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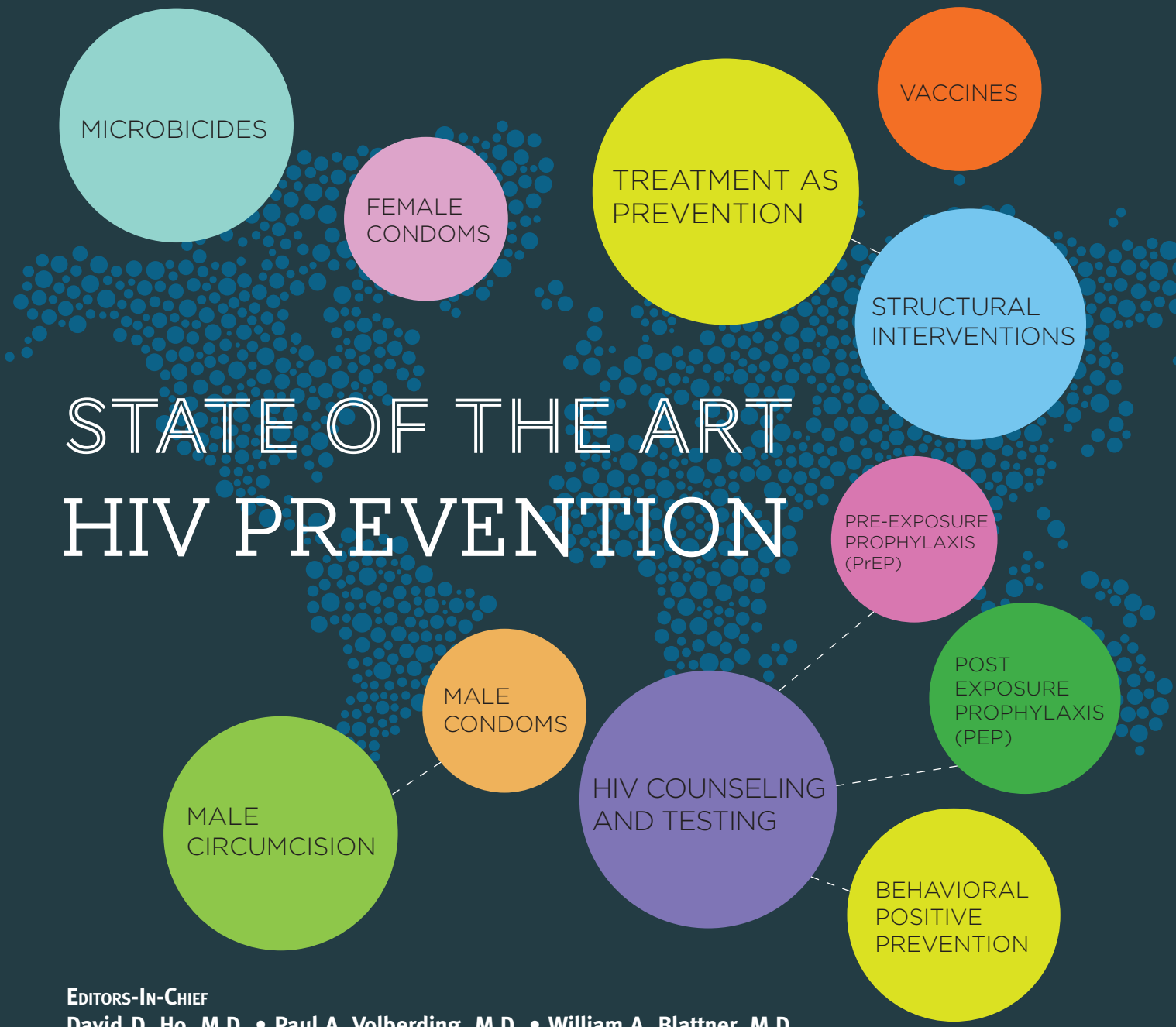

STATE OF THE ART HIV PREVENTION

HIV Prevention: Great Achievements, More Challenges Ahead

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Key Words: HIV prevention, research agenda

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The response to the HIV epidemic has made remarkable advances in the past decade with expansion of access to HIV care and treatment for populations that had hitherto no hope of such treatment.[1] At the same time, it is heartening to note that after many years of limited progress, the field of HIV prevention has been greatly energized by several recent findings. The dawn of the recent optimism began with the release of the results in 2005 and 2007 of 3 randomized clinical trials that demonstrated the efficacy of voluntary medical male circumcision for prevention of HIV acquisition by heterosexual men in sub-Saharan Africa, highlighting this intervention as a potential "surgical vaccine."[2–4] CAPRISA 004 demonstrated the efficacy of vaginal tenofovir gel for the prevention of HIV acquisition by women in South Africa, providing the long-awaited proof of concept for the use of topical microbicides as pre-exposure prophylaxis (PrEP).[5] This finding was followed closely by other evidence of the efficacy of oral antiretroviral drugs for PrEP in men who have sex with men (MSM),[6] discordant couples,[7] and heterosexual women.[8] Concomitantly, the HPTN 052 study generated further excitement with the demonstration of 96% prevention of the sexual transmission of HIV in heterosexual discordant couples in whom the infected sexual partner was on antiretroviral therapy (ART).[9] The latter findings lent credibility to mathematical modeling research, which indicated that expansion of ART could provide substantial impact on HIV incidence.[10,11]

However, the news has not been consistently positive. Further studies failed to confirm the efficacy of oral and topical PrEP due to limited adherence to the antiretroviral regimen provided.[12,13] In addition, the recent failure to demonstrate any efficacy of DNA prime/rAD5 boost vaccine candidate in the HVTN 505 study was a great disappointment.[14]

Nonetheless, the sum of successful biomedical prevention interventions served to inspire the concept of combination prevention in which behavioral, biomedical, and structural interventions are integrated into one strategy that is tailored to a specific population. Remarkably, the advances in HIV prevention science have inspired political leaders and funders to broadly discuss the possibility of an AIDS-free generation, an aspiration that would have seemed impossible at the turn of the century. This optimism is also complemented by encouraging advances in the search for a cure for HIV infection itself.[15]

Yet, this optimism needs to be balanced with sobering facts. Remarkable achievements have been accomplished in terms of scale-up of HIV treatment with approximately 8 million individuals accessing ART by the end of 2011.[1] Similarly, the annual number of new HIV infections has decreased by 50% in 25 countries including 13 countries in sub-Saharan Africa. However, the total numbers of new infections globally remains staggering, with an estimated 2.5 million HIV infections noted in 2011, about 7000 per day. In addition, in certain regions of the world, HIV incidence continues to rise including in Eastern Europe, Central Asia, and the Middle East and Northern Africa, whereas the vast number of new infections continues to occur in sub-Saharan Africa.[1] In the United States, although the annual number of new HIV infections has been stable for the past decade, HIV incidence rates among MSM and particularly black MSM is alarming, and the epidemic remains entrenched.[16] Global prevalence of HIV in MSM, injection drug users, and sex workers is equally alarming, and young women from southern African countries are acquiring HIV infection at staggering rates.[1] Thus, there is an urgent need to apply the knowledge we have to find ways to implement the available efficacious prevention methods to the populations at risk and to demonstrate the effectiveness of such strategies while at the same time continuing the momentum to identify new prevention methods through continued research efforts.

In this supplement of the *Journal of Acquired Immunodeficiency Syndrome*, authors from diverse backgrounds, differing scientific expertise, and disciplines came together to contribute to a compendium on the state of HIV prevention globally. Topics included in this supplement range from prevention of HIV in specific populations such as adolescents, women, MSM, and drug users to discussions of specific

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methods for prevention such as HIV testing, pre-exposure prophylaxis, topical microbicides, vaccines, treatment as prevention, prevention of mother to child transmission, and male circumcision. Other articles address key challenges facing researchers such as the design of PrEP studies in the context of availability of an efficacious product, the use of integrated strategies for prevention that include multiple interventions that are tailored to the needs of specific populations, innovations for cross-sectional estimation of HIV incidence, ethical issues raised by the use of PrEP for prevention, the role of social and behavioral sciences in trials of biomedical prevention interventions, and a new paradigm for behavioral interventions for prevention and treatment of HIV. Important issues addressed in other articles include acute infection, pharmacology of antiretroviral drugs in mucosal tissues, and the future of phylogeny in HIV prevention research. Finally, the supplement also includes an article describing an innovative concept related to the HIV care cascade and another on the role of advocacy for prevention in this new era. Each of the articles highlight what has been achieved, remaining gaps in knowledge, and provides an agenda for future research endeavors. The articles also indicate the large gap that remains between proven interventions and their implementation and scale-up within programs. A recurring theme is the importance of measurement and modeling and critical need for evaluating the effectiveness of combination strategies that include multiple interventions.

Much work remains to be done to better understand the factors that place individuals and populations at risk, to identify safe, acceptable, and cost-effective prevention methods, and to evaluate and implement these interventions, either alone or in combination, where they are most needed. Even in settings where prevention methods may be available, there is the need to generate demand and to enable those who avail themselves of these interventions to maintain ongoing adherence. It is only through a continued commitment to HIV prevention and to the well-being of those living with HIV that we will be able to conquer the HIV epidemic and declare it as a thing of the past.

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Expanding HIV Testing: Back to the Future

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Abstract: The value of HIV testing has grown in parallel with the development of increasingly effective HIV treatment. Evidence for the substantial reductions in transmission when persons receive antiretroviral therapy creates a new impetus to increase testing and early diagnosis. Models of treatment as prevention—dubbed "test and treat"—give reason for optimism that control and elimination of HIV may now be within reach. This will be possible only with widespread testing, prompt and accurate diagnosis, and universal access to immediate antiviral therapy. Many successful approaches for scaling up testing were pioneered in resource-limited countries before they were adopted by countries in the developed world. The future of HIV testing is changing. Lessons learned from other case-finding initiatives can help chart the course for comparable HIV testing endeavors.

Key Words: HIV testing, HIV antibody tests, HIV diagnosis, HIV prevention, policy

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In the era of effective antiretroviral treatment, HIV testing serves as the gateway to improved health and survival among persons with HIV infection and decreased transmission within communities.[1] Persons with HIV reduce high-risk behaviors substantially after they become aware they are infected,[2] and early initiation of antiretroviral therapy reduces both clinical progression of HIV disease and sexual transmission to uninfected partners.[3] Models of treatment as prevention that have inspired optimism about the elimination of HIV transmission are predicated on annual voluntary testing with immediate antiviral therapy.[4,5] However, optimal HIV testing strategies, and their feasibility, acceptability, and cost-effectiveness, have yet to be established.

Although the need to expand HIV testing now seems clear, coming to this perspective required substantial evolution in epidemiology, medicine, policy, politics, and technology. Soon after HIV was first identified, immunoassays for HIV antibody were developed and deployed to screen blood donations, and in developed countries, transfusion-associated transmissions were soon eliminated.[6] However, uncertainty about the prognosis of a positive antibody test and the lack of effective therapy caused skepticism about the value of HIV testing outside the blood donor setting.[7,8] At the first International AIDS Conference in 1985, protesters with posters chanted "No Test is Best."[9] For asymptomatic persons, testing was perceived as an adjunct to HIV counseling for reducing HIV risk behaviors; client-initiated voluntary counseling and testing (VCT) became the norm.[10,11] In the United States, targeted HIV counseling and testing were recommended for persons at increased risk and diagnostic testing was recommended for persons with signs or symptoms of HIV.[12] In many resource-limited countries, HIV testing was limited to screening of blood transfusions[13] and to selected referral centers; testing was typically not available for persons with or without symptoms.[14]

INITIAL EXPANSION OF HIV TESTING

Three developments in the early to mid-1990s began to shift the HIV testing paradigm: accumulating evidence that HIV infection persisted in all persons with HIV antibody,[15,16] demonstration that administering zidovudine (or nevirapine) during pregnancy could prevent mother-to-child transmission,[17,18] and the introduction of simple, inexpensive rapid HIV tests that allowed decentralized testing without sophisticated laboratory equipment.[19–21] Initiatives for prevention of mother-to-child transmission (which included voluntary testing of all pregnant women) extended HIV testing for the first time to populations not thought to be at increased risk.[22] These efforts also stimulated studies of alternative approaches for HIV screening, including routine voluntary (opt-out) testing in prenatal clinics.[23,24] The number of persons tested annually during this early expansion was not well documented in many countries, but surveys show that by 2001 in the United States, 52% of pregnant women reported an HIV test in the past 12 months.[25] Although testing was extremely limited in Africa throughout the 1990s, this changed rapidly in the 2000s, particularly in the context of services for pregnant women. For example, in Kenya, Demographic and Health Surveys indicate the percentage of women reporting testing in the past 12 months increased from 6.7% in 2003 to 29.3% in 2008, and in Lesotho, from 6.3% in 2004 to 42.0% in 2009.[26]

Point-of-care rapid HIV tests quickly revolutionized HIV testing in resource-limited countries, and the use of 2 or more rapid tests for HIV diagnosis was endorsed by the World Health Organization and UNAIDS in 1998.[27] In the developed world, however, various hurdles delayed adoption of rapid tests. Point-of-care rapid HIV tests first became available in the United States in 2002 and in Australia, not until 2012.[28,29] Worldwide, rapid tests moved HIV testing from clinical laboratories to the point of care in health facilities with

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limited laboratory services and to community sites, including dedicated testing sites, religious facilities, schools, workplaces, transport hubs, and homes.[30–32] Mobile services have used creative approaches to deliver HIV testing via vans, trucks, bicycles, and even camels. Notwithstanding, many persons with HIV remain undiagnosed. UNAIDS estimated in 2012 that globally only about 50% of persons living with HIV infection knew their HIV status[33] compared with 82% in the United States by the end of 2009.[34,35]

IMPETUS FOR FURTHER SCALE-UP OF HIV TESTING

Three subsequent developments led to the current efforts to further scale-up HIV testing and case finding: access to antiretroviral therapy in resource-limited settings,[36] increasing evidence that therapy is beneficial for asymptomatic HIV,[33,37] and definitive evidence that antiretroviral therapy can prevent sexual transmission.[3]

In 2004, Botswana introduced routine, opt-out HIV testing; it was widely accepted and seemed to reduce barriers to testing.[38] Lesotho followed in 2005, and in 2006, the US Centers for Disease Control and Prevention (CDC) recommended routine opt-out screening in health-care settings.[39] CDC also launched an expanded HIV testing initiative to facilitate adoption of HIV screening in healthcare settings. From 2007 to 2010, health departments conducted nearly 2.8 million HIV tests under this initiative, of which 29,503 (1.1%) were positive.[40] Among those who tested positive, 62% had been unaware of their HIV infection.

