</th>
<th>Expected Results</th>
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<tr>
<td>IAVI E001 and E002</td>
<td>Serodiscordant couples and at-risk men and women</td>
<td>Kenya, Uganda</td>
<td>TDF/FTC</td>
<td>Daily oral; intermittent oral (twice weekly + coital dosing)</td>
<td>150</td>
<td>Full enrollment expected 2010</td>
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<tr>
<td>HPTN 066</td>
<td>Low-risk men and women</td>
<td>United States</td>
<td>TDF/FTC</td>
<td>Different dosing strategies planned</td>
<td>48</td>
<td>Intense pharmacokinetic study</td>
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<tr>
<td>HPTN 067</td>
<td>High-risk women and MSM</td>
<td>Thailand, South Africa</td>
<td>TDF/FTC</td>
<td>Fixed interval vs coitally dependent</td>
<td>360</td>
<td>In planning stages</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; FTC, emtricitabine; TDF, tenofovir; IAVI, the International AIDS Vaccine Initiative; and HPTN, the HIV Prevention Trials Network.
CONCLUSIONS: FUTURE OF ART FOR PRIMARY PREVENTION

The promise of ART chemoprophylaxis for uninfected individuals is great, but the field is still in an early stage, and major questions remain. The discussion about using ART as a means of primary HIV prevention has moved to the forefront of public health discourse because of the increased tolerability of the medications, the decreased cost, the ever expanding formulary, and the limitations of other behavioral and biomedical approaches. Optimizing the use of antiretroviral agents for HIV prevention will require careful consideration of adherence, sustained access, behavioral risk reduction, and STI diagnosis and treatment. The ability to implement ART for primary prevention in the United States will depend on effectively engaging at-risk individuals and educating their providers and decreasing the economic impediments to optimal use.

It is conceivable that in the future certain drugs may be reserved for specific preventive and therapeutic interventions. Further research in pharmacology, virology, behavioral science, and health care service delivery will be needed to better understand the intended and unintended consequences of widely using ART for prevention. PEP and PrEP will likely be part of a larger HIV prevention toolbox that will be used to reduce the number of new infections, a toolbox that would also include behavioral risk reduction strategies, expanded HIV testing, male circumcision, prevention of mother-to-child transmission, and possibly STI treatment.\(^\text{458}\) The search for an effective HIV vaccine must continue as well. But in the mean time, the use of multiple partially effective interventions could significantly slow the epidemic.

REFERENCES


Lessons Drawn From Recent HIV Vaccine Efficacy Trials

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Abstract: A safe and effective HIV vaccine is needed to curtail the US and global epidemics. However, the search for one has been elusive despite more than 25 years of focused research. Results from the RV144 Thai efficacy trial have renewed hope that a vaccine may protect against HIV acquisition. We can draw several scientific and operational lessons from RV144 and other recent tests-of-concept efficacy trials. Here we describe how trial results, some unexpected, highlight the fundamental role these clinical studies play in HIV vaccine discovery. These trials also teach us that transparency in data analysis and results dissemination can yield substantial rewards and that efforts to engage communities, particularly those most heavily affected by the epidemic, are needed to augment research literacy and trial recruitment. Future efficacy trial designs may incorporate novel, partially effective prevention strategies. Although greater in size and complexity, these trials may offer unique opportunities to explore synergies with vaccines under study.

Key Words: clinical trials, combination prevention, efficacy trials, HIV vaccines

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INTRODUCTION

Approximately 56,000 people in the United States become infected with HIV each year—one new HIV infections every 9½ minutes—reinforcing the urgent need to expand access to proven prevention strategies and identify new ones.1 Historically, vaccines have been the most effective method to combat a wide range of infectious pathogens and in the United States are responsible for eradicating the threat from smallpox and poliomyelitis. It is widely believed that a vaccine must be a component of the HIV prevention armamentarium, yet more than 25 years of vaccine research has not delivered one. A recently completed vaccine efficacy trial has inspired new hope that an HIV vaccine is achievable. Here we describe how the results from these large clinical studies, some unexpected, are driving vaccine discovery. We also outline important lessons about data analysis, dissemination, and recruitment of communities at risk.

HIV VACCINE EFFICACY TRIALS TO DATE

Since the first gp160 vaccine entered clinical testing in 1987, more than 150 trials of different vaccine candidates have been conducted.2 These trials reflect 3 distinct waves of vaccine development, including approaches designed to elicit broadly neutralizing antibodies and cell-mediated immune (CMI) responses, and the latest wave, focused on generating combined humoral and CMI responses.3 However, only 6 trials testing 4 distinct strategies have advanced to efficacy trials (Table 1). We have previously outlined several lessons gleaned from the VAX 004 study, conducted largely among US men who have sex with men (MSM).9 Here we will focus attention on more recent efficacy trials.

LESSONS LEARNED

Good Science Often Leads to Surprising Results

The pair of test-of-concept efficacy trials evaluating a replication incompetent adenovirus serotype 5 (MrKAd5) trivalent HIV vaccine has advanced our understanding of vaccines designed to induce CMI responses. In September 2007, the first interim analysis of the Step trial in men and women from North and South America, the Caribbean, and Australia demonstrated that the MrKAd5 HIV vaccine failed to prevent infection or reduce early viral load.6 Unexpectedly, post hoc analysis revealed that male participants who were uncircumcised and Ad5 seropositive at baseline were at higher risk for HIV acquisition if they received the vaccine than if they received placebo. Investigators have suggested mechanisms by which the vaccine could increase susceptibility to infection among participants with preexisting Ad5 antibody,10,11 although none have been demonstrated in actual trial volunteers.12,13 On the other hand, several analyses suggest that the vaccine may have caused transient modest reductions in early viral load,14,15 giving leads about potentially effective vaccine-induced immune responses to build upon. In the Phambili trial, a companion trial to the Step trial among heterosexuals in South Africa, vaccinations were halted after only 801 of 3000 participants were enrolled. No
overall efficacy was seen, although analyses among female vaccinees vs. placebo recipients found a nonsignificant trend toward lower early viral load (12,000 vs. 35,000, \( P = 0.14 \)) and a significant reduction in progression to CD4 <350 cells per cubic millimeter (hazard ratio: 0.33, 95% confidence interval: 0.12 to 0.91).\(^7\) 

Taken together, findings from Step and Phambili offer a number of key lessons. First, the field is looking beyond the gamma interferon ELISpot assay as the central measure of CMI; responses were detected in a majority of vaccinees but were not found to correlate with either protective or harmful effects in these trials.\(^6\) Although developers are using a number of strategies such as DNA priming of vector-based regimens\(^17,18\) and novel HIV inserts\(^19\) to produce immune responses of greater magnitude, breadth, or quality, laboratory correlates of protection must be determined in clinical trials.

Second, the Step trial reinforced limitations of nonhuman primate (NHP) challenge models to predict efficacy in humans. We learned that a challenge model using a chimeric...
simian immunodeficiency virus (SHIV 89.6P) failed to predict the results of human trials. In addition, NHP studies were not designed to evaluate the potential for increased susceptibility to infection nor the impact of vector-based preexisting immunity or the role of foreskin on vaccine effects. NHP models can be used to study events that cannot be adequately monitored in human trials, such as events shortly after simian immunodeficiency virus exposure. Clinical trials must inform how best to use NHP models and to ultimately validate the utility of these models to predict responses in humans.

Another lesson from these trials is the potential for heterogeneous vaccine effects in different populations. The Phambili trial, although limited in size and power, suggested potential for gender-based differences in vaccine effects, as has been seen in studies of a herpes simplex vaccine. Although more than one third of enrolled participants in the Step trial were women—many of whom reported high levels of unprotected sex with numerous partners—HIV incidence was quite low in this group. Despite a substantial HIV epidemic in subpopulations of US women, identifying high seroincidence cohorts of US women has been challenging. Two feasibility studies testing novel approaches to recruit at-risk women in the United States are currently underway in the NIAID-sponsored HIV Vaccine and Prevention Trials Networks.

The RV144 study, conducted by the US Military HIV Research Program in collaboration with several Thai institutions, met with early skepticism among members of the scientific community due to the vaccine regimen's relatively poor immunogenicity by standard cytotoxic T lymphocyte assays. As a welcome surprise to many, the trial demonstrated a 31% reduction in HIV incidence, a marginal but statistically significant result. More than 30 investigators working in teams are actively attempting to identify potential correlate(s) of immune protection in this study, with a particular focus on antibody-mediated mechanisms, including binding antibodies and antibody-dependent cell-mediated cytotoxicity. Also surprising was the suggestion of increased efficacy among participants with lower reported baseline risk behavior, raising the possibility that vaccines with modest efficacy may have a threshold effect, with limited efficacy for participants who are heavily exposed to HIV.

Transparency Yields Many Rewards

The standards of Good Participatory Practices outlined by AVAC and the Joint United Nations Program on HIV/AIDS state that research teams must engage with relevant stakeholders at all stages of the trial life cycle. In the Step and Phambili trials, study sites released results to participants and the public beginning within 72 hours of the Data and Safety Monitoring Board review of interim Step efficacy results. In addition, when the suggestion of increased susceptibility in the Step study came to light, the protocol team worked closely with trial sites, community advisory boards, and advocates to develop a clear communication plan to disseminate these complex results and make decisions about study unblinding. The RV144 study team developed a communication plan that chose to share results with participating communities before presenting data to scientific audiences at the AIDS Vaccine 2009 conference and in print. These studies have opened up data and specimens to the broad scientific community, which has established an important standard in advancing HIV vaccine science and increasing transparency during the discovery process.

It Takes a Village (Several, Actually)

The success of large-scale efficacy trials depends heavily on the mobilization and participation of communities at risk for infection. Sustained community engagement efforts are needed to address the lack of urgency about HIV/AIDS and limited knowledge of HIV vaccine research, particularly among African Americans, Latinos, and MSM. Recruitment into large-scale efficacy trials, an activity distinct from but inextricably linked to community education, has become increasingly challenging yet pressing because the rate of new HIV diagnoses in MSM is 44 times that of other men in the United States. In HVTN 505, an ongoing trial of the Vaccine Research Center's DNA prime Ad5 boost regimen, the early phase of enrollment has been slower than anticipated. This may be due, in part, to the need to identify men and transgender women who are fully circumcised and Ad5 seronegative (inclusion criteria based on data from Step that this group was not at elevated risk for HIV after Ad5 vaccination). But several other complex social forces may be at play including prevention fatigue, saturation of HIV messages in public media, and competition for MSM participants across different HIV prevention studies, among other reasons.

Operationally, the Step trial highlighted the importance of centrally coordinated recruitment strategies and sharing of materials and techniques across participating trial sites. The most effective campaigns may be those that feature the altruistic motivations that encourage MSM to come forward to join trials in the first place. In addition, both Step and HVTN 505 have made significant use of new Internet-based recruitment strategies, including online social media sites, to attract MSM who often use the Web to find sexual partners. The effectiveness of these online recruitment approaches requires further evaluation and should be optimized to accelerate recruitment efficiency.

There is No Silver Bullet for HIV Prevention

A first-generation HIV vaccine will likely be partially protective—a fact evidenced by the RV144 findings. Ultimately, it is hoped that such a vaccine can be combined with other partially protective biomedical and behavioral strategies to achieve synergistic effects. For example, Hallet et al have modeled HIV incidence in Southern Africa and have found that a circumcision intervention applied with behavioral risk reduction interventions will lead to a much greater impact than would be expected on the basis of either alone. A partially effective antiretroviral-based microbicide was identified in July 2010 and several clinical trials of preexposure prophylaxis regimens will report results over the next 3 years. To detect vaccine-induced effects, future trial designs that incorporate any of these new strategies with ongoing risk reduction counseling may be greater in size and complexity. But they may also provide new opportunities to explore potential synergies with vaccines under study. Ultimately, there is no silver bullet for HIV prevention. Incremental
successes in vaccine and drug discovery are the norm and will continue to be driven by our large-scale efficacy trials enrolling engaged and willing participants from communities at risk.

**ACKNOWLEDGMENTS**

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**REFERENCES**


Structural Interventions for HIV Prevention in the United States

Adaora A. Adimora, MD, MPH* and Judith D. Auerbach, PhD†

Background: Structural interventions change the environment in which people act to influence their health behaviors. Most structural interventions research for HIV infection has focused on developing countries, with the United States receiving substantially less attention. This article identifies some social determinants of HIV vulnerability in the United States and structural interventions to address them.

Methods: Review of the medical, public health, and social science literature.

Results: Evidence supports widespread implementation of a number of structural interventions in the United States clearly proximate to HIV, including comprehensive sex education, universal condom availability, expanded syringe access for drug users, health care coverage, and stable housing. Sociological plausibility supports evaluation and implementation of other interventions that target social determinants more distal but of relevance to HIV, such as initiatives to eliminate racial and ethnic disparities in criminal sentencing, to promote early childhood education and to decrease poverty.

Conclusions: Structural interventions that address social determinants of HIV infection may be among the most cost effective methods of preventing HIV infection in the United States over the long term.

Key Words: HIV, structural interventions, United States

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INTRODUCTION

In July 2010, the Obama Administration released the first National HIV/AIDS Strategy for the United States. The strategy targets and coordinates the nation’s response to the domestic HIV epidemic. With its goals of reducing new HIV infections, increasing access to care and improving health outcomes for people living with HIV infection, and reducing HIV-associated health disparities, the strategy envisions a United States “where new HIV infections are rare and when they do occur, every person, regardless of age, gender, race/ethnicity, sexual orientation, gender identity or socioeconomic circumstances, will have unfettered access to high quality, lifetime extending care, free from stigma and discrimination.”1

This vision reflects an understanding increasingly shared by public health researchers and practitioners that social determinants—the conditions in which people are born, live, work, and age—are critical influences on health and that these determinants, which are shaped by the distribution of money, power, and resources, can be influenced in positive ways. Structural interventions for HIV prevention attempt to affect these determinants by changing the environment in which individuals engage in health-related behaviors.3 Evidence suggests that interventions that address the contextual factors that influence people’s behavior are more successful than interventions that focus solely on individuals and ignore the larger context.4 In addition, financial analyses show that structural changes, although costly, may have the greatest effect over the long term in reducing the number of new HIV infections, and yielding other social benefits, such as improvements in economic productivity and advances in human rights.5

Structural interventions for HIV prevention typically involve at least one of the following: effecting policy or legal changes; enabling environmental changes; shifting harmful social norms; catalyzing social and political change; and empowering communities and groups.6,7 Interest in structural interventions has grown in recent years, but most research and programmatic efforts in this realm have focused on developing countries.8–10 We argue, however, (as have others11–12) that much can be done in the United States to address key social determinants of the nation’s epidemic and help achieve both the goals and the vision of the National HIV/AIDS Strategy by implementing structural interventions of various types. After identifying some key social determinants, we outline examples of structural interventions to address them. Some of these have been well described elsewhere; others may seem more novel in their connection to HIV/AIDS.

SOCIAL DETERMINANTS UNDERPIN THE US HIV EPIDEMIC

Substantial evidence documents the role of social determinants in health outcomes at the individual level and community level.14 Macroeconomic and social forces, such as poverty, racism, sexism, and homophobia, help fuel HIV
epidemics, although the pathways between these forces and HIV infection are complex and not always clear.\textsuperscript{15–19} The US epidemic—with its disproportionate impact on gay and other men who have sex with men (MSM), people of color, drug users, and people living in the South—concentrates HIV among groups that often overlap demographically and geographically and share some core social determinants of infection.

More than half of new HIV infections in the United States (53\%) occur among gay and other MSM.\textsuperscript{20} Homophobia and homonegativity promote HIV transmission. Negative attitudes about homosexuality have been translated into legal and policy restrictions on sexual behaviors (eg, sodomy) and relationships (eg, marriage) among gay people. These restrictions tend to marginalize and exclude gay people and drive their relationships underground. Thus, many MSM do not publicly identify (or self identify) as “gay,” or seek HIV prevention and sexual health information services targeted to gay communities. Internalized homonegativity has been associated with unprotected anal intercourse, a major route of HIV transmission, particularly for gay and other MSM.\textsuperscript{21}

About 12\% of new HIV infections in the United States occur among injecting drug users.\textsuperscript{22} Lack of access to sterile needles and syringes and addiction treatment programs contributes to the spread of HIV among injectors, their sex partners, and others within their social/sexual networks.\textsuperscript{6} Although harm reduction services markedly decrease HIV incidence and prevalence,\textsuperscript{22} their availability is limited, in large part because of the ban on the use of federal funds to support syringe exchange programs that existed under US law until January 2010 and the persistent shortage of addiction treatment and substitution therapy programs.\textsuperscript{6} Despite the fact that drug misuse and addiction are fundamentally biological, psychological, and social problems manifest at the individual level, society dictates the availability of programs and services to combat them. Resistance to harm reduction efforts is ideological and political; the United States has adopted a no-tolerance approach, aggressively criminalizing drug use but with relatively little public health response.