In 2007, World Health Organization issued guidelines recommending provider-initiated testing and counseling in countries with generalized epidemics, and many countries with high HIV burden began to expand HIV testing in the context of health services.[41] For example, funds from President's Emergency Plan for AIDS Relief supported the provision of 1.9 million testing sessions in 2004; this increased to more than 46 million in 2012.[26] However, the rapid expansion of testing services, the increasing reliance on lay testers, and the difficulty of providing supervision and quality assurance raised concerns about accuracy of test results.[42] Although immediate, on-site confirmation from 2 or 3 different rapid tests remains the dominant model in most high-burden countries, concerns regarding quality have led a few countries to consider piloting alternatives, such as screening with only one test in community venues or homes, with referral to HIV care sites after a reactive rapid test result for confirmatory testing and immediate enrollment in care and treatment. Similar strategies have been adopted in the United States in an effort to facilitate entry into HIV care.[43]

With the mandate to scale-up testing, debate ensued between human rights advocates (who expressed concerns about privacy, confidentiality, counseling, and consent) and some clinicians and public health officials (who sought to normalize testing).[44] The latter, asserting that routine HIV testing and case finding were essential to increase access to HIV treatment, feared that the exceptional procedures characteristic of the traditional VCT approach might actually perpetuate the stigma associated with HIV and HIV testing and so limit its availability and acceptability.[45,46] Increasingly, calls appeared for application of traditional public health principles, such as named reporting, routine testing, and partner notification, to the HIV epidemic.[47,48]

The percentage of US adults who had ever been tested for HIV increased from 40% in 2006 to 45% in 2010, but the percentage of those who had been tested in the past 12 months remained unchanged at 10% from 2000 to 2010.[49] Meanwhile, even though emergency departments have long been recognized as promising venues for reaching vulnerable populations disproportionately affected by HIV and for identifying previously undiagnosed HIV infections,[50–52] only 1 in 5 emergency departments had a systematic HIV testing program in place in 2009[53] and few seem to conduct targeted testing based on documented risk factors.[54] Paradoxically, despite enthusiasm for compulsory preoperative and preadmission testing early in the HIV epidemic,[55–57] fewer than half of US hospitals surveyed in 2009 to 2010 intended to implement CDC's recommendations to screen their patients for HIV.[58] The Veterans Administration Health System is a notable exception: the number of unique patients who had an HIV test in the calendar year increased by 268% after a directive was issued to offer HIV testing to all patients, from 142,000 in 2009 to 523,000 in 2011.[59]

NOVEL METHODS ON THE PATH TO UNIVERSAL TESTING

Kenya offers an informative example of how HIV testing has evolved.[32] In 2000, the government of Kenya, faced with a generalized epidemic and estimated HIV prevalence of 9% in adults, made a commitment to the rapid extension of VCT services. National guidelines for VCT were developed by a committee composed of multiple stakeholders, including government officials, counselors, laboratory representatives, donors, and persons living with HIV. Simple, whole-blood rapid tests were adopted, which resulted in several unexpected benefits. Counselors reported that persons receiving VCT liked to see their own test strips and engage in interpretation of test results.[32] This enhanced confidence in the test results, reduced waiting time, virtually eliminated loss to follow-up for confirmed test results, and decreased the potential for clerical errors. In 2000, 3 sites provided VCT services to approximately 1100 persons in Kenya. By 2005, 680 VCT sites (75% of which were in healthcare facilities) provided HIV tests to 545,000 persons.[32]

Emphasis on diagnostic testing was also needed to achieve Kenya's treatment targets. Testing in rural areas remained limited, and self-initiated VCT was not ideal for identifying large numbers of persons with advanced HIV infection. Consequently, the Kenya Ministry of Health issued new guidelines in 2004 for HIV testing in clinical settings.[60] These outlined definitions and standards for routine and diagnostic testing and advocated an opt-out approach for testing in antenatal clinics, tuberculosis clinics, sexually transmitted infection services, and other clinical services. The prevalence of HIV among persons tested subsequently in health facilities ranged from 11% among women attending child health clinics to more than 70% among rural patients with tuberculosis.[61,62] To reach their ambitious goal (80% of Kenyans knowing their HIV status by the year 2010), the government of Kenya also updated guidance for HIV testing and counseling that incorporates traditional VCT, testing in health facilities, community-based

outreach testing, and innovations such as door-to-door HIV testing, self-testing, and couples and family testing.[63]

Couples testing and counseling have been provided in the context of research studies in Rwanda since 1987 and in Zambia since 1994 and has proven highly effective for identifying serodiscordant couples and assisting them with mutual disclosure and follow-up services.[64] Reminiscent of the experience with rapid test adoption, couples testing is now gaining attention in the United States after its widespread implementation in Africa.[65] However, fear of adverse consequences for the HIV-positive member of the couple discourages many couples from accepting couples testing and counseling, and the proportion of people who know both their own status and that of their sexual partner(s) remains low, both in the United States and elsewhere.

By removing distance as a barrier, home-based testing might be an effective out-of-facility approach for identifying HIV-infected people at an earlier stage of their disease. In door-to-door home-based testing, the test provider approaches the client regardless of his or her perceived risk of having HIV. In an analysis of studies of more than 500,000 people who were offered home-based testing in Africa, the proportion who accepted ranged from 59.1% to 99.7%; of those tested, 99.6% received their test result.[66] Acceptance was highest among persons who had not tested previously. Qualitative research found that the most common reasons for the popularity of home-based testing were fear of stigmatization and emotional vulnerability associated with receiving results from public facilities.

Self-testing offers another new opportunity to expand HIV testing. In the United States, home sample collection for HIV testing has been available since 1996. Home collection users obtain a dried blood spot sample, mail it to a laboratory, and telephone to receive their test results. When home collection kits were first introduced, 0.9% of users tested positive; nearly 60% of users, and 49% of those who tested positive, had never been tested before.[67] In July 2012, a true rapid HIV self-test—one that persons perform themselves on oral fluid—was approved by the US Food and Drug Administration. The self-test might facilitate testing among persons who have not been tested before and promote more frequent testing by persons with ongoing risk behaviors. In the hands of home users, the sensitivity of the rapid self-test was 91.67% and specificity was 99.98%.[68] Participants in initial studies found the test very easy to use, and most performed the test without mistake while being observed.[69] In Malawi, 92% of 283 study participants elected an oral fluid self-test after a demonstration. Overall accuracy was 99.2% (2 of 48 participants with positive finger-stick blood rapid tests obtained negative oral fluid self-test results).[70] In a study of oral fluid self-testing in Singapore, 977 (99.1%) participants obtained correct results and more than 80% said they would purchase a self-test.[71] Self-testing may have considerable potential for regular re-testing of persons engaged in high-risk behaviors for whom retesting is recommended annually.[39,72] Especially in high-burden countries, with large numbers of persons who have never tested and shortages of health manpower, encouraging people with on-going risk who have been tested previously to use self-tests might help achieve the regular testing needed to identify persons early in infection.

CHALLENGES AHEAD

The "test and treat" approach for prevention entails expanded testing to identify all persons with HIV as early in the course of their infection as possible. Testing expansion depends on routinizing HIV testing, which in turn, must take full advantage of all the testing modalities now available while reducing stigma, assuring accuracy, maintaining quality, and controlling costs. Achieving broad coverage will require expanded testing in health facilities, traditional VCT sites, community settings including the home, and self-testing, all in the context of respect for autonomy and the highest standards of confidentiality. Treatment and care must be available, and post-test counseling must include linkage to HIV care and support for persons who test positive to notify their sex partners, either through couples VCT (where both partners learn their results together), disclosure in a medical setting (ideally with both partners together), or through partner notification.

The future of HIV testing is changing. Lessons from the eradication of smallpox might prove illuminating, despite the many differences between the 2 diseases. In the 1960s and 1970s, eradication efforts were initially dominated by an emphasis on mass vaccination, which proved impossible to achieve. A different, and at the time controversial, approach ultimately proved to be the key to success—intensive case finding, with immediate vaccination of all household members of identified patients. A similar shift in emphasis toward case finding might be as important for HIV elimination as it was for smallpox eradication. In the words of Foege,[72] this controversial approach "proved itself ideally suited for eradicating a virus that had eluded the best efforts of mass vaccination programs for 175 years." Absent a vaccine, case finding and treatment hold the most promise for the control of HIV.

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Preexposure Prophylaxis for HIV Prevention: Where Have We Been and Where Are We Going?

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Abstract: Preexposure prophylaxis (PrEP), in which HIV-uninfected persons with ongoing HIV risk use antiretroviral medications to reduce their risk of acquiring HIV infection, is an efficacious and promising new HIV prevention strategy. The past 2 years have seen significant new advances in knowledge regarding PrEP, including definitive demonstration that PrEP reduces the risk of HIV acquisition, regulatory approval of combination oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as the first PrEP agent with a label indication for sexual HIV prevention, and the development of normative guidance for clinical prescribing of PrEP. In PrEP clinical trials, HIV protection was strongly correlated with PrEP adherence; therefore, understanding and supporting adherence to PrEP are key to maximizing its public health impact. As would be expected for any new HIV prevention approach, questions remain, including how to motivate uptake of and sustain adherence to PrEP for HIV prevention in high-risk populations, how much use is sufficient to achieve HIV protection, and the potential of "next-generation" PrEP agents to improve this effective prevention strategy. At this important transition point—from demonstration of efficacy in clinical trials to thinking about implementation and effectiveness—this review addresses where we have been and where we are going with PrEP for HIV prevention.

Key Words: HIV prevention, preexposure prophylaxis, sexual HIV transmission

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INTRODUCTION

In July 2012, the US Food and Drug Administration approved the first label indication for an antiretroviral agent—the oral combination emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), sold as branded Truvada—to be used as preexposure prophylaxis (PrEP) to reduce the risk of sexual acquisition of HIV infection by persons at high risk.[1] More than 2.5 million persons are newly infected with HIV each year worldwide, resulting in a growing treatment and care burden,[2] and thus, novel strategies to prevent HIV acquisition, such as PrEP, remain urgently needed. This review will address where we have been and where we are going with PrEP for HIV prevention.

WHERE HAVE WE BEEN?

Rationale and Demonstration of PrEP Efficacy for HIV Prevention

The idea of prophylaxis to reduce the risk of an infectious disease is well established—one example is malaria chemoprophylaxis in travelers. Evidence to suggest that PrEP could reduce HIV risk grew out of successful HIV prevention of mother-to-child HIV transmission with antiretroviral prophylaxis[3–6] and from non-human primate studies showing that PrEP before mucosal simian HIV challenge provided partial or full protection against infection.[7–11] TDF and FTC had biologic properties that made these reverse transcriptase inhibitors attractive as first-generation PrEP agents: potent antiretroviral activity against all HIV subtypes, activity early in HIV's life-cycle, long-intracellular half-life, able to achieve high concentrations in the genital tract, convenient daily dosing with few drug interactions, and established safety profiles from their use as part of combination antiretroviral therapy (ART) regimens. When used for HIV treatment, TDF is a once-daily 300 mg dose, and FTC/TDF includes 200 mg of FTC; these standard

doses were chosen for clinical trials of PrEP. In non-human primate studies, there was some evidence of greater HIV protection using FTC/TDF compared with TDF alone, suggesting that combination PrEP could provide greater benefit than from a single agent.[8]

Five efficacy trials of TDF and/or FTC/TDF as PrEP for HIV prevention have been completed and 2 are ongoing (Table 1). Trial protocols included monthly study visits with HIV serologic testing, clinical safety evaluation, and individualized adherence counseling, as well as a package of HIV prevention services provided to all participants (including HIV and risk-reduction counseling, screening and treatment for sexually transmitted infections, and free provision of condoms).

Three of these trials[12,14,18]—involving men who have sex with men (iPrEx) and heterosexual men and women (Partners PrEP and TDF2) from a diversity of geographic settings—demonstrated that PrEP reduced the risk of HIV acquisition, with intention-to-treat comparisons against placebo showing HIV protection efficacies between 44% and 75%. Importantly, although pharmacokinetic studies suggested lesser accumulation of tenofovir in vaginal compared with rectal tissue after

TABLE 1. Placebo-Controlled Efficacy Trials of PrEP for HIV Prevention

Study (Location)	Population	Design	Relative Reduction in HIV Incidence in Intention-to-Treat Analysis
Completed trials (ordered by decreasing HIV risk reduction in primary intention-to-treat analysis)			
Partners PrEP Study (Kenya, Uganda)	4747 heterosexual men and women with known HIV-infected partners (serodiscordant couples)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	TDF: 67% (95% CI: 44% to 81%, $P < 0.0001$). FTC/TDF: 75% (95% CI: 55% to 87%, $P < 0.0001$)
TDF2 Study (Botswana)	1219 heterosexual men and women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 63% (95% CI: 22% to 83%, $P = 0.01$)
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, United States)	2499 MSM and transgender women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 44% (95% CI: 15% to 63%, $P = 0.005$)
FEM-PrEP (Kenya, South Africa, Tanzania)	2120 women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 6% ($P = 0.8$). No statistically significant reduction in HIV incidence
VOICE (South Africa, Uganda, Zimbabwe)	3019 women (plus 2010 women receiving tenofovir or placebo gel)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	TDF: −49% ($P = 0.07$). FTC/TDF: −4% ($P > 0.2$). No statistically significant reduction in HIV incidence
Trials in progress			
Bangkok Tenofovir Study (Thailand)	2413 injection drug users	1:1 randomization to daily oral TDF or placebo	TDF: results expected, 2013
IPERGAY (France, Canada)	1900 MSM	1:1 randomization to FTC/TDF or placebo, used "on demand"	FTC/TDF (intercourse-associated use): Results expected, 2016

Study (Location)	PrEP Detection in Blood Samples From Nonseroconverters	HIV Protection Estimate as Related to High Adherence	Ref
Completed trials (ordered by decreasing HIV risk reduction in primary intention-to-treat analysis)			
Partners PrEP Study (Kenya, Uganda)	81%	86% (TDF), 90% (FTC/TDF) in subjects with detectable tenofovir levels	Baeten et al[18]
TDF2 Study (Botswana)	79%	78% excluding follow-up periods when subjects had no PrEP refills for >30 d	Van Damme et al[13]
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, United States)	51%	92% in subjects with detectable tenofovir levels	Grant et al[12]
FEM-PrEP (Kenya, South Africa, Tanzania)	35%–38% at a single visit, 26% at 2 consecutive visits	Trial investigators assessed use of PrEP as too low to evaluate efficacy	Thigpen et al[14]
VOICE (South Africa, Uganda, Zimbabwe)	<30% of samples; ~50% of women never had tenofovir detected in any sample	Trial investigators assessed use of PrEP as too low to evaluate efficacy	Marrazzo et al[15]
Trials in progress			
Bangkok Tenofovir Study (Thailand)	Not available	Not available	Martin et al[16]
IPERGAY (France, Canada)	Not available	Not available	Ref.[17]

CI, confidence interval.

TDF dosing,[19,20] subgroup analyses in the 2 trials that included both sexes (Partners PrEP and TDF2) found comparable HIV protection for both women and men. Thus, these randomized placebo-controlled trial results provide definitive evidence that PrEP "works" for HIV prevention.

PrEP Adherence and HIV Protection

A strong dose–response relationship between adherence to PrEP pill taking and HIV protection was demonstrated across PrEP efficacy trials (Table 1). Higher HIV protection was seen in trials with higher adherence, and no HIV protection was found in 2 trials (FEM-PrEP and VOICE[13,15]) in which adherence to PrEP, as measured by detection of PrEP medications in blood samples from a random subset of subjects, seems to have been very low. In iPrEx and Partners PrEP, analyses of detection of PrEP medications in blood samples suggests that those using PrEP may have achieved an ~90% reduction in HIV risk, which likely hints at the true biologic efficacy of PrEP for HIV protection. Thus, just as consistent use of ART is needed to achieve HIV treatment benefits,[21] adherence is critical to the efficacy of PrEP.

One important factor for achieving high adherence in PrEP trials seems to have been external support. In qualitative work, support from the HIV-infected member of a serodiscordant couple seems to be related to better PrEP pill taking in the Partners PrEP Study, and participants in iPrEx noted the importance of support from research staff, family, and friends.[22,23] Conversely, low perception of HIV risk may explain low PrEP adherence—in FEM-PrEP, 70% of women reported they felt themselves at little risk for acquiring HIV, despite a nearly 5% annualized HIV incidence in that trial.[13] In iPrEx, PrEP efficacy was higher in men reporting (versus not reporting) unprotected receptive anal sex at baseline, suggesting that self-perception of risk might increase PrEP use.[12] Additional factors associated with lower adherence in Partners PrEP included younger age, male gender, higher socioeconomic status, and heavy alcohol use[24]; in iPrEx, younger age and region (non-US sites compared with US sites) were also associated with lower adherence.[25] In VOICE, adherence was lower in younger unmarried women, who also had the highest HIV incidence in this trial.[15]

Additional Outcomes From PrEP Trials: Safety, Resistance, and Sexual Behavior

Trials have found that TDF and FTC/TDF PrEP seem to be well tolerated, with the rate of both serious and mild adverse events generally balanced between those receiving PrEP and those receiving placebo. The most prominent side effects were gastrointestinal (eg, nausea), and these symptoms were present only in a minority of subjects (~10% or less), were mild in severity, and were generally limited to the first month after initiation of the medication. PrEP has been associated with an average ~1% reduction in bone mineral density but not with increased fracture risk over the study period.[14,26,27] Although TDF has been associated with renal complications in HIV-infected persons, PrEP clinical trials did not find increased risk of renal complications in healthy HIV-uninfected persons. Finally, data from Partners PrEP[28] and from the Antiretroviral Pregnancy Registry[29] suggest that the use of TDF and FTC/TDF in early pregnancy is not associated with increased rates of birth defects, although more data are needed to fully assess the safety of these medications through pregnancy.

Antiretroviral resistance was rare and limited to those with seronegative acute infection at the time of PrEP initiation. The absence of PrEP-selected drug resistance among persons acquiring HIV during the trials is potentially a manifestation of the strong correlation between PrEP use and protection: low use of PrEP provides little HIV protection but little risk of resistance if infection is acquired, whereas high adherence blocks most transmissions. Taking a public health perspective, the number of cases of antiretroviral resistance in PrEP trials is presented against the number of HIV infections prevented by PrEP in Table 2.

Finally, the question of increased sexual risk taking accompanying PrEP use was explored in iPrEx and Partners PrEP, where self-reported condom use increased and sexually transmitted infection diagnoses decreased during follow-up. Although the self-reported data are potentially limited by recall and social desirability biases, these data potentially suggest that PrEP could work synergistically with other components of the HIV prevention package provided to trial participants.[30]

WHERE ARE WE GOING?