Criminalization of drug users and the war on drugs have helped make US incarceration rates the highest in the world,\textsuperscript{23} about 1\% of Americans were incarcerated in jail or prison in 2007.\textsuperscript{24} Blacks and Hispanics are imprisoned at dramatically disproportionate rates—not only because of the war on drugs, which has targeted blacks,\textsuperscript{25} but also because of pervasive ongoing racial disparities in sentencing related to many other types of convictions.\textsuperscript{26} High incarceration rates disrupt sexual partnerships, impoverish individuals and communities, and alter the ratio of men to women that, together, help drive sexual network patterns, and ultimately increase the vulnerability of communities and individuals to HIV infection.\textsuperscript{16}

HIV prevalence is higher in the United States among people who are poor than among those who are not poor.\textsuperscript{27} A number of pathways link poverty and HIV infection.\textsuperscript{16} For example, poverty decreases health care access, which can increase the duration of treatable sexually transmitted diseases, which facilitate HIV transmission.\textsuperscript{28} Targeted marketing of crack cocaine to poor neighborhoods\textsuperscript{29} increases residents’ risk of exposure to crack use and exchange of sex for drugs. Poverty increases the risk of unstable housing and homelessness, which in turn increase likelihood of HIV risk behaviors.\textsuperscript{30}

**STRUCTURAL INTERVENTIONS TO TARGET SOCIAL DETERMINANTS**

A number of structural approaches effect policy–legal changes, enable environmental changes, shift harmful social norms, catalyze social and political change, or empower communities and groups to address social drivers that fuel HIV in the United States. Some are well researched and documented by strong empirical evidence, and others have sociological plausibility\textsuperscript{31} but have not yet been connected as directly to HIV/AIDS.

**Structural Interventions With Evidence of Efficacy**

**Comprehensive Sex Education With Access to Male and Female Condoms**

Sex education is an essential HIV prevention strategy, and access to accurate sexual health information is a fundamental human right.\textsuperscript{31,32} Comprehensive sex education programs include respectful acknowledgement of gender and sexual diversity, and health promotion and disease prevention information and access to the tools to engage in safer sex (ie, condoms). Such programs have frequently met with opposition at federal, state and local levels despite their effectiveness in decreasing risky sexual behaviors (promoting delayed initiation of intercourse, reduced frequency of intercourse, decreased number of sex partners) among young people.\textsuperscript{33,34} Nevertheless, broad implementation of comprehensive sex education and condom availability through, for example, contingent funding policies ought to and can be put in place now as a structural intervention with potential for significant impact in reducing both gender and racial disparities in HIV rates.

**Syringe Exchange Programs**

Syringe exchange programs, a harm reduction intervention, aim to reduce risk of disease transmission in the context of continued drug use. These programs, usually initiated by community-based organizations and advocates, have demonstrated efficacy in reducing HIV transmission,\textsuperscript{35,36} are cost-effective,\textsuperscript{37,38} and do not promote injection drug use.\textsuperscript{39} However, wider implementation of syringe exchange programs in the United States has been limited by the previous long-standing ban on the use of federal funds to support them, by state and local legal and regulatory restrictions, and, at times, by local community opposition.\textsuperscript{39} The recent policy–legal change allowing federal funding of syringe exchange programs and the guidance documents developed by federal agencies for the use of such funds themselves constitute a structural intervention that should have significant impact on drug-use–driven HIV and hepatitis epidemics in the United States and should mitigate some of the racial disparities in HIV infections.

**Health Care Availability**

Health care availability and quality are important social determinants of health.\textsuperscript{14} Disparities in access to health care are much greater in the United States than in other
industrialized countries and contribute to the dramatic racial and ethnic disparities in rates of chronic diseases, including HIV.\textsuperscript{40} In 2008, 46.3 million people in the United States (15.4\% of the population) lacked health insurance.\textsuperscript{41} Health care reform, a structural intervention that was finally enacted in 2010, should substantially reduce the number of uninsured persons. Effective health care involves access to services and medications shown to be effective, such as HIV testing and antiretroviral therapy.

### Stable Housing

A growing body of evidence indicates that provision of stable housing is an effective strategy for both reducing HIV-associated risk behaviors and increasing access to care and adherence to antiretroviral medications.\textsuperscript{32,45} Guaranteed housing, provided through laws and subsidies, would not only affect a substantial number of the estimated 3.5 million people in the United States who experience homelessness annually\textsuperscript{45} but would also decrease morbidity from HIV/AIDS and numerous other chronic diseases.

### Sociologically Plausible Structural Interventions

Most of the structural interventions mentioned above target immediate conditions of social life that increase vulnerability to HIV and its negative health outcomes. Few evaluated interventions actually target the social determinants that underlie those conditions—that is, those that render people homeless or drug addicted in the first place.\textsuperscript{45} Nevertheless, there is substantial sociological plausibility that addressing these upstream factors would decrease the domestic HIV epidemic.

For example, as noted earlier, the high incarceration rates in the United States that contribute to the domestic HIV epidemic, especially among blacks and Hispanics, are maintained in part by pervasive and ongoing racial disparities in sentencing.\textsuperscript{50} One of the stated goals of the Department of Justice’s Strategic Plan for fiscal years 2007 through 2012 is to ensure fair and efficient administration of justice.\textsuperscript{46} Yet none of the objectives selected to achieve this goal involves addressing sentencing disparities. While passage of legislation decreasing sentencing disparities between crack and powder cocaine convictions constitutes a major step forward,\textsuperscript{47} incarceration’s impact on HIV and a host of other societal problems makes elimination of the persistent racial bias in sentencing for all crimes an obvious target.

Early childhood academic enrichment programs can lead to improved mental health outcomes, higher socioeconomic status, and lower rates of participation in crime.\textsuperscript{48–50} Health outcomes have improved after income supplementation.\textsuperscript{51,52} Investments in disadvantaged children and adults can reduce crime and improve economic productivity, realizing positive economic returns.\textsuperscript{53} Given the pathways that link low educational attainment, poverty, incarceration, and HIV in the US epidemic, such investment would likely decrease not only HIV infection rates but also other disease outcomes.

Similarly, structural interventions that decrease poverty should be evaluated and implemented. Microfinancing and cash-transfer interventions have been tested in developing countries\textsuperscript{10} and, to a much lesser degree, in the United States.\textsuperscript{54} Projects are currently being piloted in the United States as structural interventions to decrease the economic dependency that promotes high-risk behaviors and resultant HIV infection (Kevin Fenton, personal communication, July 8, 2010).

### CONCLUSIONS: IMPLEMENTATION AND RESEARCH

Addressing the social determinants of the domestic HIV epidemic through widespread implementation of structural interventions, although essential, is not without scientific and political challenges. Establishing the evidence base for the efficacy and effectiveness of such interventions requires seriously embracing this approach as a legitimate research pursuit and expanding efforts beyond the traditional biomedical and behavioral research paradigms. Research must clearly trace the pathways between social determinants and HIV infection and develop new methodologies to develop and test structural interventions to disrupt these pathways.\textsuperscript{49} Given the scope and scale of this research, it will require development and strengthening of collaborations among communities, academia, government, and the private sector.\textsuperscript{52} Findings from such research will help convince the public, policy makers, and funders that understanding and successfully addressing the social and structural determinants of HIV infection in the United States will ultimately save money and help us achieve the goals of the National HIV/AIDS Strategy.

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Challenges in the Design of HIV Prevention Trials in the United States

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Abstract: The design of studies evaluating the safety and efficacy of interventions for HIV prevention is challenging in the US context, where there is low generalized prevalence. HIV incidence is sufficiently high in the at-risk US population of men who have sex with men that prevention trials using HIV infection end points are feasible. In other US populations at higher risk of HIV exposure, efficacy trials of HIV prevention are likely not feasible. However, for interventions where efficacy is already established, conducting trials that test different implementation strategies in these populations could provide definitive evidence about how to achieve high levels of coverage.

Key Words: prevention trial, trial design, HIV seroincidence, implementation

PUBLIC HEALTH IMPACT AND HIV PREVENTION

Three elements are essential if an HIV prevention program is to meaningfully reduce the annual rate of new HIV infections in the United States.

1. A large identifiable target population that is at risk for exposure to HIV.
2. An intervention with established effectiveness in the target population.
3. A mechanism for delivery and uptake of the intervention by a substantial fraction of the target population.

Programs to prevent mother-to-child transmission of HIV illustrate a case that has achieved considerable impact: The population of pregnant women with HIV infection is identifiable (although not large in the United States); a variety of antiretroviral regimens in the mother and the newborn infant have efficacies ranging from 33% to 98%; and high coverage has been achieved using existing antenatal care facilities in the United States. In resource-limited countries, however, achieving high coverage remains the greatest impediment to reducing perinatal HIV transmission. In the United States, other HIV prevention interventions that target small or hard-to-reach populations face a fundamental public health challenge, especially if efficacy is modest. As a hypothetical example, suppose a behavioral intervention for stimulant-using men who have sex with men (MSM) achieves a 30% reduction in HIV transmission. If a quarter of the 50% of new HIV infections attributed to MSM in the United States each year occur in stimulant-using MSM, and 50% coverage of this target population is achieved, we would expect to avert only 2% of the new infections currently occurring annually in the United States (50% new infections in MSM 3 25% occurring in stimulant using MSM 3 50% coverage 3 30% effectiveness).

In this article, we briefly discuss the challenges of designing HIV prevention trials in the context of the US epidemic, utilizing the 3 elements cited above that determine the public health impact of potential interventions.

ELEMENT 1: TARGETING POPULATIONS AT RISK FOR HIV IN THE UNITED STATES

The first prevention design challenge is identifying a population at substantial HIV risk. The general population in the United States is at very low risk, with estimated 56,300 new infections in 2006 and annual incidence of 22 per 100,000. Low event rates necessitate very large studies: In the low incidence setting of the Thai vaccine trial, even though 16,402 volunteers were followed for 3 years, only 132 HIV infections occurred. Thus, research evaluating HIV prevention in the United States needs to be conducted in targeted populations having approximately 100-fold the level of HIV risk in the overall population. As noted in the 2008 Centers for Disease Control and Prevention Surveillance Report and Table 1, the US subpopulations accounting for the highest proportion of newly detected infections are MSM (55%), especially black and Hispanic MSM (32%), black and Hispanic women, primarily at heterosexual risk (20%), and injection drug users (IDUs) (13%). MSM, women, and IDUs have each been enrolled in HIV trials in the United States. Table 2 summarizes seroincidence rates in targeted HIV risk cohorts since 1995. In MSM cohorts at a high risk of HIV exposure, incidence has consistently been above 1.5 per 100...
for blacks and 13 per 100,000 for Hispanic women and Latinas—is low.\textsuperscript{7} Cohorts of women at heterosexual risk, selected for elevated risk of HIV exposure through personal sexual behavior and risk behavior of their sexual partners, have found low HIV incidence (Table 2). A new strategy for identifying women at risk for HIV according to sociodemographic characteristics is being tested in an ongoing study in the HIV Prevention Trials Network (HPTN), the ISIS study (HPTN 064).\textsuperscript{20} However, until we can identify characteristics that distinguish women at a high risk for HIV (ie, 20–40 times the background rate) and until we can demonstrate the ability to recruit and retain such women in a trial, the feasibility of conducting studies of the efficacy of new interventions for reducing HIV risk in such US populations is limited.

IDUs in cities with high HIV prevalence are readily identifiable and have been successfully enrolled and retained in HIV seroincidence studies (Table 2). However, the number of new HIV/AIDS cases attributed to injection drug use in the United States has fallen steadily since 1993,\textsuperscript{21} and recent US cohorts of IDUs with high risk for HIV exposure through needle use have had low HIV incidence, even in settings of high HIV prevalence (Table 2). Ironically, the study of prevention interventions for IDUs cannot proceed unless it is possible to enroll a large IDU population that remains at risk for HIV.

Heterosexual HIV risk can be identified through cohorts of HIV discordant couples. The National Institute of Mental Health and State and local health departments continue to enroll women and men at high HIV risk through personal sexual behavior and risk behavior of their sexual partners. The results of Table 2 show that such efforts are feasible even in settings of high HIV prevalence.
Health’s EBAN study enrolled 535 US African American discordant couples in stable relationships. But HIV incidence was low (Table 2), and the study took 4 years to accrue, making this population, too, challenging to be utilized for studying HIV prevention interventions in the United States.

**ELEMENT 2: EFFICACY TRIAL DESIGN IN A US TARGET POPULATION**

The design of randomized clinical trials to test prevention efficacy is intimately linked to the specifics of an intervention, its intended mechanism, and its target population. An intervention that targets HIV-uninfected individuals is most efficiently studied with an individually randomized design. These have been used in most HIV prevention trials, with targeted intervention efficacies ranging from modest decreases (25%–35%)\textsuperscript{12,11,22,23} to substantial reductions (50%–60%).\textsuperscript{24–28} The resources required to evaluate HIV prevention interventions increase exponentially with decreased effectiveness and linearly with decreased incidence of HIV infection: In an individually randomized trial, to achieve 90% power with 1-sided 2.5% false-positive error rates for detecting anticipated effectiveness of 50%, 40%, and 30%, it requires 88, 161, and 330 events, respectively. For a trial with (control arm) incidence of 2.0 per 100 person-years, achieving these targeted numbers of events requires planning for 5866, 10,062, and 19,412 person-years of follow-up, respectively; a rate of 1.0 per 100 person-years requires double the person-years of follow-up. Given these constraints, it would be feasible to conduct individually randomized trials in the United States with HIV incidence end points in MSM populations. But trials in other risk populations in the United States are not feasible until we are able to identify substantial subpopulations with HIV risk levels similar to the risk found in MSM cohorts.

Interventions that target HIV-infected persons to prevent sexual transmission to their HIV-uninfected partners require an HIV discordant couple or community randomized design. The resources required to enroll and follow a discordant couple cohort are close to double that of an individually randomized design, which largely offsets the potential design efficiency achieved from relatively high incidence. It should also be noted that a substantial fraction of the transmissions in the HIV-uninfected partner may occur outside the couple,\textsuperscript{29} resulting in a dilution of effectiveness and consequently necessitating an increase in the sample size. Finally, discordant couple studies require stable long-term partnerships—short-term partnerships compromise the study design because HIV-uninfected partners who leave the partnership are no longer exposed to the intervention (dilution of the effect) and new partners identified after randomization may be subjected to referral bias. In sub-Saharan Africa, HIV discordant couples have been rapidly accrued, and HIV seroincidence has remained sufficiently high to allow successful completion of prevention trials with HIV end points,\textsuperscript{29,30} a situation that has not yet been replicated in stable discordant couples in the United States.\textsuperscript{16} Discordant partner studies appear better suited to generalized epidemic settings such as sub-Saharan Africa, where the high prevalence of stable discordant couples facilitates rapid accrual, rather than to the United States, where the epidemic is concentrated in specific risk populations.

Structural interventions or community-wide delivery of prevention services mandate a community randomized trial (CRT) design to evaluate effectiveness.\textsuperscript{31–33} However, CRTs are inevitably more costly than individually randomized trials. Several factors lead to increased study size for CRTs: partial coverage and/or adherence lead to effect dilution; correlation of outcomes within a community increases the variance of the estimated intervention effect; and the intervention mechanisms of action are often indirect. For example, in Project ACCEPT (HPTN 043), a CRT of mobile voluntary counseling and testing,\textsuperscript{33} only a subset of the community (ie, those who receive voluntary counseling and testing) experience the intervention, diluting the anticipated effectiveness. Also, the expected mechanism of action—decreasing risky behavior in HIV-infected individuals through awareness of their infection—results in indirect protection of HIV-uninfected individuals. Finally, underlying variation in the HIV epidemics across communities leads to a need for a large number of participating communities to detect an intervention effect.

Conducting HIV prevention CRTs in the United States presents unique difficulties. First, defining communities in the United States is challenging. The ideal community is closed: to prevent contamination and/or dilution of the intervention effect, neither people nor the intervention would travel among communities during the trial. High mobility and efficient communication in the US adult population makes defining a community problematic and may result in rapid diffusion of the intervention between control and intervention communities. Second, low incidence in the general US population means that HIV incidence must be measured in a sentinel population, raising concerns about bias, retention, and generalizability. These factors are particularly relevant for a HIV prevention community randomized trial because the intervention effect may take several years to be fully realized,\textsuperscript{34} thereby requiring the communities to remain largely intact (ie, stable, with constant background prevention efforts) for an extended period.