Unanswered Questions From PrEP Trials and Progress With PrEP Demonstration Projects

First-generation PrEP trials have demonstrated proof-of-concept that antiretroviral PrEP provides protection against HIV acquisition, but, as expected for this new prevention strategy, a number of important scientific and implementation questions remain (Table 3); many of these same questions are

TABLE 2. Antiretroviral Resistance in PrEP Trials Demonstrating Efficacy of PrEP for HIV Prevention

	No. HIV Seroconverters Assigned FTC/TDF or TDF PrEP With HIV Resistance		Comparison: No. HIV Infections Averted in the PrEP Trial [(No. Infections in Placebo Arm) − (No. Infections in FTC/TDF PrEP Arm)]
	Individuals With Seronegative Acute HIV Infection at Enrollment	Individuals Who Acquired HIV After Enrollment	
iPrEx	2/2	0/36	28
Partners PrEP	2/8	0/30	74
TDF2	1/1	0/10	16

In iPrEx, the 2 subjects with seronegative acute HIV infection at the time of PrEP initiation both developed M184I/V mutations, conferring resistance to FTC. In Partners PrEP, of 8 subjects with seronegative acute HIV infection at the time of PrEP initiation, 2 developed antiretroviral resistance: 1 K65R substitution (conferring resistance to TDF) and 1 M184V substitution. In TDF2, 1 subject, also with seronegative acute HIV infection at the time of randomization to the FTC/TDF PrEP arm, developed both the K65R and M184V substitutions.

TABLE 3. PrEP for HIV Prevention: Priority Questions for Implementation

Topic	Questions
Priority populations	In different geographic and economic settings, who should be prioritized for PrEP?
	How does PrEP interface, and ideally synergize, with other HIV prevention strategies?
	What are the key messages about PrEP for priority populations, including ways to minimize the potential for stigma related to PrEP?
Delivery	Where is PrEP best delivered—primary care settings, voluntary counseling and testing centers, specialized HIV prevention or care settings, or other settings?
	Who are appropriate prescribers for PrEP? Who can appropriately monitor PrEP use and safety?
	What is the appropriate delivery model for adherence and risk behavior counseling coupled to PrEP?
Uptake	Do those who might benefit most from PrEP want to take it?
	What level of uptake in a population is sufficient to justify the resources needed for PrEP delivery?
	Can PrEP use be matched to individuals during periods of highest HIV risk—in order to maximize PrEP utility?
Adherence	Who takes PrEP? Do they take it often enough to achieve protection against HIV?
	Is PrEP adherence high when risk of HIV infection is high?
	How can PrEP be safely discontinued when HIV risk is low (since PrEP use will be time-limited and not lifelong as with ART)?
Sexual behavior	How does PrEP use vary with sexual behavior?
	If sexual risk taking increases for persons receiving PrEP, to what degree and with what potential impact will it have on PrEP effectiveness and other related harms (eg, sexually transmitted infections)?
	What are the best counseling approaches and behavioral interventions to minimize risk compensation?
Clinical risks	What is the longer-term safety of PrEP use by healthy HIV-uninfected persons, particularly renal and bone safety?
	Do clinical risks, if present, resolve with PrEP discontinuation?
	What is the safety of PrEP use for peri-conception risk reduction and through pregnancy and breastfeeding?
	How frequently should HIV testing be conducted for persons receiving PrEP?
	What is the risk of antiretroviral resistance for persons who have break-through HIV infection while receiving PrEP, particularly if HIV testing is less frequent than in clinical trials?
Impact	How can the cost-effectiveness of PrEP be maximized when delivered in real-world settings?
	How should PrEP be prioritized along with other effective HIV prevention strategies?

also relevant for implementation of ART to reduce the infectiousness of persons with HIV infection as a prevention intervention.[31] For PrEP, the overarching unknown is whether HIV protection efficacy, as proven in clinical trials, will translate into substantive effectiveness in real-world practice. A number of considerations influence the priority questions for PrEP implementation. First, levels and patterns of adherence to PrEP in the setting of known efficacy are unknown. Although medication adherence is often lower when moving from clinical trials to practice settings,[32] individuals with ongoing HIV risk who seek out prescription PrEP that is known to "work" may be highly motivated to adhere. Second, sexual risk taking in the context of known PrEP efficacy is unexplored, including whether risk compensation might result in reduced PrEP benefits and the level and types of behavioral intervention(s) needed to maximize prevention synergy.[33] Third, further study is required to identify optimal HIV testing approaches to reliably detect HIV infections among individuals initiating and continuing PrEP and to minimize selection of resistance. Fourth, the longer-term health effects of oral FTC/TDF in HIV-negative PrEP users, including renal safety and bone mineral density, require further evaluation, particularly for those with underlying comorbidities (eg, hypertension, diabetes) and for women who may use PrEP during pregnancy and breastfeeding. No PrEP clinical trials included pregnant women; however, PrEP has the potential to reduce the risk of seroconversion during conception and pregnancy, particularly for HIV serodiscordant couples desiring pregnancy. Pregnancy is a high-risk period for HIV acquisition, and acute infection during pregnancy is associated with higher risk of transmission to the fetus,[34] and thus, studies of PrEP safety and use in pregnancy should be a priority. Finally, additional research is needed to determine how best to prioritize populations who will benefit most from PrEP, the best time period for use of PrEP as an intervention (eg, in women when they cannot negotiate safer sex or in women wanting to get pregnant), level of interest in taking PrEP in these communities, and optimal delivery settings for PrEP to maximize public health impact.

To address unanswered questions for PrEP implementation, PrEP demonstration projects are being planned or underway (Table 4). Target populations include men who have sex with men (MSM) and transgender women, heterosexual serodiscordant couples, young sexually active heterosexual men and women, and female sex workers, across 5 continents and in a diversity of delivery settings. Common objectives across demonstration projects include assessing (1) feasibility, acceptability, and uptake of PrEP; (2) levels and patterns of PrEP adherence; (3) changes in sexual risk behavior; (4) safety and tolerability; and (5) HIV incidence and resistance among seroconverters. Three projects are open-label extensions of PrEP clinical trials and will provide opportunities to determine the impact of providing information about efficacy and safety of PrEP in well-characterized cohorts.

Although the current portfolio of PrEP demonstration projects is scientifically, programmatically, and geographically diverse, PrEP is not being evaluated in all populations, with

TABLE 4. PrEP Demonstration Projects

Study	Population (N)	Design, Product, and Follow-up Duration	Locations	Timeline
Extensions of PrEP clinical trials, ordered by timing of initiation				
iPrEx Open-Label Extension	MSM and transgender women (n = 2499)	Open label, daily oral FTC/TDF, follow-up: 72 wk	Brazil, Ecuador, Peru, South Africa, Thailand, United States	Enrollment began: June 2011; results expected: 2014
Partners PrEP Study (postplacebo phase)	Heterosexual men and women with known HIV-infected partners (HIV serodiscordant couples) (N = 4747 couples)	Randomized daily, oral TDF vs. FTC/TDF (blinded), follow-up: 12 mo	Kenya, Uganda	Enrollment began: July 2011; results expected: 2013
CDC 494/TDF2 Open-Label Extension	Heterosexual men and women (N = 1219)	Open label, daily oral FTC/TDF, follow-up: 12 mo	Botswana	Enrollment began: February 2013; results expected: 2014
New populations, ordered by timing of initiation				
US PrEP Demonstration Project (Demo Project)	MSM and transgender women in STD clinic setting (n = 500)	Open label, daily oral FTC/TDF, follow-up: 48 wk	United States (San Francisco, Miami)	Enrollment began: September 2012; results expected: 2014
Partners Demonstration Project	Heterosexual men and women with known HIV-infected partners (HIV serodiscordant couples) (N = 1000 couples)	Open label, daily oral FTC/TDF, provided as a "bridge" to ART initiation by HIV-infected partners, follow-up: 24 mo	Kenya, Uganda	Enrollment began: November 2012; results expected: 2014/2015
ATN 110 and 113	Young MSM, ages 15–22 (N = 300)	Open label, daily oral FTC/TDF, follow-up: 48 wk	14 US sites	Enrollment began: December 2012; results expected: Fourth quarter 2014
PROUD	Gay men in genitourinary medicine clinics (N = 500)	Open label, immediate vs. deferred daily oral FTC/TDF, follow-up: 2 yrs	United Kingdom	Enrollment began: November 2012; results expected: November 2015
CCTG 595	MSM and transgender women (N = 400)	Open label, daily oral FTC/TDF, participants randomized to a text messaging adherence intervention or standard of care, follow-up: 48 wk	United States (Long Beach, Los Angeles, San Diego, Torrance)	Enrollment planned: First to second quarter 2013; results expected: 2016
PATH—PrEP	375 MSM and transgender women (N = 375)	Open label, daily oral FTC/TDF for high-risk individuals; PEP for low/moderate-risk individuals, follow-up: 48 wk	United States (Los Angeles)	Enrollment planned: April 2013; results expected: 2017
HPTN 073	Black MSM (N = 225)	Open label, daily oral FTC/TDF, follow-up: 12 mo	US (Los Angeles, Washington DC, Chapel Hill)	Enrollment planned: June 2013, results expected: December 2015
SCOPE	Female sex workers (N = 500)	Open label, daily oral FTC/TDF, follow-up: until April 2014	Kenya	Enrollment planned: June 2013; results expected: 2014

HPTN, HIV Prevention Trials Network.

important gaps including young African women; projects still in planning or proposal stages may address some of these gaps. In addition, coordination across projects will be important, so that core data are collected and can be compared across time, minimizing duplication and maximizing synergy across projects.[35] The World Health Organization is currently compiling a framework for country-level protocol development of PrEP demonstration projects. Key messages include involvement of high-risk populations and measurement of adherence as a primary outcome. A key consideration for PrEP demonstration work is that projects should not simply track retention on PrEP alone but particularly when PrEP is needed (ie, during period of high risk) and as PrEP use relates to other HIV prevention services (eg, condoms, male circumcision).

What Adherence Means for PrEP Outside of Clinical Trials

Understanding adherence to PrEP in implementation settings must consider whether PrEP is needed and desired. In

contrast to ART, which is lifelong, PrEP is likely best used for periods (months to a few years) of highest behavioral risk—for example, when attempting to conceive,[36] around the time of sexual debut or coming out, and when previously safe sexual behavior patterns are modified. Perfect adherence during times of no risk (eg, no sex) is not likely cost-effective or appropriate, but good adherence during periods of higher risk is essential. In iPrEx and in Partners PrEP, participants reporting no sex (and therefore no risk of HIV acquisition) were more likely to have low adherence,[24] suggesting that self-assessment of risk may be possible to some degree—analogous to other prevention strategies that are not lifelong (eg, oral contraceptives). PrEP implementation should assess when individuals want to take PrEP (ie, the "season of PrEP") and how long they take it (ie, persistence of adherence). Guidance for when and how to start and stop PrEP and still achieve effective protection is needed. In one study (the Partners Demonstration Project), PrEP will be provided to HIV serodiscordant couples as a "bridge" to stable ART initiation by the HIV-infected partner.[37]

PrEP studies have used several adherence measures, each with important strengths and weaknesses (Table 5). Objective measurements likely provide the most reliable data, and electronic monitoring is the only way to capture patterns of adherence, which are particularly important for assessing adherence behavior as related to periods of risk. A number of demonstration projects are incorporating drug-level testing to monitor PrEP adherence. If resources in demonstration projects and implementation settings are limited, use of objective adherence measures may still be considered for a subset of the study population.

The level of adherence needed to achieve HIV protection is not clear; however, PrEP use may potentially permit behavioral imperfection. In the iPrEx study, statistical modeling combining pharmacokinetics and drug data estimated that 2 PrEP doses per week might achieve a 76% reduction in HIV, rising to >95% for ≥4 doses per week.[38] However, PrEP concentrations necessary for HIV protection are potentially related to the intensity and route of viral exposure (eg, penile, vaginal, parenteral, rectal) and the drug (TDF, FTC/TDF, or other agents). There are currently no data to guide less-than-daily dosing of oral FTC/TDF as PrEP. In addition, it is not clear if less-than-daily dosing would necessarily achieve higher adherence: in one small study among MSM in Kenya and serodiscordant couples in Uganda, adherence to intermittent (twice weekly and postcoital) PrEP was lower compared with daily PrEP.[14,18] Adherence may change over time depending on variable risk, preferences, and other factors in an individual's life (eg, alcohol use, income). Although tailoring PrEP to those most likely to adhere may be an attractive strategy for increasing cost-effectiveness, those individuals may be difficult to identify and may be a moving target.

An important question will be how best to motivate and support ongoing PrEP use, highlighting the need to develop and rigorously evaluate effective, scalable PrEP adherence interventions for diverse populations. PrEP demonstration projects will research a range of interventions to support adherence, risk reduction, and other psychosocial needs. Client-centered brief counseling sessions, directed approaches based on cognitive behavioral therapy and problem-solving

TABLE 5. Strengths and Weaknesses of Adherence Measures

Measure	Strengths	Weaknesses
Subjective		
Self-report	Easy to collect	Often overestimates adherence due to social desirability bias and failure to remember missed doses; highly discrepant with objective measures in multiple clinical trials
	Inexpensive	Unclear which self-reported measures are optimal for measuring PrEP adherence
	Highly specific	
Objective		
Clinic-based pill counts	Easy to collect	Susceptible to manipulation before the clinic visit (ie, pill dumping)
	Relatively inexpensive	
Unannounced home-based pill counts	Highly objective measure	Labor intensive and expensive
		May be challenging to conduct due to stigma, logistics
		Still susceptible to manipulation, although less than with clinic-based pill counts
Pharmacy refill	Relatively easy to collect	Requires close control over pharmacy use and record keeping
		Only provides maximal predicted adherence (ie, not all pills picked up will be used)
Electronic adherence monitoring	Typically the most accurate adherence measure	Requires adherence to the adherence monitoring device, which may be limited due to factors such as stigma, inconvenience (eg, while traveling)
	Allows for assessment of patterns of use	Subject to misclassification (eg, removal of multiple pills at a single bottle opening)
		Expensive
		Potential for technical challenges
Drug levels	Highly sensitive to detecting drug use	Impractical in many settings (no commercial assay, not viable currently in low-resourced settings)
	Reflects actual ingestion of drug	Plasma levels susceptible to manipulation in that participants may take medications just before a scheduled blood drawn
	PrEP detection correlates with HIV protection	Subject to both behavioral (ie, time of dosing) and biological variation (ie, pharmacokinetics)
		Expensive

therapy for those with low adherence, and use of electronic reminders or text messages are being evaluated in demonstration projects. Good adherence support will be critical to ensure the behavioral success of this biological agent for HIV prevention. That said, counseling should not be so onerous as to present logistical or financial barriers to access the medication. Demonstration projects should explore standardized approaches for providing appropriate counseling within the real-world context.

PrEP Use Outside of Demonstration Projects

Normative guidance for prescribers regarding PrEP for MSM and high-risk heterosexuals has been released in the United States.[39,40] The guidance stresses the importance of delivering PrEP as part of a package of prevention services, including HIV testing, risk-reduction counseling, and prevention and treatment of sexually transmitted infections, as well as adherence messaging. HIV testing and PrEP refills are recommended no less frequently than every 3 months, and attention to acute HIV infection, particularly at PrEP initiation (or reinitiation), is important. To maximize the potential benefits of PrEP, it will need to be accessible to at-risk populations, who are most often not engaged in care. PrEP is a primary prevention intervention, and prescribing by primary and community care providers, who are more likely to encounter the populations most at risk, is needed. For individuals not regularly engaged in care, collaboration with community-based organizations will be needed to identify at-risk HIV-negative individuals, provide education about PrEP, and link them into primary care.[41] Providers in a variety of settings—public clinics, antenatal care, and sexually transmitted infection clinics—might be PrEP prescribers or initiate linkages to primary care. Counseling support might be delivered through community-based nonclinical settings with strong linkages to PrEP clinical providers.[42]

Next-Generation PrEP Studies

Demonstration of efficacy and regulatory approval of daily oral FTC/TDF PrEP was a milestone for HIV prevention,[43] but potentially only the first step in developing a suite of PrEP options. Both TDF and FTC have long half-lives (~150 hours and ~48 hours, respectively), which provides substantial drug concentrations to be present for several days after each dose,[44] and non-human primate models indicate that dosing even as infrequently as once a week may be sufficient for protection if postexposure dosing is also used.[8,45] The HIV Prevention Trials Network is evaluating different intermittent dosing strategies, and theory-based determinants of sexual and pill taking behavior in heterosexual women in Africa and in MSM in the United States and Thailand (HIV Prevention Trials Network 067). Nonetheless, careful attention to adherence will be critical in studies of less-frequent PrEP dosing. Alternative PrEP agents to FTC/TDF, including oral and topical vaginal maraviroc, dapivirine and other agents formulated into long-acting vaginal rings, and injectable agents (eg, rilpivirine), are being evaluated; importantly, formulations to address adherence challenges (eg, sustained release injections, long-acting vaginal rings) are under study.