Given the low incidence in most US populations, surrogate end points such as self-reported behaviors, viral load, or acquisition of other sexually transmitted infections are often proposed as more feasible outcomes. Ideally, a surrogate end point lies in the causal pathway between the intervention and the end point (HIV incidence) and captures the entire intervention effect.\textsuperscript{35} Unfortunately, none of these surrogates have proved reliable as a proxy for HIV incidence, and the use of imperfect surrogates can be misleading. A potentially useful role for surrogate end points in HIV research in the United States might be in the evaluation of strategies for the implementation of known effective interventions.

**ELEMENT 3: DESIGNS TO STUDY IMPLEMENTATION STRATEGIES FOR HIV PREVENTION IN THE UNITED STATES**

For any intervention that is proven to be effective in a trial outside the United States, important research questions remain about implementation in the US setting. Assuming the
evidence for effectiveness from randomized clinical trials is strong and fundamental principles suggest the intervention will be equally effective in US populations, we can conduct rigorous studies that compare methods to achieve high coverage. This addresses the critical third element of public health prevention, delivering the intervention to a substantial fraction of the target population. A comparative study of program implementation strategies is feasible in major populations exposed to HIV risk in the United States, using well-defined program target populations and outcomes that measure program uptake rates.

To illustrate the opportunity for rigorous study of implementation strategies for prevention in the United States, we describe the Test, Link-to-Care Plus Treatment study (HPTN 065: TLC-Plus\(^\text{25}\)), which includes a component designed to assess the impact of financial incentives to achieve high linkage to care and high adherence to antiretroviral therapy for HIV-infected individuals in the United States. Definitive trials are underway to evaluate the efficacy of HIV testing and linkage to care for HIV prevention\(^\text{35}\) and the efficacy of antiretroviral treatment for prevention of HIV transmission.\(^\text{96}\) However, there is clear therapeutic benefit for the HIV-infected person in improved linkage to care and treatment.

TLC-Plus will compare the use of financial incentives to the standard of care for linking newly diagnosed and out-of-care HIV-infected patients to a medical provider, using a cluster randomized trial design, with 40 HIV test facilities assigned at random to either strategy. For HIV-infected participants who have initiated antiretroviral therapy, 40 medical care facilities will be cluster-randomized to compare financial incentives with the standard of care for achieving viral suppression, which for most is achieved through high adherence to antiretroviral therapy. In most prevention trials, specific procedures and facilities must be developed for collecting outcome data. TLC-Plus will use the US national HIV/AIDS surveillance systems maintained by local health departments and funded and supported by the Centers for Disease Control and Prevention to evaluate key trial end points—the proportion of cases linked to care for each test facility and the proportion of a care facility’s patients with suppressed viral load—using laboratory tests captured in the surveillance data. Using these process outcomes, the trial is well powered to assess the financial incentive strategies.

CONCLUSIONS

HIV prevention efficacy trials can be conducted efficiently only in large target populations having HIV incidence rates that are at least as high as approximately 2 per 100 person-years; the only risk population in the United States that currently meets this requirement is MSM. Ongoing efforts are needed to understand how to target high-risk subgroups within other major populations affected by HIV.

Rigorous trials for evaluating how to implement effective HIV prevention interventions are feasible within the United States because coverage and uptake are the primary outcomes of interest. These trials are likely to be community based and conducted in tandem with pilot program implementation. Compared with efficacy trials, such trials could be rapidly completed. The national HIV/AIDS surveillance data provide a unique and promising resource for assessment of community-based implementation trials within the HIV-infected population.

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Lessons From Africa

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Abstract: Delayed access to HIV care and treatment in sub-Saharan Africa meant that the early years of HIV scale-up were characterized by a largely North-to-South transfer of knowledge and resources. Clinicians from wealthy countries were among the first to gain experience with antiretroviral treatment and care of people living with HIV and shared key lessons with their colleagues in sub-Saharan Africa. Ten years later, lessons from Africa learned from the remarkable achievements of HIV programs now have the potential to inform the response to the US domestic epidemic.

Key Words: HIV scale-up, program implementation, lessons, Africa

(J Acquir Immune Defic Syndr 2010;55:S141–S143)

INTRODUCTION

The global response to the HIV epidemic has often been perceived as a North-to-South transfer of expertise, as well as resources. Because HIV care and treatment, including antiretroviral therapy (ART), were first widely available in wealthy countries, practitioners from the United States, western Europe, and similarly well-resourced settings were among the first to gain experience treating people living with HIV (PLWH, the first to develop clinical guidelines, and the first to design and implement HIV service delivery programs. The delayed initiation of HIV care and treatment programs in sub-Saharan Africa created a “lost decade,” in which millions of PLWH were deprived of life-saving interventions and only a few African clinicians gained experience with HIV care and treatment. When resources finally became available, key insights from years of experience in the North informed the scale-up in the South. Examples include the importance of combination ART and the perils of sequential monotherapy, the critical role of retention in care and adherence to treatment, the need for multidisciplinary teams of providers, and the key role for PLWH in shaping the response to the HIV epidemic. These principles are now accepted as fundamental to effective HIV programs.

Times have changed, however, and the flow of information and experience is no longer a one-way street. Clinicians and public health practitioners in many lower-income countries have rapidly acquired proficiency in the prevention, care, and treatment of HIV and now lead the development and implementation of their national guidelines and trainings. The response to the African HIV epidemic has provided successful models of rapid program scale-up and highlighted the fact that global health requires global financing. Fiscal sustainability is unlikely to be achieved in the near future, but technical sustainability is much more promising. Although funds and technical assistance from the global North are still welcome and necessary in many settings, local solutions and expertise often provide the most effective interventions. This new equilibrium highlights the fact that innovations and best practices are generated worldwide—and that South–South and South–North transfers and technical assistance have important roles to play. Indeed, despite marked differences in the magnitude and characteristics of the HIV epidemics in the United States and in sub-Saharan Africa, the response to the US HIV epidemic may be enhanced by some of the lessons learned from the enormous success of HIV program scale-up in Africa.

CONTRASTING REALITIES

Sub-Saharan Africa has a generalized HIV epidemic with high seroprevalence rates in many countries, although recent data indicate that specific subpopulations are more severely impacted. For example, young women in southern Africa are at particular risk for HIV infection when contrasted with young men of the same age, and there are high rates of HIV infection among drug users and men who have sex with men in some countries.1 In contrast, the overall HIV prevalence in the United States is much lower, and the US epidemic is a localized one, with foci of high prevalence rivaling that in some parts of sub-Saharan Africa, particularly among men who have sex with men and African Americans.2

Another contrast is the state of health systems in the United States compared with those in sub-Saharan Africa. In 2007, per capita total expenditure on health was $7285 in the United States, compared with $819 in South Africa, $79 in Zambia, and $39 in Mozambique.3 Out-of-pocket expenditures represent 12% of the total health expenditures in the

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United States, compared with 33% in the African region as a whole. There is a glaring difference in the availability of health workers, with approximately 27 physicians and 560 health workers per 10,000 inhabitants in the United States compared with 2 and 23 per 10,000 inhabitants in the African region. The United States has 31 hospital beds per 10,000 people, compared with 1.8 in Ethiopia, 4 in Côte d’Ivoire, and 13 in Lesotho. In 2007, healthy life expectancy at birth was 70 years in the United States and 45 years in the African region. Although precise data are lacking, PLWH in the United States have far greater access to HIV care and treatment than those in Africa. However, the US response to the HIV epidemic has not been without its challenges, including continued HIV transmission and disparities in access to HIV services.

LESSONS FROM AFRICA

The response to HIV in Africa is as diverse and heterogeneous as the epidemic itself, with important within-country and between-country differences. Although generalizations about the 47 different countries in sub-Saharan Africa are not always helpful, several recurrent lessons have emerged. We note that these innovations are not limited to the African region and that additional important lessons are available from around the world.

- **National plans:** Since 2004, the UNAIDS has emphasized the importance of the “Three Ones”: a single national AIDS coordinating authority, a single national HIV/AIDS action framework, and a single national monitoring and evaluation system for HIV programs. Countries such as Kenya and Ethiopia have had national plans for years, with targets and budgets supporting concrete objectives and activities. Although clinical guidelines have been available for many years, the United States released its first-ever National HIV/AIDS Strategic Plan in 2010.