CONCLUSIONS

During the past 2 years, PrEP has moved from hypothesis to proof of principle: for persons at ongoing risk of HIV infection, PrEP provides a time-limited highly efficacious HIV prevention strategy. As with all prevention strategies, PrEP is only effective if used, and maximum PrEP benefits, at both individual and population levels, will likely be achieved by combining PrEP with other effective HIV prevention interventions. Implementation of PrEP, in research demonstration projects and implementation settings, is the next step. As we move from where we have been to where we are going with PrEP, there is a tremendous opportunity to maximize the benefits of this promising HIV prevention strategy.

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Study Design Considerations for Evaluating Efficacy of Systemic Preexposure Prophylaxis Interventions

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Background: The development of interventions for systemic preexposure prophylaxis (PrEP) faces several significant challenges following the US Food and Drug Administration's approval of emtricitabine/tenofovir (FTC/TDF) for HIV prevention. This development is particularly complex because of inconsistency of efficacy results of FTC/TDF PrEP trials for HIV prevention.

Methods: Possible designs for a PrEP phase 3 efficacy trial are obtained by considering scenarios for potential experimental PrEP and control regimens, including consideration of placebo and active controls, longer acting PrEP and alternate dosing schedules.

Results: Noninferiority (NI) trials with hazard ratio NI margins ranging from 1.10 to 1.25 can be justified in the contexts of the 3 PrEP trials demonstrating efficacy of FTC/TDF. However, these HIV endpoint trials may require extremely large number of participants, particularly in settings where FTC/TDF has been shown to reduce the risk of HIV acquisition. NI trials also are often difficult to interpret because they depend on previous placebo-controlled efficacy results. Superiority trials for PrEP are plausible in settings where FTC/TDF efficacy is not yet established, possibly due to low adherence (ie, women at risk as in FemPrEP and VOICE): a new product with potential for higher adherence and potency would be a promising candidate in this setting.

Conclusions: Following Food and Drug Administration's approval of FTC/TDF for PrEP, trials to establish efficacy of new PrEP regimens require stringent design standards, together with rigorous debate about adherence within study populations and many important ethical issues.

Key Words: preexposure prophylaxis, noninferiority, efficacy, phase 3, clinical trials, adherence

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INTRODUCTION

The US Food and Drug Administration approved daily dosing of emtricidabine/tenofovir (FTC/TDF) for prevention of HIV acquisition in July 2012. Although this provides an important advance in HIV prevention, there is need for more than 1 option for preexposure prophylaxis (PrEP). In settings where daily FTC/TDF results have been disappointing, there is particular interest in new products that could improve prevention efficacy through improved adherence or potency. Furthermore, FTC/TDF is currently a first-line choice for treatment of HIV infection, raising concerns about potential for resistance and competing resource demands for a drug used for both treatment and prevention.

The development of new interventions for PrEP faces several significant challenges. A study evaluating the effectiveness of a PrEP intervention requires HIV seroincidence endpoints because we do not have evidence to justify a biomarker as a replacement endpoint. To use a biomarker endpoint, we would need to establish that the effect of PrEP on the biomarker reliably predicts whether PrEP has a clinically meaningful effect on the risk of HIV acquisition. Trials with HIV endpoints may be large. This is particularly likely in settings where FTC/TDF has been shown to reduce the risk of HIV acquisition and then would be used as the standard of care (SOC) in the trial of the new intervention because the overall seroincidence rates in the trial could be below 2 per 100 person-years. Even larger sample sizes may be required if we conduct noninferiority (NI) trials, that is, trials designed to determine whether we can rule out that use of a new intervention rather than FTC/TDF would cause an unacceptable increase in the risk of HIV acquisition. The inconsistency of efficacy results for FTC/TDF, across recent PrEP trials in Table 1,[1–5] makes NI trials with FTC/TDF as the active control regimen problematic because an NI trial is appropriate only when the effect of the active control in the NI trial setting is (1) large and (2) precisely estimated from previous randomized trials conducted in similar settings. In settings where FTC/TDF has been shown to provide little, if any, reduction in the risk of HIV acquisition, superiority designs could be justified for drugs that could plausibly achieve higher adherence or potency.

In this manuscript, we will explore potential study designs for randomized efficacy trials evaluating experimental PrEP regimens for prevention of HIV acquisition.

TABLE 1. Settings, Population and Principal Results From Clinical Trials Evaluating the Daily Oral TDF/FTC Regimen for PrEP for Risk of HIV Acquisition

Study and Setting (% Total Population)	Risk/Gender	Adherence, %	No. Events	Efficacy (95% CI), %
Partners PrEP; Kenya, Uganda (100)	Discordant heterosexual couples	~80	13 vs. 52	75 (55 to 87)
TDF2; Botswana (100)	Heterosexual men and women	~80	9 vs. 24	63 (22 to 83)
iPrEx; Peru, Brazil, Ecuador (82)	Men who have sex with men	~50	48 vs. 83	42 (18 to 60)
FemPrEP; South Africa, Kenya (98)	Heterosexual women	~35	33 vs. 35	6 (−69 to 41)
VOICE; South Africa (81)	Heterosexual women	~29	61 vs. 60	−4 (−50 to 30)

A FRAMEWORK FOR CONSIDERING PREP PHASE 3 EFFICACY TRIALS

Designs for PrEP phase 3 efficacy trials are obtained by considering potential experimental and control PrEP regimens.

1. Potential experimental PrEP regimens:
   a. Oral daily drug(s) other than FTC/TDF.
   b. A long-acting formulation (oral or injectable) of an experimental agent(s).
   c. Oral FTC/TDF with a different dosing strategy (eg, event-based dosing; event-based dosing + weekly dosing).
2. Potential control regimens:
   a. Active control: Daily FTC/TDF is provided as the control; daily FTC/TDF is assumed to be a SOC regimen.
   b. Add-on placebo control: Placebo is the control; participants in both arms of the trial have access to background use of daily FTC/TDF with level of use matched to the clinical setting of interest.
   c. Placebo control: Placebo is the control, where there is justification that background management does not include use of daily FTC/TDF.

The potential scenarios for a PrEP phase 3 efficacy trial are obtained by combining the choice of experimental and control PrEP regimens (Table 2).

POTENTIAL SCENARIOS FOR A PREP PHASE 3 TRIAL

We discuss the 8 scenarios in Table 2, considering strengths and weaknesses of superiority and NI designs, as well as anticipated level of interest or priority.

Scenario A: Experimental Oral Drug Versus Daily FTC/TDF

In this scenario, daily FTC/TDF is assumed to be SOC for PrEP, most justified where adherence rates and levels of efficacy for that regimen are high, as in the Partners PrEP trial setting of discordant heterosexual couples in committed relationships.[1] If an experimental oral drug is of interest, even though its efficacy might be only similar to or modestly better than that of FTC/TDF, it could be evaluated in a FTC/TDF-controlled NI trial. By design, the intention of such an NI trial is to determine whether we can rule out that the efficacy of the experimental oral drug is "unacceptably worse" than daily FTC/TDF in preventing HIV acquisition. The NI trial requires specification of a threshold, called the "NI margin," for what constitutes unacceptable loss of efficacy. NI is established if the estimated relative effect of the experimental drug to FTC/TDF is sufficiently favorable and precise that the confidence interval for that relative efficacy does not include the NI margin. High adherence to a daily FTC/TDF active control regimen is necessary in an NI trial because justification for the NI margin includes an assumption that the historical randomized trials establishing efficacy of FTC/TDF (where adherence was necessarily high enough to prevent a substantial proportion of infections) provide an unbiased estimate of FTC/TDF's effect (relative to a hypothetical placebo) in the NI trial.[6–9]

In NI trials in Scenario A, participants randomized to the experimental arm receive the new oral agent instead of the FTC/TDF control, even though there is substantive evidence establishing FTC/TDF meaningfully reduces the risk of HIV acquisition. For such a trial to be ethical, there needs to be strong previous proof-of-concept for efficacy of the new oral agent.[9]

The sample size of an NI trial can be very large (Table 3). Suppose we decide (1) it is unacceptable for the relative rate of HIV acquisition on the new oral agent to be 1.25-fold higher than on FTC/TDF [ie, the NI margin is selected to be a hazard ratio (HR) of 1.25] and (2) the probability of a false-positive conclusion should be only 2.5% when the HR truly is 1.25. In this setting, if we want to rule out the prespecified NI margin with 90% probability when the experimental drug and FTC/TDF truly have the same effect on HIV acquisition, the sample size and duration of follow-up in the NI trial need to be sufficiently large that 844 trial participants have HIV acquisition events (Table 3). This would be reduced to 211 HIV acquisition events if we believe that the new oral agent is somewhat better than daily FTC/TDF and require 90%

TABLE 2. Schema for Potential Experimental and Control Arms in PrEP Trials

Control/Experimental Regimen	2a: New Daily Oral Drug(s)	2b: Long-Acting Drug (Oral or Injectable)	2c: Different Oral FTC/TDF Dosing Strategy
1a: FTC/TDF daily as active control	Scenario A	Scenario B	Scenario C
1b: Placebo add-on to FTC/TDF daily	Scenario D	Scenario E	Not applicable
1c: Placebo add-on to "Standard-of-care"	Scenario F	Scenario G	Scenario H

TABLE 3. Sample Sizes and Critical Observed Effects for NI Trials of PrEP

HR to be Ruled out to Establish NI, for a Trial With 90% Power Under True HR	Total No. HIV Events	Maximum Estimated HR to Conclude NI	Sample Size, When 2.25 Events per 100 Person-years and 2 Year Follow-up
Rule out 1.10 against true 1.00	4628	1.0384	104,015
Rule out 1.10 against true 0.90	1044	0.9743	23,654
Rule out 1.10 against true 0.80	415	0.9075	9403
Rule out 1.10 against true 0.67	171	0.8151	3800
Rule out 1.20 against true 1.00	1265	1.0748	28,430
Rule out 1.20 against true 0.90	508	1.0084	11,510
Rule out 1.20 against true 0.80	256	0.9392	5800
Rule out 1.20 against true 0.67	124	0.8439	2756
Rule out 1.25 against true 1.00	844	1.0922	18,969
Rule out 1.25 against true 0.90	390	1.0250	8766
Rule out 1.25 against true 0.80	211	0.9543	4742
Rule out 1.25 against true 0.67	108	0.8572	2400

NI margins ranging from 1.10 (justified by iPrEX) to 1.25 (justified by Partners PrEP). The HR compares an experimental regimen to active control for HIV acquisition. Calculations are conducted assuming the analysis have a 2.5% probability of a (one sided) false-positive error rate.

probability to rule out the NI margin when the experimental drug to daily FTC/TDF HR is 0.80 (Table 3).

Scenario A is of interest when adherence rates and levels of efficacy of FTC/TDF are high and an experimental oral drug has strongly favorable evidence from proof-of-concept trials. There is interest in this setting in part because a new oral agent could preserve daily FTC/TDF for first-line HIV treatment and reduce the risk of emerging resistance. However, given the above considerations of ethics and feasibility, Scenario A may be a low priority unless there is favorable evidence for the new oral agent from, for example, a previously completed superiority trial (eg, Scenario D or F.)

Scenario B: Long-Acting Formulation (Injectable or Oral) of Experimental Agent(s) Versus Daily FTC/TDF

In Scenario B, as in Scenario A, daily oral FTC/TDF is assumed as an effective SOC regimen for PrEP. Because participants receiving the experimental long-acting agent are not receiving daily FTC/TDF in a randomized head-to-head comparison trial, the ethics and level of priority of this scenario again is dependent on the strength of evidence from proof-of-concept trials of the long-acting experimental agent.

Even where the daily FTC/TDF control regimen has been proven effective, it might be possible to conduct a superiority trial for a new PrEP drug because exploratory analyses in the Partners PrEP and iPrEx trials suggested that 85% to 90% efficacy might be achieved with higher adherence. To illustrate sample size requirements, a trial with 88 patients having HIV acquisition events would be required to rule out equal effectiveness of experimental and FTC/TDF regimens with 90% "true-positive" probability, when the experimental regimen truly reduces relative risk of HIV infection by 50% (assuming a 2.5% "false-positive" probability if regimens are truly equally effective). If this trial was conducted in settings where HIV acquisition would be approximately 2% per year, then approximately 2250 participants would need to be enrolled, followed up for an average of 2 years.

Alternatively, an NI trial design might be preferred. Suppose we derive the NI margin using the Partners PrEP or the Botswana TDF2 trial to estimate the effect of FTC/TDF (vs. hypothetical placebo) in the NI trial, which assumes adherence levels in the NI trial will be as high as was seen in those trials. Using the "95–95" approach for derivation of the NI margin[7,8] and the Partners PrEP result to estimate that FTC/TDF provides a 75% (95% CI: 55 to 87) reduction in the risk of HIV acquisition, and requiring the experimental regimen to preserve at least 75% of FTC/TDF's effect, the NI margin is an experimental to FTC/TDF HR of 1.25. In such a setting, a trial with 108 patients having HIV acquisition events will have 90% power to rule out that the experimental regimen to daily FTC/TDF HR is 1.25 when the experimental regimen truly provides a 33% reduction in the risk of HIV acquisition relative to FTC/TDF [requiring only 2.5% probability of a false-positive conclusion when the HR truly is 1.25 (Table 3)]. Applying the same "95–95" approach in the men who have sex with men setting and using the iPrEX trial to estimate FTC/TDF provides a 42% (18%–60%) reduction in the risk of HIV acquisition; even if the margin ensures preservation of only 50% of FTC/TDF's effect, only a modest 1.10 NI margin for experimental to daily FTC/TDF HR would be justified. In this setting, approximately 171 HIV acquisition events would be required (Table 3).

Suppose, however, that adherence to daily FTC/TDF is not expected to be high. If FTC/TDF still is used as an active control, the experimental regimen needs to be established to be superior to conclude it is effective. This is plausible if the experimental regimen is a long-acting drug. If an experimental regimen is shown to be superior to daily FTC/TDF active control when adherence to FTC/TDF is not high, trial results may not generalize to settings with high adherence to FTC/TDF.

Scenario C: Alternative Dosing of Oral FTC/TDF Versus Daily FTC/TDF

A trial to assess potential superiority of an alternate dosing strategy for FTC/TDF, compared with daily, could be justified if it were thought that the new dosing might substantially reduce the risk of HIV acquisition, perhaps by achieving substantially higher adherence. However, if alternate dosing for FTC/TDF became an established standard regimen in real world settings (eg, it became common practice to use

FTC/TDF shortly before and after risky sex) or if alternate dosing would be expected to reduce the risk of serious toxicities, conducting a trial to verify that the alternate dosing was not inferior to the daily regimen could be justified. However, since Scenario C does not achieve replacement of FTC/TDF for PrEP, it likely would not be a priority to conduct a large-scale clinical trial simply to establish that an alternate dosing strategy would be noninferior to daily dosing, keeping in mind that establishing NI does not mean the alternative dosing strategy is "at least as good as" daily FTC/TDF but rather that it is "not unacceptably worse than" daily FTC/TDF.[7,8]

Scenarios D and E: New Oral Drug, or Long-Acting Experimental Drug (Injectable or Oral) Versus Placebo, Where Trial Participants Have Access to Background Use of Daily FTC/TDF

Daily FTC/TDF is available for use in the clinical setting addressed by these scenarios. However, we want to improve the level of protection against HIV acquisition by developing a long-acting drug or a new drug with mechanisms of action complementary to FTC/TDF. This approach is particularly appealing in settings where adherence to FTC/TDF was not high, such as in iPrEx, and yet relatively high levels of adherence to the new intervention are expected. In this setting, superiority trials would be conducted, with careful assessment of drug–drug interactions. Such trials could be of moderate to high priority, especially Scenario E, because a drug with a long-acting formulation should have a favorable adherence profile.

An important decision is whether daily oral FTC/TDF should be supplied by the trial in Scenarios D and E. The following considerations should guide this decision. First, to enhance the clinical relevance and interpretability of results, the use of FTC/TDF as a background intervention should match that in the clinical setting of interest. Second, by the principle of "distributive justice,"[9] the trial should provide results that are relevant and informative for the population in which the trial is conducted. By not supplying daily FTC/TDF to trial participants, efficacy and safety results from the trial become directly relevant to the context of FTC/TDF as it is currently delivered. However, it is appropriate to supply daily FTC/TDF to all trial participants if it is expected that the use of FTC/TDF in clinical practice will evolve so that the level of use in the trial matches what will become standard use of FTC/TDF after the trial is completed.

Scenarios F and G: New Oral Drug, or Long-Acting Experimental Drug (Injectable or Oral) Versus Placebo, Where Background Management Properly Does Not Include Daily FTC/TDF

In settings where patients are not willing or able to adhere to daily FTC/TDF, or where communities are not willing or able to provide or support daily FTC/TDF for prevention, finding safe and effective PrEP regimens that are affordable and feasible is a moderate to high priority. Lack of community willingness to support daily FTC/TDF for PrEP could reflect a desire to reserve this regimen for first-line HIV treatment.

To satisfy the unmet needs in these settings, a new drug has to overcome the barriers encountered by daily FTC/TDF. Hence, drugs with long-acting formulations are of greater interest (Scenario G) than alternative daily oral products (Scenario F). Either scenario requires a superiority trial, with a potential need to establish super-superiority by statistically ruling out modest levels of efficacy, such as a 30% reduction in the risk of HIV acquisition.

Of note, it is ethical to conduct placebo-controlled trials of new PrEP agents only in populations where it is anticipated that the new agent, if effective, would become available for use. In particular, it is not acceptable to evaluate a new agent in a population if the reasons that preclude availability of FTC/TDF would also apply to the new agent.

Scenario H: Alternative Dosing Strategy for FTC/TDF Versus Placebo, Where Background Management Properly Does Not Include Daily FTC/TDF

For this scenario to arise, an alternative dosing strategy for FTC/TDF would be viewed as promising, even though daily FTC/TDF regimen is judged to be unaffordable, impractical, or not effective. For illustration, from a closely related field: clinical trials are ongoing to evaluate effectiveness of coital use of a tenofovir gel microbicide in women,[10] even though daily use of the same product was demonstrated to be ineffective.[5,11,12]

To justify a trial of alternative dosing strategies for FTC/TDF, we would need data establishing proof-of-concept that alternate dosing addresses the deficiencies of daily FTC/TDF. The level of priority of this superiority trial would depend on the strength of those previous data.

DISCUSSION

An important goal in HIV prevention research is the identification of safe and effective PrEP regimens that are affordable and feasible and do not interfere with the effects of drugs integral to HIV treatment. With initial progress that has resulted in the availability of FTC/TDF for PrEP, it is likely that subsequent trials will require larger sample sizes and longer duration, whether we pursue settings where FTC/TDF has been shown to reduce the risk of HIV acquisition to relatively low levels or settings where FTC/TDF has failed to provide clinically meaningful protection.

NI trials provide a potentially appealing study design in settings where FTC/TDF has been established to be effective, yet there is still interest in alternative PrEP interventions that are better tolerated, more convenient, less costly, or not involving drugs commonly used for HIV treatment, even if these alternative interventions would have efficacy that is only similar to or slightly better than that of FTC/TDF. Unfortunately, NI trials often require large sample sizes and often yield results that are difficult to interpret due to uncertainty about the validity of their strong underlying assumptions. One key assumption is that historical trials can

provide an unbiased estimate of the active control's effect for the NI trial. When experimental and FTC/TDF regimens demonstrate similar efficacy in an NI trial, if we cannot rely on the validity of that key assumption, how can we distinguish whether the regimens are similarly effective or similarly ineffective? For illustration, suppose the FemPrEP trial conducted in heterosexual women in South Africa and Kenya[4] had been a comparison between an experimental PrEP drug that truly provided no benefit, versus FTC/TDF as the active control. Since daily FTC/TDF provided essentially no benefit in that setting (Table 1), the regimens would have had similar rates of HIV acquisition. If the placebo-controlled evaluation of FTC/TDF provided by the Centers for Disease Control and Prevention's TDF2 PrEP trial conducted in heterosexual men and women in Botswana[3] had been used as the historical trial providing an estimate of the effect of FTC/TDF in the setting of this hypothetical FemPrEP trial (Table 1), we would have concluded that this experimental drug was very beneficial even though it was, in reality, ineffective.

The influence of level of adherence will be an important consideration in the design and interpretation of NI trials of PrEP regimens. A requirement of NI trials is that the active comparator regimen has strong efficacy that is precisely estimated by historical trials conducted in settings similar to the setting of the NI trial. As indicated by the evidence from Table 1, the level of adherence has strong influence on efficacy for PrEP regimens, such as FTC/TDF. Hence, it is likely that NI trials of PrEP regimens will be appropriate only when (1) the active comparator (ie, FTC/TDF) is a potent agent, (2) the active comparator's efficacy was established in a setting of high adherence, and (3) there is reliable evidence that the level of adherence to the active comparator will be equally high in the setting of the NI trial. It is problematic that it is unknown why the participants in Partners PrEP and TDF2 were highly adherent to FTC/TDF while the women enrolled in FemPrEP and VOICE were not. The reasons for these differences must be better understood to be able to justify the NI trial assumption that an unbiased estimate of efficacy of the active comparator in the NI trial can be obtained from data in the historical trials. Without that justification, NI trials will not be interpretable.

Superiority trials provide a clearer path to obtaining reliable evidence of clinically meaningful advances. There are important populations at demonstrated high risk of HIV acquisition where daily FTC/TDF has been found to be inadequately effective. A new product with high potential to achieve protection, either because adherence requirements were less onerous or the drug was more potent, may be the highest priority for moving into efficacy evaluation. Conducting such a superiority trial against the evolving background of PrEP SOC would seem to be addressing a particularly relevant public health question.

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Ethics and Pre-exposure Prophylaxis for HIV Infection

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Abstract: There is increasing evidence that the use of antiretroviral agents (ARVs) can be a safe and effective means of preventing HIV infection. In fact, a combination of ARVs, tenofovir–emtricitabine, was recently approved by the US Food and Drug Administration (FDA) for use as "pre-exposure prophylaxis"(PrEP), and the US Centers for Disease Control and other regulatory authorities have issued guidance concerning PrEP use. Clinicians and policy makers are now faced with questions about the appropriateness of prescribing ARVs to healthy persons who are at risk of becoming infected with HIV, and those at risk of being infected must decide whether to use PrEP. In addition, researcher stakeholders must grapple with determining whether and how PrEP should be included in future HIV prevention research. In addressing such issues, it is important that their ethical dimensions are identified. When using PrEP, 2 broad ethical domains are of special relevance: well-being and justice. Ethical issues related to well-being include safety, parameters of use, risk behaviors, resistance, stigma, and diversion. Those related to justice include access and competing priorities. In research involving PrEP, ethical issues include determining the appropriate control arm and whether PrEP should be included as a part of the prevention package provided to all at risk participants. Although PrEP could play an important role in HIV prevention, understanding and addressing the related ethical issues is critical to its safe, effective, and appropriate use in practice and future research.

Key Words: pre-exposure prophylaxis, HIV prevention, ethics

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There is increasing evidence that the use of antiretroviral agents (ARVs) can be a safe and effective means of preventing HIV infection. Despite mixed data from efficacy trials, the US Food and Drug Administration (FDA) recently approved co-formulated tenofovir–emtricitabine for daily use as "pre-exposure prophylaxis" (PrEP).[1] In addition, the US Centers for Disease Control,[2] the World Health Organization,[3] and other normative bodies have issued guidance regarding PrEP.[4] Clinicians and policy makers are now faced with questions about the appropriateness of prescribing ARVs to healthy persons who are at risk of becoming infected with HIV, and those at risk of being infected must decide whether to use PrEP. In addition, research stakeholders must grapple with determining whether and how PrEP should be included in future HIV prevention research. In addressing such issues, it is important that their ethical dimensions are identified; yet, to date, there have been limited discussions on point, most focusing on population-level issues.[5–7] Accordingly, after briefly delineating current evidence and guidance regarding PrEP, we describe some of the ethical challenges that are associated with PrEP.

EVIDENCE AND GUIDANCE REGARDING PrEP

Although a comprehensive review of the research related to PrEP is beyond the scope of this article, having a sense of the major lessons from this research, especially as they have been interpreted by those with particular expertise in HIV prevention,[8–10] is essential to analyzing the ethical issues associated with PrEP. Data from 3 major clinical trials support the safety and efficacy of oral PrEP: one conducted among men who have sex with men in several countries,[11] one among serodiscordant heterosexual couples in Africa, and one among young high-risk heterosexuals in Botswana.[12,13] Nevertheless, in 2 other major trials involving women in Africa, these results have not been confirmed.[14,15] A study of pericoital vaginal use of a 1% tenofovir gel demonstrated a 39% decrease in HIV incidence compared with a placebo gel among South African women,[16] but a study of daily use of the same product in a similar population did not demonstrate efficacy.[15] A third vaginal gel study is underway in South Africa to see if the initial findings can be confirmed, but currently, the only approved PrEP regimen involves a single oral daily tablet containing tenofovir–emtricitabine.

The discordant results seem to at least be due in part to different patterns of adherence to PrEP regimens.[10] Furthermore, it is important to note that the studies published to date have all used either tenofovir alone or in combination with emtricitabine. Although these agents are well tolerated, there can be mild gastrointestinal side effects, and concerns have been raised about the possibility of renal toxicity and bone density in a minority of patients, particularly in those with preexisting medical conditions, who were not included in the earlier trials. In addition, there are not yet data regarding the long-term safety and efficacy of PrEP. Finally, data are

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currently unavailable regarding the safety and efficacy of PrEP for those at risk for HIV infection due to injection drug use, although it is anticipated that data from a Thai study should be available soon.[17]

Nevertheless, the US FDA approved tenofovir–emtricitabine as PrEP to decrease transmission of HIV among both men who have sex with men and heterosexuals. In addition, guidance regarding oral PrEP has been issued. For example, the US CDC has provided interim guidance for PrEP among men who have sex with men[2] and heterosexual adults.[18] The World Health Organization has issued guidance for PrEP among both men who have sex with men and heterosexuals in the context of demonstration projects, that is, translational projects to assess real-world implementation of PrEP in diverse settings.[3] Each of these documents makes clear the need for PrEP to be accompanied by behavioral counseling, safer sex practices, HIV testing, and safety monitoring.

USING PrEP FOR PREVENTION

When using PrEP for prevention, 2 broad ethical domains are of special relevance: well-being and justice.

Well-being

The use of PrEP promises to help meet the strong moral claim to prevent infection with HIV. However, meeting this claim must be balanced against an array of other threats to the well-being of individuals and communities.

Safety

Safety is a critical consideration in the provision of PrEP. First, the willingness of individuals to consistently use ARVs for prevention raises concerns about safety, in light of adherence challenges when ARVs are used to treat infected persons. In fact, suboptimal adherence has been observed in several of the PrEP efficacy trials.[19] The extent to which adherence is linked to the side-effect profiles is unclear, but it is conceivable that this plays at least some role. For example, PrEP with TDF/FTC may be associated with mild gastrointestinal symptoms, which could result in nonadherence. If a person used PrEP erratically to mitigate side effects, or because of intercurrent psychosocial issues, such as depression or substance use, and continued to engage in unprotected sex, HIV transmission and selection for a drug-resistant viral strain could occur, compromising future treatment options. Second, there are known adverse effects associated with ARVs, such as renal toxicity with tenofovir. Participants in efficacy trials are typically selected because of their lack of concomitant medical conditions, but as PrEP becomes more widely accessible, it is possible that side effects could become more common. These safety issues underscore the need to monitor adherence and potential adverse effects of PrEP.

Parameters of Use

Data regarding the safe and effective use of PrEP are currently limited with respect to particular ARVs, dosing, and populations. As the recent history of randomized trials of PrEP make clear, at present, it would be imprudent to use PrEP outside of the parameters in which data are available because doing so could prove harmful. Along these lines, it is relevant that existing data about safe and effective use were obtained in settings where routine testing and counseling services were available, which may be challenging, but necessary, to reproduce outside of the setting of clinical trials to achieve similar results.

Risk Behaviors

Although PrEP can be effective in preventing HIV infection, it obviously does not prevent the transmission of other sexually transmitted infections, such as gonorrhea, chlamydia, viral hepatitis, and syphilis. Thus, an important concern is that the administration of PrEP in practice does not lead to an increase in risk behaviors, sometimes termed either "risk compensation" or "behavioral disinhibition" that would be expected to enhance the likelihood of acquiring other STIs.[7,20,21] Risk behaviors might include unprotected sex, having additional sexual partners, or engaging in riskier behaviors such as unprotected receptive anal intercourse. Furthermore, it is conceivable that increased risk behaviors might overwhelm the ability of PrEP to prevent HIV infection itself, particularly if adherence is suboptimal, and/or amplifying factors, such as concomitant sexually transmitted infections, mucosal trauma, or a highly infectious partner are present. Although evidence of such changes in risk behaviors has not been reported in the context of the efficacy trials, whether this will remain true outside the research setting is unclear. Consequently, it is critical that effective messages about safer sex practices accompany the use of PrEP.

Resistance

Current treatment of HIV infection involves the use of HAART (highly active anti-retroviral therapy), which entails the use of several ARVs to combat the virus and prevent the development of viral resistance. In contrast, 1 or 2 ARVs are currently used for PrEP. Accordingly, there is a worry that if a person using PrEP becomes infected with HIV and continues to use these ARVs, resistance may develop. This could have implications not only for treatment of the individual but also to the transmission of resistant HIV to others. These concerns highlight the need for frequent high-quality HIV testing among users of PrEP. To this end, the boxed warning for tenofovir–emtricitabine includes cautionary language regarding the need to ensure that those using the product for PrEP are HIV uninfected before initiating use and that they are regularly tested. In addition, the FDA is requiring the manufacturer to test HIV isolates for resistance from those who become infected while using tenofovir–emtricitabine as PrEP.

Stigma

PrEP may be associated with stigma due to the mistaken belief that the use of ARVs indicates that the PrEP user is HIV infected, subjecting that person to the stigma sometimes associated with HIV infection. Furthermore, stigma might arise from moral or cultural attitudes and beliefs about risk behaviors and the character of those who engage in them. It is easy to imagine that those who use PrEP may be assumed to be irresponsible because of perceived promiscuity, despite the responsibility inherent to taking preventive measures. Of related concern is that those using PrEP in some settings

may face difficulty with respect to obtaining insurance and employment given its association with risk behaviors. Obviously, whether and how stigma arises is an empirical matter that will need to be tracked carefully. Successful PrEP implementation may require culturally tailored stigma mitigation strategies that would need to be developed by public health and community leaders.

Diversion

Because the ARVs used for PrEP can be components of HAART, drug diversion is a possible sequel, especially in settings where access to ARVs is limited. Diversion might arise from the well-intended desire to help treat those who are sick or more nefariously from a desire to profit, assuming that a market for these ARVs exists. Nevertheless, the incomplete and likely unmonitored treatment of those who are sick may in the long run be harmful to patients and be associated with the development, and perhaps transmission, of resistant virus.

Justice

As a matter relevant to clinical practice and public health, PrEP involves issues related to justice. In its broadest sense, justice is concerned about fairness, both in terms of processes and the distribution of benefits. Of special importance are the ethical tensions related to access to PrEP and adjudicating competing priorities for the allocation of resources.

Access

For any HIV prevention modality to realize its effectiveness, it must be acceptable to potential users. To date, there are limited data concerning the acceptability and desirability of PrEP among those it would be expected to benefit.[22] Furthermore, it is unclear how acceptability might be related to the delivery systems for PrEP. However, a delivery system based in a hospital or clinic may be well suited to address medical aspects of PrEP but may be less capable of conducting effective behavioral counseling than a nonclinical system (eg, a community-based organization). Moreover, a clinical setting may be costly and may pose barriers to access for healthy persons, who may perceive health care providers as insensitive to their concerns. Such factors need to be considered in designing appropriate delivery systems. Nonetheless, assuming that PrEP is a desirable part of a local HIV prevention effort, it would arguably be reasonable to prioritize access to PrEP regimens for populations for which there are adequate data about safety and efficacy. Where such data do not exist, appropriate research trials should be conducted. Finally, there is a critical set of unanswered questions related to accessing underserved populations (eg, what should be included in the package of essential PrEP services),[6,7] the cost of PrEP, and who should and will pay for it,[23] which directly affect access.

Competing Priorities

Although PrEP offers an important option for HIV prevention, there are now other safe and effective methods that can decrease HIV transmission.[9] Accordingly, justice demands considering the fairness in the distribution of resources for the range of prevention modalities and their expected benefits in reducing the burden of infection among populations and subgroups. After all, the fundamental moral claim for using any of these approaches relates to decreasing the burden of new HIV infections. As a related matter is the distribution of resources not only for the prevention of new infections but also for the treatment of those already infected with HIV.[5] Given the very promising results of early treatment for HIV prevention,[24] determining how best to allocate resources is especially complex. Assuming that funding for ARVs is limited and insufficient to treat those who are infected, some have argued for prioritizing the use of ARVs first to those in certain need of treatment, next for treatment as prevention, and finally for PrEP.[25] In contrast, others have argued at a broader level for privileging prevention over treatment, given that effective prevention will ultimately decrease the numbers of individuals needing treatment.[26] However, given the host of unanswered empirical assumptions regarding the safety, efficacy, and cost of both early treatment for prevention and PrEP among population subgroups, a simple conclusion is not feasible at this time.[6,27] In moving forward, the range of benefits and possibilities should be considered.[20,21] Furthermore, the distribution of such health-related resources must also be sensitive to a variety of other prevalent diseases and conditions that are common among individuals at risk for HIV and among the general population.

HIV PREVENTION RESEARCH AND PrEP

The emerging data regarding the safety and efficacy of PrEP raise important scientific and ethical questions about future HIV prevention research, for both other forms of PrEP[28] and other modalities.