- **Targets and accountability:** The United States can learn from many African countries that have developed specific numeric targets for HIV testing, care, and treatment based on the best available information about the local prevalence and need. Enrollment and coverage targets have been developed for the site, district, province, and national levels, and the progress against targets is reported and shared. In Ethiopia, for example, the Federal Ministry of Health and the Federal HIV/AIDS Prevention and Control Office publish monthly data on the enrollment in HIV care and ART for each region, and for every health care facility providing HIV services in the country. ART coverage is an indicator in WHO’s World Health Statistics report, which publishes annual estimates of national ART coverage among people with advanced HIV infection and prevention of mother-to-child transmission coverage among HIV-infected pregnant women in more than 100 countries; these data are difficult to ascertain for the United States.

- **Algorithmic guidelines:** The development of simple algorithmic HIV treatment guidelines in response to physician shortages has enabled not only rapid scale-up of HIV services but also the standardization of first- and second-line treatment, streamlined drug procurement, and task shifting from physicians to nurses and other health workers. In many settings, these guidelines have also averted the “pharmacologic chaos” seen in some resource-rich settings, in which personalized prescribing and disregard of guidelines can devolve into unnecessarily complex care, over-use of laboratory investigations, and even reported misuse of ART.

- **Know your epidemic:** With the exception of data from the National Health and Nutrition Examination Survey, the United States lacks the detailed information found in Demographic Health Surveys, Multiple Indicator Cluster Surveys, antenatal sentinel surveillance, and initiatives such as the 2007 Kenya AIDS Indicator Survey, which provides a detailed and profoundly useful snapshot of the epidemic in that country. On the other hand, national disease surveillance systems (especially those based on case reporting) are typically much more robust in resource-rich settings like the United States.

- **Task shifting:** Driven by a critical shortage of physicians and nurses, the HIV response in sub-Saharan Africa has been characterized by health workforce innovations, task shifting, and task sharing. For example, in some countries, nurses and clinical officers can now prescribe and/or refill antiretroviral medications, whereas in the United States, these activities are limited to physicians and nurse practitioners. Similar vision and creativity about professional roles and responsibilities may help the United States face one of its key challenges—substantially expanding and improving HIV screening and testing programs, identifying the estimated 250,000 undiagnosed HIV-infected individuals, and linking them to care and treatment services and providing services to an increased number of newly identified PLWHs. In addition, addressing the disparities in access to services for PLWHs as priorities in the national HIV strategy will require availability of ever increasing numbers of providers.

- **Diagnostics and case finding:** Although countries in sub-Saharan Africa have a long way to go in achieving broad access to HIV testing for their populations, these same countries were quick to adopt rapid HIV testing assays, utilizing algorithms that do not include Western blot assays. They also pioneered the provision of such testing by lay workers trained to perform rapid HIV tests in mobile, community, and even home-based settings. At health facilities, provider initiated point-of-service screening for HIV enables rapid testing at multiple venues, from antenatal care, to tuberculosis (TB) clinics, to outpatient departments.

- **Integration of services:** Although access to integrated service delivery varies from site to site and country to country, some types of integrated services are often more developed and more accessible in African programs than in the United States. The integration of HIV and TB services, including TB screening for patients with HIV and HIV testing for patients with TB, is one example; the use of antenatal care programs for the provision of prevention of mother-to-child transmission and the identification and enrollment of women and families with HIV into HIV services is another.

- **Research:** Studies conducted in sub-Saharan Africa have contributed substantially to the world’s knowledge base on HIV/AIDS, directly influencing practice elsewhere. After years of productive research in descriptive and analytic
epidemiology focusing on natural history, risk factors and disease associations. Africa is now a vibrant setting for clinical trials of relevance worldwide, in areas such as prevention and treatment of HIV-associated tuberculosis, HIV prevention, microbicides, and other interventions.\textsuperscript{16–19}

**CONCLUSIONS**

Despite the horrific impact of the HIV epidemic, it has also triggered an outpouring of solidarity within and between nations. Again and again, we see the impact of generous support from individuals, communities, and countries. Although common wisdom suggests that financial and technical inputs from resource-rich settings can and should continue to inform the design and implementation of HIV programs in the global South when appropriate, the potential benefits of South–South and South–North contributions should also be acknowledged. Remarkable innovations have germinated in Africa in the process of scaling up HIV prevention, care, and treatment programs; many of these can inform the response to the HIV epidemic. As the United States continues its quest to control the epidemic in its midst, we should pause and consider what we can learn from Africa.

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Abstract: In July 2010, the Obama Administration released a National HIV/AIDS Strategy for the United States to refocus national attention on responding to the domestic HIV epidemic. The goals of the strategy are to reduce HIV incidence; to increase access to care and optimize health outcomes among people living with HIV; and to reduce HIV-related disparities. The strategy identifies a small number of action steps that will align efforts across federal, state, local, and tribal levels of government, and maximally impact the domestic HIV epidemic. In this article, we outline key programmatic and research issues that must be addressed to accomplish the prevention goals of the National HIV/AIDS Strategy.

Key Words: HIV/AIDS, National, Obama, President, strategy (J Acquir Immune Defic Syndr 2010;55:S144–S147)

INTRODUCTION

More than 1.1 million people are living with HIV in the United States, and more than 56,000 Americans become infected with HIV each year.1,2 Notwithstanding our nation’s significant achievements in caring for people with HIV and the development of effective therapies, our ability to address the domestic epidemic depends on sustaining and expanding successful prevention strategies.

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In July 2010, the Obama Administration released a National HIV/AIDS Strategy for the United States, which represents an effort to refocus national attention on ending the domestic HIV epidemic.3,4 The strategy is structured around 3 key goals and is intended to identify a small number of action steps to focus and align efforts across federal, state, local, and tribal levels (Table 1). Although the nation initially succeeded in reducing new HIV infections from 130,000 per year in the 1980s to 56,000 in the 1990s, overall HIV incidence in the United States has remained stable for more than a decade and continues to increase among men who have sex with men, while remaining stable or decreasing in other populations.1,5

The National HIV/AIDS Strategy sets a goal of reducing annual incidence by 25% by 20156 and recently published mathematical models confirm that this goal is achievable.7 To achieve this result, we must refocus prevention efforts on those communities at greatest risk. The nation must also adopt a more strategic and coordinated approach that utilizes a combination of effective HIV prevention interventions and stimulates innovation to develop additional effective scalable tools.

IMPROVING OUR PROGRAMMATIC RESPONSE TO REDUCE HIV INCIDENCE

Analogous to antiretroviral therapy (ART), which is highly effective when multiple medications are combined, effective prevention should involve multiple interventions to reduce risk behavior, reduce opportunities for transmission, and lower biological susceptibility of transmitting or acquiring infection. Despite the availability of evidence-based behavioral and biomedical tools that reduce HIV transmission or HIV risk (Table 2), the challenge for federal agencies and state and local partners responsible for delivering prevention services is understanding which combinations of prevention interventions will produce the most robust results in specific high-risk communities.

There is significant potential to reduce HIV transmission by scaling up prevention interventions targeting people who are diagnosed with HIV. Although studies show significant reductions in the HIV transmission rate when people with HIV are tested and learn their status, some HIV-infected individuals continue to engage in high-risk behaviors with partners who are HIV negative or of unknown status.7 For these HIV-infected individuals, it is important to provide a tailored approach that promotes physical, emotional, and sexual health.
TABLE 1. National HIV/AIDS Strategy Goals and Targets*