New PrEP Research

Although there is currently strong evidence regarding the specific use of certain ARVs for prophylaxis in some groups, there is arguably a need for additional research to (1) explain the disparate results from earlier research (ie, African women); (2) establish alternative dosing strategies that might be both effective and associated with improved adherence (eg, pericoital oral use, or topical gels, rings, and injectable delivery mechanisms); (3) determine the safety and efficacy of alternative ARVs for PrEP (eg, dapivirine and maraviroc); and (4) determine the safety and efficacy of PrEP in other populations (eg, people who inject drugs). A key ethical issue that will be faced in such trials relates to the selection of an appropriate comparator arm. Assuming that most of the study populations will be similar to those in which PrEP has been shown to be safe and effective, there could be a presumption favoring the use of established PrEP regimens as the comparator arm. However, this could create challenges in trial design. For example, providing oral TDF-FTC to all participants in a study that compared an antiretroviral-containing gel with a placebo gel could be associated with drug interactions and the need to enroll a much larger sample, given that all participants would have access to chemoprophylaxis. None of the potential scenarios are simple, but the ethical principles of well-being and justice must be factored into decisions about trial designs.

Other HIV Prevention Research

Despite recent considerable progress in HIV prevention, additional research will be directed at combination prevention and HIV prevention among hard to reach populations. As in all HIV prevention research, all participants in these trials would be expected to be provided with a "prevention package," that is, a set of established methods for preventing infection with HIV, such as counseling and male condoms. Therefore, it will be essential to consider whether PrEP should be included in the prevention package for HIV prevention trials going forward. Although determining the correct "standard of prevention" to be provided is always complex, this issue will become increasingly knotty given the advances in HIV prevention science and the associated number of possible modalities that could be incorporated in such packages. Although an extensive discussion of this issue is beyond the scope of this article, a fundamental tension arises when providing preventive modalities besides what is being tested in the trial because while doing so may protect participants, it may also undermine the ability of the trial to answer the research question at hand. Furthermore, should participants be provided with preventive methods that are not available outside the trial, questions of fairness to those outside the trial arise. Finally, even if individual methods of prevention are known to be safe and effective, the effects of combining them may remain unclear. Ethics guidance on what should be included differs.[29–31] Given the complexities of these issues, and the likelihood that knowledge will continue evolve, it is critical to engage stakeholders when determining the standard of prevention for each new study and to periodically revisit study designs as new information becomes available.[32]

If PrEP is not provided to study populations where it is known to be effective, researchers need to account for the possibility that some participants may access PrEP outside of the trial, which could affect the integrity of the trial. Furthermore, the informed consent process for enrollment should clearly articulate that PrEP will or will not be provided and should discuss any limitations on use among participants while they are enrolled. It will be important for the trial staff to create a supportive environment for the trial participants, so that any subsequent use of chemoprophylaxis will be reported.

One recent example of an adaptive trial design is HVTN 505, a phase IIB study involving HIV vaccines in high risk American men who have sex with men. The study was conceptualized and implemented before the announcement of the iPrEX results, so access to PrEP was not part of the protocol. However, once the results were available, the protocol was subsequently modified to allow participants to use PrEP, but it was not provided routinely. In addition, participants were educated about the iPrEX study results, asked about PrEP use at subsequent study visits, and the sample size of the study was increased in anticipation of a partial PreP impact on HIV incidence.[33]

CONCLUDING COMMENTS

PrEP is positioned to play an important role in HIV prevention, but its ultimate optimal implementation will require further evaluation. In the meantime, clinicians who prescribe PrEP have an ethical obligation to not only be keenly aware of the current and emerging data concerning PrEP but also of the ethical issues associated with its use. Moreover, learning how to address and manage these issues is central to providing competent care. Accordingly, consideration should be given to developing educational and training programs that include explicit consideration of these ethics issues and their management so that clinicians may be appropriately prepared. That is, there is a tangible need for capacity building in many clinical settings. Similarly, those crafting policies regarding PrEP need to be sensitive to these issues so that resulting programs might be optimally designed. Finally, given the ethical complexities that will be invariably faced regarding PrEP in future research efforts concerning PrEP and those evaluating other promising means of preventing HIV, it is essential that appropriate ethics expertise is incorporated into this work from its outset. Continued analyses of the ethical issues related to PrEP in clinical practice and research will need to accompany evolving data and policies concerning PrEP if its promise is to be fully realized.

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Adult Male Circumcision: Reflections on Successes and Challenges

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Abstract: Voluntary medical male circumcision (VMMC) is a cost-effective HIV-prevention intervention that reduces the risk of HIV acquisition in men by 60%. Although some countries are successfully scaling up VMMC, not all are doing this. When VMMC scale-up experiences are viewed in the context of models for the diffusion of innovation, some important themes emerge. Successful VMMC programs have in common locally led campaigns, a cultural tolerance of VMMC, strong political leadership and coordination, and adequate human and material resources. Challenges with VMMC scale-up have been marked by less flexible implementation models that seek a full-integration of VMMC services at public medical facilities and by struggles to achieve geographic parity in access to care. Innovation diffusion models, especially the endogenous technology model, and multiple levels of influence on diffusion—individual males and their sex partners, communities, and health systems—remind us that the adoption of a prevention intervention, such as VMMC, is expected to start out slowly and, as information spreads, gradually speed up. In addition, the diffusion models suggest that customizing approaches to different populations is likely to accelerate VMMC scale-up and help achieve a long-term, sustainable impact on the HIV epidemic.

Key Words: male circumcision, global scale-up, diffusion of innovation models

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As approaches to improving public health move along the discovery "pipeline," evolving from investigational concepts to evidence-based, effective interventions, the challenge of implementing these interventions on a large scale has often turned out to be quite daunting. Certainly, this has been the case with family planning interventions,[1] and the hepatitis B,[2] and polio vaccines.[3,4] HIV-prevention interventions are now progressing along this pipeline, and the implementation challenges are again underscoring the presence of the gap between evidence and application.

Male circumcision, the oldest and most common surgical procedure performed on newborns and young boys for non-medical reasons, was first proposed as an HIV-prevention intervention for men over a decade ago, based on observational data.[5] There are several plausible biologic reasons as to why the removal of the foreskin would reduce the risk of HIV acquisition among men. The foreskin has a tendency to develop epithelial disruptions, or tears, during intercourse, which may allow HIV a portal of entry, and compared with the tissue of the outer foreskin, the foreskin's HIV target cells (Langerhans cells with CD4 receptors) are closer to the epithelial surface.[6,7] By 2007, three randomized controlled trials conducted among young HIV-uninfected men in Africa demonstrated that voluntary medical male circumcision (VMMC) reduces the risk of HIV infection for men by 53%–60%,[8–10] and additional studies have found that VMMC offers durable protection, with prevention benefits documented 5 years after VMMC,[11] and is cost saving.[12]

In response to these findings, in 2007, the World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS) published recommendations supporting VMMC for HIV prevention in 13 priority countries,[5] all in sub-Saharan Africa, with generalized HIV epidemics and low MC prevalence. Because the impact of the VMMC at the population level is thought to depend on a combination of prevailing MC and HIV prevalence rates and major modes of transmission, the WHO/UNAIDS recommendations did not endorse VMMC as an approach to HIV prevention in countries such as the United States, China, or India.

Despite the scientific evidence and the formal recommendations by WHO/UNAIDS, efforts to scale up VMMC in the priority countries have yielded mixed results,[13] which can be attributed, in part, to the limited supply of health care resources needed for VMMC. The recognition of this shortage has spurred the development of new MC devices which require minimal or no surgery, such as the Shang Ring and PrePex, and new efficiencies, such as the WHO-recommended MOVE model,[14] which increases productivity through task sharing, task shifting, diathermy for hemostasis, and prepackaged surgical instruments. Beyond supply issues, however, demand for VMMC services by sexually active men in many of the priority countries has been low, and it is unlikely that the devices alone will solve all the demand creation challenges.

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Models explaining the diffusion, or adoption, of new technologies may prove to be useful in understanding the factors that contribute to the successes and challenges of accelerating the uptake of VMMC in priority countries. These models, based on the theory of innovation diffusion, largely stem from the work of Rogers[15] who looked at how new technology or new consumer products, such as hybrid seeds or cell phones,[16] are adopted across different populations and cultures. The basic concept is that as new technology is introduced, innovators and early adopters, who are willing to take a risk, try out the new technology. Word spreads about who used the new technology and their experience with it and more people take it up until the local population is saturated. Rogers' epidemic or logistic model[15] is often represented as a symmetric S-shape adoption curve to indicate the initial slow rate of adoption, followed by a rapid rate, and then a slow rate of adoption again, as the new technology matures, the population is saturated and other technologies are introduced into the environment.

Other innovation diffusion models incorporate external sources of information that may influence acceptability,[17] and the heterogeneity of the population[18,19] into the understanding of diffusion and therefore may go further in bridging the gap between research and implementation. For example, the new product growth model incorporates the idea of external sources of information, such as mass media, by categorizing a population into 2 groups: innovators—those who adopt the new technology after learning about it from exogenous information, and imitators—those who learn directly about the new technology from early adopters. A third model, the endogenous technology choice model,[20] goes another step beyond the new product growth model in that it assumes that people in different circumstances make different choices about new technology based on individual preferences. For example, in theory, circumstances such as local customs or community beliefs may make one method of HIV prevention more appealing than another, but in practice, several competing factors may impact choices, as in the scale-up of VMMC.

MC SUCCESSES: CAMPAIGNS, CULTURE, AND POLITICAL LEADERSHIP

A number of countries have used campaigns to create high demand and expand access to services for a defined, short period of time. For example, in Kenya, the government launched the Rapid Results Initiatives, a series of public and clinical health campaigns for several interventions, including a VMMC Rapid Results Initiative in both 2009 and 2010, which resulted in approximately 85,000 VMMCs.[13,21] In Tanzania, VMMC services have been successfully offered through a series of local campaigns,[22] including highly mobile campaigns to remote Lake Victoria islands, where HIV prevalence is higher than that in neighboring regions.[23] Because these remote islands lack health facilities, motor boats bring tents and equipment and staff who then offer MC services.

In both Kenya and Tanzania, where tribal MC is common, VMMC is a concept that has cultural familiarity. For example, young Masai men between the ages of 15 and 20 years undergo circumcision as part of a tribal ceremony marking the coming of age. Over a year ago, Kenya achieved over one-third of its target of 860,000 VMMC procedures,[6] well ahead of other priority countries. This success may reflect the cultural acceptance and almost universal coverage of MC among certain populations, like the Maasai,[24] and the Ministry of Health's (MOH's) efforts to engage traditional leaders in the Luo community to embrace MC as both a traditional practice and a public health intervention.

Political leadership has also been another key ingredient in the expansion of VMMC. In Rwanda, strong leadership by the MOH and the Ministry of Defense and a commitment to forge ahead with new devices have led to approximately 5,700 VMMC procedures performed with PrePEx, the nonsurgical device mentioned above.[25] In Zambia, where the majority of men are not circumcised, leadership and coordination by the MOH, for example, through its "Country Operational Plan for the Scale-Up of Male Circumcision" document,[26] and engagement at the district level during the development of the operational plan may well have contributed to the success of a recent MC campaign, with >60,000 procedures performed in both standing facilities and at mobile sites in August and September 2012.[27] South Africa and Uganda's MC programs started only recently but are now rapidly accelerating. South Africa stands out for the contribution of substantial national treasury funds specifically for VMMC. Although all countries contribute financial support, as government staff and space used for VMMC are not free, few governments budget and allocate tax revenue for this specific service.

MC CHALLENGES: INTEGRATION, PARITY, LOCAL OWNERSHIP, AND QUALITY

Rather than pointing out the countries that have had the most difficulty with their MC programs, it is perhaps more useful to point out themes common to the settings that have not realized their targets. In some locations, VMMC programs began with a strategy that called for MC services to be fully integrated within public medical facilities, rather than using dedicated mobile medical facilities. This goal of an integrated strategy may have been motivated by the possibility of broadly strengthening infrastructure within the health system. But without allocated space and staff time to provide VMMC regularly, even if not full time, the refurbished facility space and staff trained to conduct VMMC are absorbed by the larger needs of the system. Also, demand is rarely constant, so it is understandably difficult to dedicate space and staff when there is no guarantee of clients. Parity, or equity of access, has also posed a challenge in some areas. Although a focused approach is often recommended for multiple reasons, including epidemic impact, logistics, and the likelihood of achieving early successes to catalyze subsequent services, decisions about services are often political. Countries that aim to make services available in all locations at the same time struggle with substantial coordination difficulties.

Although campaigns in Kenya and Tanzania have been successful, especially among adolescents, not all large campaigns have done well. According to mathematical models, the impact on the HIV epidemic increases as the pace and scale of a VMMC campaign increases, making

a rapid and broad campaign desirable. However, such ambitious campaigns may seem to be externally driven and run the risk of losing local leadership, ownership, and eventually, buy-in of communities and then individuals.

Of course, other implementation challenges exist. Donor organizations have fluctuating political priorities and funding. Although there has been focus on the supply side of scaling up VMMC (e.g., MOVE model), demand creation has received less attention, and fear of too much demand has limited the use of mass media in some countries. Some targets may have been unrealistic. Mathematical models describing the potential impact of rapidly achieving high VMMC coverage levels are meant to galvanize commitments and action. Such coverage levels, however, should not define the success or failure of the program any more than failure to achieve antiretroviral therapy (ART) saturation would be regarded as a failure of a treatment program. Although achieving 80% MC prevalence in all WHO-defined priority countries[9] in 5 years has the potential to dramatically reduce HIV incidence, achieving a lower level of coverage or taking a longer time to do so will still reduce HIV incidence.[12] Setting aspirational targets, such as universal access to ART or 80% coverage of MC, in all 13 countries at once is difficult at best, and risks setting the stage for a perceived failure.

PUTTING THE PIECES TOGETHER

Adoption and impact of a new HIV prevention intervention will be driven by efficacy, choice, and complexity. Some interventions may be very effective but have low rates of adoption, whereas others may be less effective but have high rates of adoption. In some instances, the choice about whether to adopt an innovation will be made by men and at other times by women, parents, or medical personnel. Some interventions will be hard to understand, some will be expensive, and some will conflict with social norms.

How do we understand the uptake of VMMC in the light of the diffusion models presented above? None of the diffusion models explain all the elements, but the endogenous technology model may offer a better fit than the other models do, because it accounts for circumstances such as local customs and individual preferences. Local customs are reflected in part by local MC prevalence, and it is not a surprise that this would play an important role in VMMC adoption. But the scale-up of VMMC will also reflect the collective individual decisions within a network, or community, of potential adopters. Instead of relying on diffusion models that focus on the uptake by individuals alone to understand VMMC, a more comprehensive view of VMMC considerations at all levels—individual, community, and within systems—may be better for explaining successful scale-up.

Individual motivations, of course, remain important. Individual perceptions of risk and benefit need to favor VMMC for an individual to choose to adopt this innovation. Related to risk perception, individual need perception has been important to vaccine uptake in general[28] and to polio vaccine uptake in particular.[3] In the case of VMMC, men weigh their perceived need for, and the benefits of, VMMC against other wants and needs, including those related to health. But in many ways, HIV has become much less visible recently, with wider access to ART and lower death rates. It is quite plausible that need perception around VMMC would have been quite different 10 or 15 years ago, when ART was less widely available, and at that time, VMMC may have scaled up rapidly. Improved uptake may be generated by including motivators for male circumcision beyond those related to individual risk perception, such as improved hygiene, perceptions of responsible masculine choice, perceptions of sexual partner preferences, and improved health for their female sexual partners, including a reduced risk of cervical cancer.[29]

In the community, local buy-in is critical and is easier if a new health innovation is already familiar, as seen in Kenya, where local MC rituals make it easier to introduce the related procedure of VMMC. In addition to local customs, it is important to have strategies to increase trust in the "expert system" that is introducing the new health innovation.[30] Confidence in the efficacy of the MC technology, the manufacturers of MC devices, the managers of VMMC programs, and the health care providers conducting the procedures are all critical to the diffusion of MC. Finally, strong central leadership, political commitment, and efficient coordination, and sufficient human and material resources, all contribute to successful uptake.

At the health systems level, there have been challenges with integrated models of MC delivery and in some instances with placing a priority on geographic parity, as described above. In contrast, there has been some success with campaigns. Although campaigns are the antithesis of an integrated model, in that they are time limited and often vertical, the most successful campaigns make VMMC scale-up appear to expand organically from the local community. Hybrid strategies that blend an integrated model with periodic campaigns to propel the rate of adoption, while using phased approach to providing equitable access, appear promising and are starting to yield results. In addition, target setting spans both the community and the health system and plays an important role in determining successes and failures. Setting and maintaining realistic targets, especially local targets, at a pace determined by community leaders and health system stakeholders, is likely to contribute to successful scale-up.

Scaling up HIV prevention interventions is not simple. The diffusion models predict that the adoption of a prevention intervention, such as VMMC, will start out slowly, and as information spreads, adoption rates will increase, slowly, and then speed up. In a setting where the social acceptance of male circumcision is mixed, a strong information campaign might help bring acceptance to a tipping point, where adoption rates can accelerate. In a setting where social acceptance is already relatively high because of cultural and tribal customs, adoption rates may be driven by factors other than information, like perceived cost to individuals. VMMC programs in such settings may need to include some form of a subsidy to cover transportation costs or lost wages as a way to encourage men to actively seek out MC services.

Perhaps then the best strategy for scaling up VMMC lies in customizing the approach to different populations and remembering that scale-up may move more slowly than anticipated or desired, especially at first. Embracing these complexities may help to accelerate the implementation of VMMC scale-up and achieve a long-term, sustainable impact on the HIV epidemic.

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Topical Microbicides—What's New?

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Abstract: Topical microbicides are an important, promising but complex HIV prevention technology under development. After 11 disappointing effectiveness trial outcomes of 6 candidate products (some tested as multiple doses and formulations) over the past 20 years, there is renewed optimism that a safe and effective microbicide will soon be available if the recent success of coitally linked use of the antiretroviral-based microbicide, 1% tenofovir gel, is confirmed. Studies of new antiviral agents, novel delivery mechanisms, and combination/multipurpose products that address challenges of adherence, enhance the effectiveness of tenofovir gel, and address sexual and reproductive health needs of men and women, including preventing HIV infection, are already underway.

Key Words: HIV prevention, microbicide, women, tenofovir gel

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WHAT ARE MICROBICIDES AND WHY ARE THEY IMPORTANT?

Microbicides are promising prophylactic agents under development for use in the vagina or rectum to prevent sexual acquisition of HIV. It is likely that in the future effective microbicides will include an array of products delivered in several formulations, such as gels, creams, suppositories, films, sponges and vaginal rings (akin to the array of fertility control options) and/or meet multiple sexual reproductive health needs enabling users to choose what suits them best at a particular time in their life course.

Their development is critical as it addresses an important gap in HIV prevention options for vulnerable groups such as young women at high risk of acquiring HIV infection sexually but unable to implement current HIV prevention strategies, such as abstinence, use female condoms, or negotiate safer sex practices such as monogamy, medical male circumcision or use of male condoms with their partner. Microbicides, when used rectally, also have the potential to expand the HIV prevention options available to men who have sex with men (MSM) and women who practice anal sex and although less advanced than topical vaginal products, research is already underway to meet this need.

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C.B. was an investigator on the CAPRISA 004 tenofovir gel trial. Q.A.K. and S.A.K. are co-inventors of 2 pending patents (61/354.050 and 61/357,892) of tenofovir gel against HSV-1 and HSV-2 with scientists from Gilead Sciences and are the co-principal investigators of the CAPRISA 004 trial of tenofovir gel. S.A.K. was also the principal investigator on the clinical trials to assess the efficacy of nonoxynol-9 gel, BufferGel, and PRO2000 gel.

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HISTORY OF MICROBICIDE EFFICACY TRIALS

Early Microbicides: Surfactants, Blockers, and Buffers

Notwithstanding their importance, efforts to find an effective microbicide has been hampered by limited investments in the development of candidate products for clinical testing; an unchartered product development pathway; formulation and delivery method challenges; methodological, ethical, and design challenges; limited understanding of mechanism of HIV acquisition in the female genital tract; insufficient advocacy efforts; and uncertainty about user acceptability and demand.

Over the past 20 years of microbicide development, 11 advanced clinical trials of 6 candidate products (some tested as multiple doses and formulations) have been completed. The first microbicides to enter phase III trials were surfactants that act by inactivating pathogens, including HIV, in the lumen of the vagina. The best-known product in this category is nonoxynol-9 (Advantage 24; Columbia Research Laboratories, Rockville Center, NY), an FDA licensed vaginal contraceptive and widely distributed impregnated in condoms for HIV prevention. In its definitive trial among sex workers in gel formulation, it was shown to increase the risk of HIV infection among women who used the product more frequently.[1] Several years later, another surfactant, SAVVY (C31G; Cellegy Pharmaceuticals, Inc., Huntingdon Valley, PA), tested in 2 separate studies in Ghana and Nigeria, was shown to be safe but had no significant effect on HIV prevention, primarily as a result of lower-than-expected HIV incidence rates in the target population[2,3] (Fig. 1).

Studies of the polyanionic sulfated polymers, which have a more limited spectrum of activity, followed. These included cellulose sulfate (Ushercell; Polydex Pharmaceuticals, Nassau, Bahamas), Carraguard (product number PDR98-15; FMC, Philadelphia, PA), and PRO2000. The cellulose sulfate trial conducted in several African countries and a site in India was stopped early because of safety concerns. Cellulose sulfate did not prevent HIV infection and may have increased the risk of HIV acquisition.[4] Carraguard, which was tested among 6202 South African women, was also shown to have no effect on HIV.[5] In 2009, the HIV Prevention Trials Network 035 study showed a 33% lower HIV incidence in women using 0.5% PRO2000 compared with placebo, although the results were not statistically significant.[6] The initial optimism was dampened by subsequent findings from the much larger MDP 301 trial,[7]

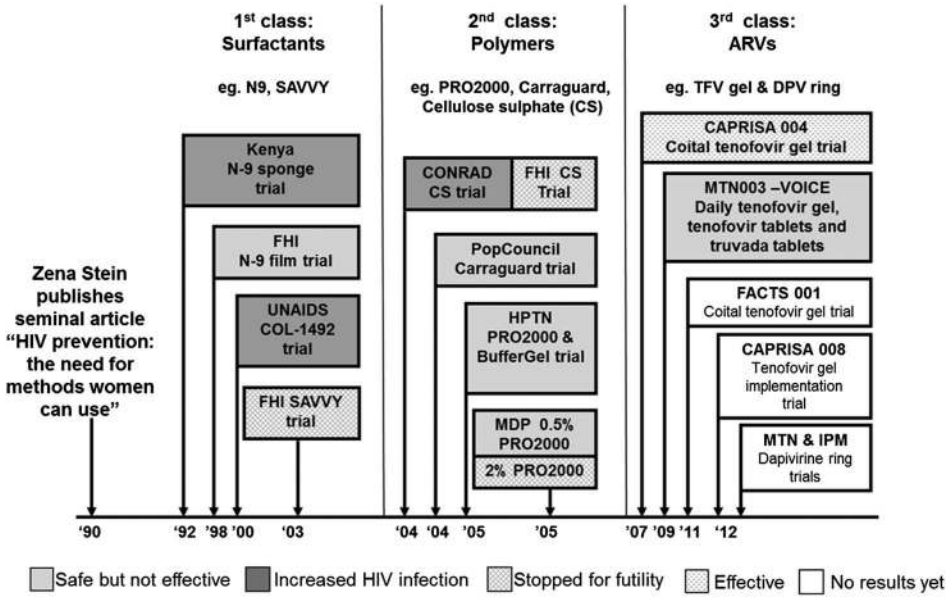

FIGURE 1. Timeline of clinical testing of topical microbicides in women.

comparing 0.5% PRO2000 with placebo groups in 6268 women with 253 HIV infections, which showed no protective effect against HIV infection (risk ratio: 1.05).

BufferGel (ReProtect LLC, Balitmore, MD), designed to maintain a healthy vaginal milieu, was tested alongside 0.5% PRO2000 in the HIV Prevention Trials Network 035 trial but had no effect on HIV acquisition.[6] Given the disappointing clinical trial results with surfactants, blockers, and buffering agents, these candidates developed by small start-up entities have essentially disappeared from the HIV prevention product development pipeline.

WHAT'S NEW

How Antiretroviral-Based Topical Products and Formulations Have Instilled New Hope in Microbicide Development

Currently, the clinical development pathway of microbicides is dominated by antiretroviral (ARV) agents. These agents, originally developed and used successfully as HIV therapeutics, are being tested in clinical trials as potential topical and oral prophylactic agents because their mechanism of action suggests that when used, they may also be able to prevent HIV infection (supported by proof-of-concept in preventing vertical transmission). The topical formulations of the ARV agents/microbicides act locally in the reproductive tract mucosa, have a long half-life, and generally have specific activity against HIV only, and therefore the potential for unwanted side effects is limited, particularly where systemic absorption is low—all desired characteristics of a prophylactic agent to be used by HIV-uninfected, healthy individuals.

Most advanced in this class of product development is tenofovir gel. Developed by Gilead Sciences, Inc. (Foster City, CA), it was the first ARV-based microbicide to enter clinical testing and provided proof-of-concept that an ARV agent can prevent sexual transmission of HIV in women.[8] In 2010, the CAPRISA 004 trial showed that tenofovir gel, applied before and after sex, reduced HIV incidence by 39% (95% confidence interval: 6 to 60), providing hope that a safe and effective microbicide would soon be available.

Following the results of the CAPRISA 004 study, and the fact that the VOICE (Vaginal and Oral Interventions to Control the Epidemic)[9] trial, that included daily use of tenofovir gel, was already in the field, there was much optimism that the first microbicide would soon be licensed and made available. Modeling the modest effects of CAPRISA 004 demonstrated that, in South Africa alone, tenofovir gel could avert 1.3 million new HIV infections and more than 800,000 deaths over the next 2 decades.[10] Disappointingly, none of the 3 products—tenofovir gel, oral tenofovir disoproxil fumarate, or oral co-formulated emtricitabine and tenofovir (Truvada)—tested in the VOICE trial were effective in preventing HIV.[11] The effectiveness of oral tenofovir and Truvada was less than 0% and the tenofovir gel was 14.7% (95% confidence interval: −21 to 40)[11] The reason for the lack of protection against HIV in the VOICE trial is partially explained by the low levels of adherence estimated, based on detectable drug levels, to be 23%, 28%, and 29% in the tenofovir gel, oral tenofovir, and oral Truvada arms, respectively.[11]

The next steps for tenofovir gel, thusfar the only product in the most advanced stage of product development, is dependent on the FACTS 001 trial[12] currently in the field across multiple sites in South Africa and testing the effectiveness of tenofovir gel using the same coitally linked dosing regimen used in the CAPRISA 004 trial. It could provide the data needed for regulatory approval of tenofovir gel. A rectal safety study of 1% tenofovir gel has been initiated in young MSM in the United States and Puerto Rico (Project gel)[13] and a range of pharmacodynamics and pharmacokinetic (PK) studies of various dosing strategies using tenofovir,[14] a reformulated tenofovir gel for rectal use,[15] and a safety study of using 1% tenofovir gel in pregnant and lactating women[16] are ongoing.

Next Steps in Product Development

New ARV Agents and Novel Delivery Mechanisms

Consistent with advances in AIDS treatment regimens that combine ARVs from different classes, microbicides based on a combination of products are seen as offering a potential for synergy, reduced drug resistance, and multiple targeting.

Long-acting, slow release, monthly vaginal rings and/or 2 monthly injectable formulations impregnated with novel ARV agents are currently being assessed as potential microbicides and may have the added advantage of improving adherence as they are less dependent on user compliance linked with oral or gel formulations. The product in the most advanced stage of development is dapivirine (TMC-120), a nonnucleoside reverse transcriptase inhibitor. Two large phase III dapivirine vaginal ring studies were initiated independently in 2012 by the International Partnership for Microbicides and the Microbicides Trial Network and will enroll more than 5000 women from 6 African countries. Preclinical studies of the vaginal ring containing the tenofovir disoproxil fumarate prodrug has been shown to provide complete protection in pigtail macaques after repeat simian human immunodeficiency virus (SHIV) challenge for more than 16 weeks and may soon enter clinical trials.[17] A safety and PK study of the combination of dapivirine and maraviroc in a vaginal ring is also underway in the United States.[18] A long-acting parenteral formulation of GSK744, an analog of the investigational new drug, dolutegravir, has been shown to provide complete protection in macaques following repeated intrarectal challenge with simian human immunodeficiency virus. GSK744 could become a next-generation pre-exposure prophylaxis (PrEP)/microbicide agent suitable for monthly to quarterly injections.[19]

The Importance of the Biobehavioral Nexus

Recent developments in the PrEP and microbicide fields have clearly shown that a successful microbicide product will require more than just an effective anti-HIV product. Despite extensive animal data, a clinical trial,[8] and PK evidence[20] showing that tenofovir gel should be highly protective against HIV, the VOICE and FEMPrEP trials produced contradictory results[11,21] to CAPRISA 004 and other PrEP trials.

Data from the CAPRISA 004 trial[8] demonstrate how adherence can impact on effectiveness. In the CAPRISA 004 trial, HIV incidence among high adherers (gel adherence $> 80\%$) was 54% lower ($P = 0.025$) in the tenofovir gel arm compared with 38% in intermediate adherers (gel adherence 50%–80%) and 28% in low adherers (gel adherence $< 50\%$).[8] More recent modeling estimates, using adherence data from CAPRISA 004, have demonstrated a 90% protection by tenofovir gel in high adherers.[22] A much better understanding of what motivates people to use a product as prescribed and how to objectively measure compliance is needed.

Objectively measuring adherence in microbicide trials has been challenging and is the Achilles heel of microbicide trials, even before the development of ARV-based products. Many of the early microbicide trials relied exclusively on self-reported data, which has several limitations.[23] Dye staining of applicators has been shown to be a reliable and objective method to test vaginal insertion in clinical microbicide trials,[24] but differences in composition of plastics, dyes, and product formulations may impact the accuracy and utility of this method.[25] Other novel technologies, such as UV light assessment of vaginal applicators[26] and wireless technologies, for example, Wisebag,[27] are also being considered for microbicide trials to monitor adherence. Trials of microbicides containing ARV drugs have made it possible to more objectively assess whether the product has been used or not, albeit at study completion. Results of recent trials that have measured levels of drug in the vaginal tract or in the plasma have provided us with a better understanding on the level of drug needed for protection[28] or why some products have not worked.[11,21] The limitation of this method, however, is that we are still unable to measure adherence in the placebo group. The recent approval by the US FDA of Truvada for HIV prevention[29] and anticipated wider access, including provision as standard of care for HIV prevention in microbicide trials, will limit the measurement of drug levels as an indicator of compliance.

The inclusion of an easily detectable marker in the product and the placebo to obtain objective measures of adherence in clinical trials is likely to be required. Exploratory studies have shown that the alcohol and ketone metabolites from vaginal products and condoms that were tagged with esters could be detected using a breath test, suggesting that a breath test for microbicide gel use is physiologically and technically possible.[30,31] The limitation of this approach, however, is that the product being tested will not be the same as the one intended to be marketed, which will result in regulatory hurdles.

Better assessments of exposure to HIV and the ability to measure this will be needed. It is not sufficient to assess exposure to semen as current assays such as Prostate Specific Antigen or Y-chromosome set out to do; it is also essential to develop markers of HIV exposure. New HIV polymerase chain reaction assays that are able to measure low levels of virus in the vagina may make it possible to measure HIV exposure in the vagina. There is a need for a better correlate of risk or protection other than HIV infection in the microbicide field that can be assessed in real-time analogous to the monitoring of viral load and CD4 counts for therapeutic success.

Although strategies for enhancing adherence through novel delivery mechanisms and ARV agents together with better ways to support and measure adherence is critical, these efforts need to be complemented with a better understanding of HIV acquisition vaginally. The establishment of, for example, the role of genital inflammation in HIV acquisition could require a different product development pathway than that used to develop highly active ARV therapy for patients with AIDS. A cellular and immunological analysis of how other biological factors blunt the effectiveness of tenofovir gel will be critically important for new product development and drug delivery systems. Empiric studies of breakthrough infections following prophylactic use of ARV-based microbicides that monitor disease progression, viral evolution, and resistance patterns are also urgently needed for evidence-based decisions on prophylactic use of ARVs.

As PrEP[29] and Treatment as Prevention[32] become standard of care, the conduct of placebo-controlled microbicide trials may become a challenge and underscores the importance of finding novel markers of safety and efficacy other than

HIV infection. The need for a correlate of protection analogous to $CD4^+$ T-cell count and viral load monitoring in treatment is urgently needed, particularly as newer and novel drugs enter clinical testing and placebo-controlled trials become more limited.

Multipurpose Technologies

Another important and emerging field includes products that are capable of meeting multiple sexual reproductive health needs of women, such as HIV risk reduction, fertility control, and treatment of other sexually transmitted infections. Examples of such products, also known as multipurpose prevention technologies, are CONRAD's A10-114 study that combines tenofovir with contraceptives[33] and a reformulated tenofovir gel containing sperm-immobilizing agents that is being tested with the SILCS diaphragm. Although the development of microbicide candidates with multiple mechanisms of action or dual-purpose products is already being tested in early clinical trials, no products have advanced to clinical effectiveness trials. Notwithstanding uncertain regulatory pathways, and logistical and intellectual property challenges of combining biophysically diverse products, effectiveness of each component needs to be demonstrated in separate trials before they can be co-formulated as a combination product. The uncertainty relating to the role of hormonal contraceptives on HIV acquisition is an additional complexity for combining HIV prevention products with a fertility control product.