<table>
<thead>
<tr>
<th>Strategy Goal</th>
<th>Recommended Action Steps</th>
<th>Targets by 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce HIV incidence</td>
<td>1. Intensify HIV prevention efforts in communities where HIV is most heavily concentrated</td>
<td>1. Lower the annual number of new infections by 25% (from 56,300 to 42,225)</td>
</tr>
<tr>
<td></td>
<td>2. Expand targeted efforts to prevent HIV infection using a combination of effective, evidence-based approaches</td>
<td>2. Reduce the HIV transmission rate (a measure of annual transmissions in relation to the number of people living with HIV) by 30%, from 5 persons infected each year per 100 people with HIV to 3.5 persons infected each year per 100 people with HIV</td>
</tr>
<tr>
<td></td>
<td>3. Educate all Americans about the threat of HIV and how to prevent it</td>
<td>3. Increase from 79% to 90% the percentage of people living with HIV who know their serostatus (from 948,000 to 1,080,000 people)</td>
</tr>
<tr>
<td>Increase access to care and optimize health outcomes for people living with HIV</td>
<td>1. Establish a seamless system to immediately link people to continuous, coordinated quality care when they are diagnosed with HIV</td>
<td>1. Increase the proportion of newly diagnosed patients linked to clinical care within 3 mo of their HIV diagnosis, from 65% to 85% (from 26,824 to 35,079 people).</td>
</tr>
<tr>
<td></td>
<td>2. Take deliberate steps to increase the number and diversity of available providers of clinical care and related services for people living with HIV</td>
<td>2. Increase the proportion of Ryan White HIV/AIDS Program clients who are in care (at least 2 visits for routine HIV medical care in 12 mo at least 3 mo apart) from 73% to 80% (or 237,924 people in continuous care) to 260,739 people in continuous care)</td>
</tr>
<tr>
<td></td>
<td>3. Support people living with HIV with co-occurring health conditions and those who have challenges meeting their basic needs, such as housing</td>
<td>3. Increase the percentage of Ryan White HIV/AIDS Program clients with permanent housing from 82% to 86% (from 434,000 to 455,800 people)</td>
</tr>
<tr>
<td>Reduce HIV-related disparities</td>
<td>1. Reduce HIV-related mortality in communities at high risk for HIV infection</td>
<td>1. Increase the proportion of HIV-diagnosed gay and bisexual men with undetectable viral load by 20%</td>
</tr>
<tr>
<td></td>
<td>2. Adopt community-level approaches to reduce HIV infection in high-risk communities</td>
<td>2. Increase the proportion of HIV diagnosed blacks with undetectable viral load by 20%</td>
</tr>
<tr>
<td></td>
<td>3. Reduce stigma and discrimination against people living with HIV</td>
<td>3. Increase the proportion of HIV-diagnosed Latinos with undetectable viral load by 20%</td>
</tr>
</tbody>
</table>

*The National Strategy identifies gay and bisexual men, black Americans, Latino Americans, and substance users as a primary focus for HIV prevention efforts. A presidential memorandum has identified the Department of Health and Human Services, Department of Justice, Department of Labor, Department of Housing and Urban Development, Department of Veterans Affairs, and Social Security Administration as lead agencies in implementing the strategy at the federal level.

In addition to promoting safer behaviors among people diagnosed with HIV, providing access to and improving the continuity of their care is critical. It is clear that ART both provides clinical benefits for people living with HIV and reduces the risk of transmission.8–10 Recent studies in Denmark, San Francisco, California, and British Columbia, Canada, have found encouraging reductions in HIV incidence associated with the uptake of ART by the majority of known positives.11–13 However, an estimated 30% of people living with HIV in the United States who are clinically eligible for ART are not receiving medical care and an additional 15% receiving medical care are not receiving ART.14 Individual

TABLE 2. HIV Prevention and Risk Reduction Tools for HIV-Negative and HIV-Positive Individuals

<table>
<thead>
<tr>
<th>Individual</th>
<th>Interpersonal</th>
<th>Community</th>
<th>Structural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention with HIV-negative individuals</td>
<td>Screening for HIV and sexually transmitted infections</td>
<td>Network-based methods to get individuals in high-risk communities tested for HIV</td>
<td>Availability of postexposure prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Postexposure prophylaxis</td>
<td>Prevention services for partners of HIV-infected individuals</td>
<td>Access to condoms</td>
</tr>
<tr>
<td></td>
<td>Risk reduction interventions (sexual and alcohol and other drug-related behaviors)</td>
<td>Utilizing disease intervention specialists and peer advocates to link and keep diagnosed individuals in care</td>
<td>Syringe services programs</td>
</tr>
<tr>
<td>Prevention with HIV-positive individuals</td>
<td>Diagnosing undiagnosed positives</td>
<td>Serosorting and safer sex counseling</td>
<td>Reducing community viral load</td>
</tr>
<tr>
<td></td>
<td>Linkage to continuous care</td>
<td>For HIV-positive individuals in serodiscordant partnerships</td>
<td>Syringe services programs</td>
</tr>
<tr>
<td></td>
<td>Sexually transmitted infections diagnosis and treatment</td>
<td>HIV status disclosure</td>
<td>Access to condoms</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral therapy</td>
<td>Risk reduction counseling</td>
<td>Social marketing efforts</td>
</tr>
<tr>
<td></td>
<td>Prevention of mother-to-child transmission</td>
<td>Condom provision and utilization</td>
<td></td>
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<tr>
<td></td>
<td>Medication adherence support</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk reduction interventions (sexual and alcohol and other drug-related behaviors)</td>
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</tbody>
</table>
clinical outcomes and population-level outcomes can be improved by increasing rates of ART usage when it is clinically indicated, as well as ART adherence. Although the decision to start ART is a personal one that every individual with HIV should discuss with his or her clinician, all HIV-infected persons in the United States should have access to uninterrupted health care that is coordinated and of high quality.

There is also an opportunity to improve our programmatic response to identifying individuals with unrecognized HIV infection. Approximately half of new sexually acquired HIV infections in the United States are transmitted by 21% of HIV-infected people who are unaware of their HIV status. Although guidelines for HIV testing in clinical settings have been in place since 2006, these recommendations have not been widely implemented. Routine HIV screening among targeted communities in reproductive health and sexually transmitted disease clinics, in emergency departments, in addiction treatment programs, and among partners of HIV-diagnosed individuals may reduce missed opportunities to identify and treat those with HIV. It is also important to concentrate testing resources in communities where testing is most likely to identify new, as well as chronic unrecognized infections. Expanded HIV testing efforts targeted among groups at highest risk for HIV infection in the District of Columbia was associated with a reduction in new AIDS diagnoses. Achieving similar outcomes nationally will require increasing provider awareness of HIV testing guidelines and addressing reimbursement disincentives for HIV testing services.

**FUTURE RESEARCH TO REDUCE HIV INCIDENCE**

Additional research is also necessary to help improve the nation’s response to the domestic HIV epidemic. The last 2 years have been marked by significant advances in HIV prevention, particularly in microbicide and vaccine research. However, we must support further research to boost the effectiveness of promising microbicide and vaccine candidates and bring newer candidates through Phase II and III trials. Should existing research studies investigating the effectiveness of preexposure prophylaxis (PrEP) yield positive results, operational research must address how PrEP can best be integrated into comprehensive HIV prevention services for populations at greatest risk for HIV infection, and the provision of PrEP given existing resource constraints. We must also evaluate the degree to which behavioral disinhibition or inconsistent adherence to medications or specific regimens may undercut potential gains from these new prevention technologies.

Research must also continue to test new, more effective, and less costly HIV therapies and drug regimens that can reduce infectiousness with fewer side effects and clinical complications associated with long-term use among people living with HIV. These therapies, however, are effective only if individuals are diagnosed and successfully access care. Additional research is necessary to identify best practices to reach undiagnosed HIV-infected individuals, to link them to care, and, when clinically indicated, to provide medications. We must also develop and deploy better methods for diagnosing acute HIV infection.

Additional behavioral research and rigorous evaluation is needed to minimize decay of behavioral intervention effects and to provide more viable adaptations of effective behavioral interventions in clinic-based and community-based settings. HIV prevention efforts must also continue to move beyond addressing individual HIV risk behavior. Individuals in some disproportionately affected communities—particularly black gay men and black women—remain at greater risk for HIV infection, despite engaging in comparable or less risk than individuals in other communities. Because individual-level risk reduction interventions alone will not meaningfully reduce HIV incidence in some disproportionately affected communities, there must be an improved understanding of network, social, and structural factors that place individuals in specific communities at elevated risk for HIV infection.

**NEXT STEPS**

Thirty years into the HIV epidemic in the United States, it is unrealistic to expect that the National HIV/AIDS Strategy or our recommendations for reducing new infections would be composed entirely of new approaches to prevention. However, the innovation of the national strategy lies in its commitment to building on an evolving evidence base of what works, in identifying common national goals toward which federal, state, local, and tribal governmental partners and community partners can align their efforts, and in a renewed commitment to collaboration and coordination.

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**REFERENCES**

A Prevention Response That Fits America’s Epidemic:
Community Perspectives on the Status of HIV Prevention in the United States

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Abstract: HIV prevention services have succeeded in limiting HIV incidence in the United States but have not prevented HIV from becoming a devastating epidemic in the communities most affected. The National HIV/AIDS Strategy represents an important opportunity to improve domestic HIV prevention efforts and to begin to reduce HIV incidence over time. Elements that are essential to improving HIV incidence outcomes include greater transparency and accountability in use of HIV prevention funds; scaling up programming for those most at risk; fostering and evaluating community-based HIV prevention efforts; and looking beyond individual behavior change programming by putting a greater emphasis on structural, network, and policy interventions. To overcome years of stagnation on HIV prevention outcomes, we need a response characterized by accountability, appropriate targeting, and sufficient scale.

Key Words: accountability, community, prevention, policy, scale, structural

INTRODUCTION
Domestic HIV prevention efforts in the United States can claim important successes over the last 2 decades. HIV incidence has plummeted from its height in the mid 1980s, and the HIV transmission rate has fallen over the years. An evidence base of effective prevention interventions has been established, and it has been estimated that HIV prevention programs averted more than 350,000 new infections between 1991 and 2006.

Yet although delivery of HIV prevention services has helped limit HIV incidence, it has not prevented HIV from becoming a devastating epidemic in the communities most affected. Progress in reducing incidence has stalled for more than a decade, with an estimated 56,000 new infections each year. Wafaa El-Sadr et al point out that the US domestic epidemic is characterized by “low prevalence in the general population, high prevalence among the disenfranchised and socially marginalized, with a concentration in geographic hotspots.” In many important ways, America’s prevention response is not designed to address this kind of epidemic. A more effective and strategic effort would be tailored to the dynamics of local epidemics, would target resources more effectively, and would deliver services appropriate to communities facing a range of health and other challenges.

The National HIV/AIDS Strategy, issued by the White House Office of National AIDS Policy in July 2010, provides a critical opportunity to reform domestic HIV prevention efforts and, ultimately, to begin to lessen HIV incidence over time. The strategy calls for targeting prevention resources where the epidemic is most acute, relying on evidence-based approaches and improving coordination between public and private providers.

Will the national strategy lead to concrete reforms in HIV prevention policy and programming that can accomplish President Obama’s goal of a 25% reduction in HIV incidence by 2015? At least 4 elements are essential to improving outcomes on HIV incidence and realizing the president’s goal, including the following: improved transparency and accountability, scaling up programming for those most at risk, fostering indigenous efforts, and looking beyond individual behavior change interventions.

ADVANCING PREVENTION ACCOUNTABILITY
Accountability for federal HIV program funds is often conceptualized in terms of prudent administration of resources. It is time to expand our notion of accountability to include strategic use of funding to reduce HIV infection rates. Primary questions include whether local epidemic profiles closely inform the targeting of resources; whether local prevention plans are designed with the clear aim of reducing incidence; and whether outcomes are tracked and reported regularly. Evidence to date suggests that use of federal HIV prevention funds by state and local entities is not well matched to the epidemic profile in many jurisdictions.

Some examples of how prevention accountability could be advanced include:

Having Centers for Disease Control and Prevention (CDC) play a more active role in supporting local and state health authorities in use of federal HIV prevention funds.

Particular attention would be placed on ensuring that local...
or state epidemiologic profiles closely inform resource allocation. In the past, CDC staff did periodic program reviews with local and state health authorities. These could be reinstated.

**Asking health departments for “Statements of Alignment.”**

These statements would accompany health departments’ annual reports to CDC, much as departments now must provide a statement of concurrence from community planning bodies. The statements of alignment would either confirm that allocation of prevention funding reasonably matches local epidemic conditions or explain why it does not.

**Improving transparency in the use of prevention funding.**

CDC should annually publish its use of funds—both funds utilized by local and state authorities and those spent by CDC’s central office. This reporting would track allocations toward different activities and target populations.

Similar types of accountability approaches should also be employed at other federal agencies engaged in HIV prevention, including the Substance Abuse and Mental Health Services Administration.

### GOING TO SCALE IN COMMUNITIES AT ELEVATED RISK

Intensive prevention services are not reaching many of those at elevated risk of infection. For example, a 2006 survey indicates that only a relatively small share of gay men and other men who have sex with men (MSM) had participated in HIV prevention interventions during the previous 12 months. A more effective prevention effort will require interventions delivered and sustained at a scale that can have impact on incidence in the communities at the center of the domestic epidemic.

Although numerous studies have established the HIV prevention efficacy of some behavioral interventions, there is scant evidence of the population-level impacts of many HIV prevention approaches. Through the Diffusion of Evidence-Based Interventions program, CDC has identified a variety of HIV prevention programs for which there is evidence of effectiveness. Yet as others have observed, many of these interventions are dated, do not adequately address some groups at elevated risk, and are difficult to deliver at scale.

Isolated small-scale prevention programs alone will not have a major impact in reducing infection rates. A much greater emphasis is needed on developing, testing, and fielding programs that can demonstrate measurable impact on incidence. In many cases, this refocus of emphasis will mean adopting approaches that combine multiple interventions tailored to those at elevated risk. Research portfolios at the National Institutes of Health and CDC should be developed with the goals of advancing knowledge about what will have impact at a population level and expanding operations research that can guide delivery of these interventions in the field.

### FOSTERING COMMUNITY-BASED EFFORTS

Community-based organizations (CBOs) are the frontline in HIV/AIDS prevention and service delivery. They play a major role in translating knowledge and cultural competence among communities of color and other high-risk populations into health promotion and behavior change. CBOs are in a position to understand the unique circumstances that drive HIV infection in the communities they serve, to develop and deliver culturally appropriate HIV prevention and related services to high-risk populations, and to form enduring partnerships with these populations.

Since the beginning of the HIV/AIDS epidemic, CBOs have developed prevention interventions in the response to HIV/AIDS, and among them are culturally competent programs that address the unique needs of racial, ethnic, and sexual minority populations. These interventions were being developed and implemented in the absence of widespread availability of evidence-based HIV behavioral interventions. Most often, the CBOs developed their interventions in collaboration with communities they serve, incorporating innovative strategies and approaches for prevention and demonstrating sensitivity to local populations’ values and norms.

Although the CDC has long recognized the importance of effective and evidence-based interventions with community-based indigenous (home-grown) prevention strategies and interventions and has recently given more attention to their development, greater support is needed for these efforts. Many CBOs need assistance in building organizational capacity; they also need additional resources to evaluate newly developed interventions. Today, many CBO-led evaluations are limited to determining participant satisfaction or are expressed simply as basic outputs (eg, quantities of condoms distributed or numbers of intervention sessions completed). To broaden the reach of locally developed interventions, CBOs need support to evaluate interventions within communities, demonstrate efficacy, and improve the effectiveness.

Perhaps most importantly, CBO-led evaluations will enable the most vulnerable populations to hold their own communities accountable and will help expand the impact of community-based, culturally appropriate, and efficacious HIV prevention interventions that can reach those most at risk.

### LOOKING BEYOND THE INDIVIDUAL

We know that context is key in the HIV epidemic. Individual behaviors are deeply influenced by social, economic, and other factors—a particularly relevant point in this epidemic because many people at elevated risk are part of communities facing multiple concerns. For them, interventions that seek only to affect individual decisions may be insufficient to address the complex factors in personal vulnerability. As Fenton and Dean have written, “It is increasingly unacceptable for those planning and delivering prevention services to claim that addressing SDH (social determinants of health) is outside their jurisdiction.”

The task ahead is to create a system in which those active in health policy and programing are supported in working collaboratively to address social factors. We need a system that fosters far more coordination across providers and establishes funding streams that support action on social determinants. Community Transformation Grants, created by

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health reform, are an important opportunity to address the community context of HIV and other health challenges.

We also know that risk is not determined solely by the behavior of an individual. Far more attention is needed to the dynamics of sexual networks in the HIV epidemic. This is clear from work by Hallfors et al who found that although risk for HIV and STD acquisition is heightened among young white adults who engage in high-risk behaviors, young adults who are black are at elevated risk whether or not their personal behaviors are “high risk.” Wohlfeiler and Ellen call for a “new generation of structural interventions on sexual networks,” that reach people through Internet sex sites, gay sex clubs, and other venues with prevention and testing services and, where appropriate, policy interventions. The authors point out that policy interventions have been fundamental to success of injury and tobacco control and can play an important role in HIV. An example: regulations mandating that sex venues in San Francisco remove doors from private rooms so that monitors can ensure clients practice safer sex. Given mounting evidence of the prevention impact of HIV treatment, wider access to and uptake of HIV treatment is another policy priority in the effort to lower HIV incidence.

The new National HIV/AIDS Strategy presents an important opportunity to improve America’s HIV prevention effort. But to overcome the years of stagnation in prevention outcomes, we need a response characterized by accountability, appropriate targeting, and sufficient scale. We also have to measure interventions by their ability to make an impact at the population level and to ensure that these interventions are addressing the central factors driving incidence.

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