RESEARCH GAPS

Options to Reduce HIV Infection in Adolescent Women

Women in the 15- to 20-year age group living in sub-Saharan Africa have a 3- to 6-fold higher rate of HIV infection and acquire HIV infection 5 to 7 years earlier than their male counterparts. This age–sex difference in HIV acquisition patterns between men and women continues to fuel the epidemic in this region through sustaining high HIV incidence rates.[34] A complex interplay of biology, gender–power disparities, and social, political, and economic factors contribute to the excess vulnerability of young women to HIV infection compared with men.[35,36] Despite their greater vulnerability, young women particularly in the 15- to 17-year-old age group currently have limited HIV prevention options available to them and would be an ideal target population for the introduction of an effective microbicide for individual and population level benefit. However, none of the microbicide studies to date have been conducted in this important age group, making the evaluation of microbicides in this group a high priority. Notably no topical or oral PrEP trials have demonstrated safety concerns, and large numbers of HIV-infected adolescents are on ARV treatment. The first trial of daily tenofovir gel use among 16- and 17-year-olds (FACTS 002) is planned and will provide important safety and effectiveness data for the use of microbicides in this group, paving the way for adolescent girls to have access to a licensed microbicide.

Rectal Use Studies and Product Formulation

Rectal microbicide development has lagged behind the development of microbicides for vaginal use but are no less important. The mucosal surfaces in the rectum are vulnerable to physical damage during sex and potentially increase the risk of HIV infection. Several surveys indicate that heterosexual anal intercourse is far more common than generally acknowledged[37–40] and women who engage in anal intercourse may be less likely to use condoms and more likely to engage in risky behaviors.[39]

Although vaginal microbicide products may also be beneficial if used rectally, the distinct differences between the vagina and rectum may mean that separate products will be needed specifically for vaginal or rectal use. With some candidate microbicide products, formulations specifically for vaginal or rectal are already available, such as a low osmolality tenofovir gel that has been specifically formulated for rectal use. Clinical trials evaluating the safety and effectiveness of rectal microbicides are under way in MSM populations[13,15] and a number of pharmacodynamics/PK studies are planned using 3 rectally applied tenofovir gel formulations.

Blueprint for Product Development Pathway—Licensure, Policy Formulation, and Programmatic Scale-up and Access to Microbicides

In anticipation of licensure of tenofovir gel and to prepare for the implementation of tenofovir gel into the public health service, an open-label implementation study (CAPRISA 008) is being undertaken as part of posttrial access of tenofovir gel for CAPRISA 004 trial participants. The CAPRISA 008 trial will assess the feasibility of integrating tenofovir gel provision into family planning services as one mechanism of rapidly translating policy to practice pending licensure of tenofovir gel.

Draft normative guidance has already been developed by World Health Organization/Joint United Nations Programme on HIV/AIDS (UNAIDS), and the South African government, who owns the royalty-free license for production of tenofovir gel, has established a public–private partnership with CIPLA-MEDPRO for manufacturing of product. The US Food and Drug Administration have also issued a draft guidance document that provides recommendations for the development of vaginal microbicides for the prevention of HIV infection. Specifically, this guidance addresses the overall development program and clinical trial designs to support the development of vaginal microbicide drug products.[41]

Investments in Microbicide Development Still Largely in Public Sector

Although funding of microbicide research has significantly increased over the years, it still lags far behind research and development funding for other HIV prevention technologies, such as HIV vaccines. In 2011, the total global investment for microbicide research and development was US$186 million. This is compared with funding of US$845 million

for HIV vaccine–related research and development in the same year: 4.5 times more than microbicides.[42] A successful microbicide product will require extensive and sustained investment in research and development. The product pipeline in general needs a large number of products in phase I because of the high attrition rate before a product warrants assessment for efficacy against HIV infection.

Anecdotal concerns about increased pressure for the emergence of resistant strains of HIV in breakthrough infections in individuals using oral or topical ARVs prophylactically have remained unfounded but attention and investments need to continue for ongoing monitoring in both the therapeutic and the prophylactic use contexts because the life span for both indications could be limited as a result of increases in circulating drug-resistant strains. A pipeline of new products will be necessary to address the declining utility of previous microbicides because of drug resistance. At present, the dearth of new classes of products in the phase I pipeline is a source of major concern.

Funding for microbicide research and development may become even scarcer in the future if limited financial resources are redirected to implementation of PrEP, other HIV prevention strategies, HIV treatment, or other diseases. The widespread availability and accessibility of PrEP and treatment as prevention may take several years to realize as the targeting and implementation of this strategy in different epidemic contexts needs to be unraveled. Even when PrEP is widely available, individuals will need access to a range of methods to protect themselves from HIV to ensure the majority of sex acts are protected. The development of other HIV prevention technologies like microbicides therefore remains important particularly for young women in sub-Saharan Africa who have limited negotiating power to implement the current and new HIV prevention options that are dependent on use by their sexual partner.

CONCLUSIONS

ARV-based microbicides provide real potential to influence the course of the HIV epidemic because they fill an important gap for women-initiated anti-HIV–specific prevention methods and could potentially offer an alternative HIV prevention option for MSM. Thusfar, only coitally linked use of tenofovir gel has demonstrated moderate effectiveness in preventing HIV infection, and the findings of a confirmatory trial, FACTS 001, are eagerly awaited as an important next step toward licensure of tenofovir gel. Studies of new antiviral agents, novel delivery mechanisms, combination/multipurpose products, and the role of biological factors in blunting efficacy of ARV agents that address challenges of adherence and enhance the effectiveness of tenofovir gel are already underway to further enhance sexual and reproductive health needs of men and women and efforts to prevent HIV infection.

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Translational Research Insights From Completed HIV Vaccine Efficacy Trials

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Abstract: The development of a safe and effective HIV vaccine remains a challenge. The modest efficacy seen in the RV144 vaccine trial represented an important milestone for the field. Results from all efficacy studies done to date have generated new information, which has advanced the HIV vaccine field in important ways. In this article, we review the translational research insights from the vaccine efficacy trials completed and fully analyzed to date. We also describe the recent advances in the search for broadly neutralizing antibodies and discuss potential approaches to circumvent the challenge posed by the enormous diversity of HIV-1. The experience from the past 5 years highlights the importance of conducting efficacy studies that continue to move us closer toward the goal of a safe, effective, durable, and universal HIV preventive vaccine.

Key Words: HIV vaccine, efficacy trials, clinical trials, vaccine design

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INTRODUCTION

The last several years have seen considerable developments in the area of HIV biomedical prevention, and the field has been reinvigorated by the results of several randomized controlled clinical trials in the area of antiretrovirals for prevention, and both systemic and topical antiretrovirals as pre-exposure prophylaxis.[1–4] Yet, it seems axiomatic that the key to the ultimate control and eradication of the HIV epidemic is development of a safe, effective, durable, and universal HIV vaccine. Despite advances in elucidating the structure of broadly neutralizing antibodies (BnAbs), approaches to circumvent the great diversity of HIV, this goal is still some years away. Yet, insights from recently completed efficacy trials have unlocked new avenues of investigation that may inform design and implementation of future HIV vaccine studies.

EFFICACY TRIALS COMPLETED TO DATE

Since 1987, more than 200 vaccine products have been tested but only 4 have advanced to efficacy trials.[5,6] These studies represent diverse approaches to inducing protective immunity, for example, by eliciting neutralizing antibodies, cell-mediated immune responses, or combined humoral and cellular responses (Table 1). The first 2 efficacy studies, VAX004 and VAX003, evaluated a bivalent gp120 subunit (AIDSVAX) designed to elicit antibodies specific to the viral envelope (Env). The products failed to prevent HIV-1 acquisition, delay progression of clinical disease, or reduce HIV viral load among those who seroconverted.[7–10] Although the vaccine was immunogenic, antibodies elicited were not capable of neutralizing genetically diverse circulating HIV strains.[11]

The next immunogen, recombinant adenovirus serotype 5 (MRKAd5) vector vaccine, evaluated in the Step and Phambili trials, represented a shift in focus to eliciting the production of HIV-specific cytotoxic T lymphocytes, which in infected individuals contribute to control of viral replication to varying degrees.[12] In non-human primates, depletion of $CD8^+$ lymphocytes has been shown to correlate with rapid increase in viremia, and, conversely, vaccine-induced potent cytotoxic T lymphocytes responses have resulted in control of viral replication and prevention of disease progression.[13–17] This evidence lent support to exploration of a vaccine strategy that may reduce HIV viral load and potentially prolong disease-free survival rather than prevent acquisition. The Step Study was halted in 2007 after the first interim analysis because it failed to achieve its primary end points of preventing HIV-1 infection and/or lowering viral load set point.[18–20] Furthermore, the vaccine demonstrated an enhanced risk of infection in uncircumcised men with preexisting immunity to adenovirus serotype 5. Extended post-unblinding follow-up data from the Step cohort revealed that the risk of HIV acquisition peaked shortly after vaccination and waned after 18 months for uncircumcised and adenovirus serotype 5 seropositive men who received the vaccine.[21]

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TABLE 1. Completed HIV Vaccine Efficacy Trials

Trial (Location; Dates)	Vaccine Regimen and Strategy	Vaccine Strategy/Platform	Study Population	Results	Key Lessons Learned
VAX004 (US, Canada, the Netherlands; 1998–2003); VAX003 (Thailand; 1999–2004)	AIDSVAX B/B: Recombinant gp120 subunit; AIDSVAX B/E	HIV envelope protein	MSM and heterosexual women (N = 5417); Male and female IDU (N = 2546)	No vaccine efficacy: VE 6% (95% CI: −17% to 24%) in VAX004 and 0.1% (95% CI: −30.8% to 23.8%) in VAX003. No effect on VL/CD4 count in infected vaccinees	Reinforced the need to (1) elicit potent neutralizing antibodies against diverse HIV strains; (2) enroll diverse participants at risk of HIV
RV144 (Thailand; 2003–2010)	ALVAC: Canarypox (gag, pol, env) + AIDSVAX B/E recombinant gp120	Viral vector prime + protein boost	Men and women at low or medium risk of HIV (N = 16,402)	31.2% (95% CI: 1.1% to 52.1%; $P = 0.04$) in primary MITT. No effect on postinfection VL or CD4 count; lower VL in semen in vaccine vs. placebo recipients	In-depth assessment of immune correlates of infection. Emphasized (1) the importance of evaluating vaccine-induced responses at the mucosa and (2) that presence of the viral envelope is likely a critical vaccine component
Step Study/HVTN 502 (North America, Caribbean, South America, Australia; 2004-2009); Phambili/ HVTN 503 (South Africa; 2006–2009)	Recombinant Ad5 (Clade B gag/pol/nef)	Viral vector	MSM and heterosexual men and women (N = 3000); Heterosexual men and women (N = 801)	No effect on HIV-1 acquisition or VL in Step or Phambili. Increased HIV infection rate in subgroup of Ad5 seropositive, uncircumcised MSM in Step. NS reduction in early VL set point among women in Phambili	Sieve analysis demonstrated a degree of vaccine-induced pressure on breakthrough viruses. Highlighted value of collecting quality specimens at key timepoints, especially at post-seroconversion timepoints

Ad5, adenovirus serotype 5; CI, confidence interval; HVTN, HIV vaccine trials network; IDU, injection drug user; MITT, modified intent-to-treat analysis; MSM, men who have sex with men; NS, nonsignificant; VE, vaccine efficacy; VL, viral load.

No efficacy was seen in the Phambili study but, in contrast to the Step trial, adenovirus serotype 5 seropositivity and uncircumcised status among men was not significantly associated with increased HIV acquisition risk; a nonsignificant trend toward lower early viral load and slower decline in CD4 count among female vaccine vs. placebo recipients was observed.[19]

The results of the MRKAd5 vector T-cell vaccine were both a disappointment and time for reflection for the field. Despite the lack of efficacy, however, viral sequencing of earliest breakthrough isolates among HIV-infected Step vaccinees (sieve analysis) demonstrated that the vaccine induced T-cell–mediated immune pressure on the viruses, particularly in individuals with protective HLA class 1 alleles.[22,23] This demonstration of an immune selective pressure, although much weaker than what had been hoped for, provided clues about potential strategies to improve on the T-cell–based vaccine concept and highlighted the importance of collecting samples at key timepoints (eg, earliest post-seroconversion) to allow assessment of whether or not vaccine-induced immune responses have the potential to block certain viruses.

After the negative results of 3 efficacy trials, the RV144 vaccine trial in Thailand was an important milestone for the vaccine field, and its results infused investigators with a renewed sense of enthusiasm. The study evaluated a heterologous prime–boost vaccination strategy consisting of a recombinant canarypox vector vaccine expressing *gag*, *pol*, and *env* followed by a bivalent gp120 subunit vaccine boost; the gp120 protein was identical to the immunogen used in VAX003/VAX004.[24] The RV144 vaccine did not elicit BnAbs nor did it elicit measurable $CD8^+$ T-cell responses to reduce viral replication. However, it induced antibody-dependent cellular cytotoxicity (ADCC) responses and neutralizing antibodies only to easy-to-neutralize viruses.[25] The vaccine's modest efficacy of 31% in preventing heterosexually acquired HIV infection approached nearly 60% through 6 months after immunization and appeared lower in higher-risk vaccinees in post hoc analyses. These results highlighted the importance of the viral challenge dose and inducing sustained antibody responses over time.

Although longer follow-up of HIV-infected individuals (roll-over study RV152) revealed that the vaccine had no effect on the plasma HIV-1 RNA levels and CD4 cell count after seroconversion, reduced HIV viral load was noted in the seminal fluid in male vaccinees (but not in cervicovaginal lavage samples in women). These results suggest that the vaccine was capable of eliciting immune responses in the

mucosal compartment that were not apparent in the peripheral blood,[26] thus underscoring the critical importance of evaluating responses at both sites. Unfortunately, limited sampling in RV144 did not permit assessment of vaccine-induced cellular or humoral immune responses at the mucosa. Thus, in the wake of these findings, concerted efforts have been made to optimize sampling techniques to assess humoral and cellular responses in the genital compartments and incorporate mucosal sample collections into vaccine trials to extend the analyses of correlates of protection or risk.

LESSONS LEARNED FROM COMPLETED CLINICAL TRIALS TO DATE TO HELP US CONFRONT MAJOR CHALLENGES IN THE FIELD

AIDSVAX failed, when administered alone in VAX004 and VAX003, but led to modest success, in RV144, in combination with a viral vector prime. The reasons for the success of RV144 remain to be fully elucidated, but these results have refocused the efforts on eliciting potent and durable humoral responses, have emphasized the desire to include an envelope containing protein boost in the regimen, and have given further stimulus to developing an immunogen that will induce broadly acting and potent neutralizing antibodies.

Intense laboratory and biostatistical analyses were launched to identify correlates of protection in a case–control study of 41 infected and 205 uninfected vaccine recipients in RV144.[27] A range of immune parameters was assessed and 6 [five different antibody responses: HIV-1 neutralizing antibodies, binding of plasma IgA antibodies to Env, IgG antibodies to variable regions 1 and 2 of gp120, IgG avidity for Env, level of Env-specific $CD4^+$ T cells, and ADCC; one cellular response: $CD4^+$ T-cell cytokine production] were chosen to evaluate their relationship with HIV-1 infection risk. Two strong correlates of risk of infection were found: (1) level of plasma IgG antibodies binding to the V1V2 loop region of gp120 was associated with decreased risk of HIV and an estimated 71% reduction in the risk of infection (odds ratio = 0.29, $P = 0.02$) was noted in vaccinees with high, compared with low, antibody responses to V1V2; and (2) high plasma level of IgA antibodies to Env was associated with increased infection risk. Further analysis of binding antibody levels revealed that in vaccinees with low, but not high, levels of IgA antibodies, the other immune parameters (IgG avidity, ADCC, nAb, and Env-specific $CD4^+$ T cells) were inversely correlated with risk of infection, although the correlations were of borderline significance.[27] It remains to be seen what the significance of these binding antibodies is, but the proposed hypotheses are that the protective effect of high concentrations of IgG antibodies to scaffolded V1V2 region and its effector functions is diminished by high plasma levels of IgA to the HIV-1 envelope.[23,28] These non-neutralizing, or binding antibodies, can recruit innate immune cells via their Fc fragments and trigger killing of infected cells via ADCC, thus underscoring the importance of exploring these Fc-related antibody activities, in addition to classic neutralization, in future vaccine strategies. The role of Fc receptor polymorphisms and other genetic factors that may play a role in modulating the immune responses to the vaccine is under evaluation.[29,30]

In parallel analyses, Rolland et al[31] compared the viruses isolated from infected vaccine and placebo recipients and found evidence that the vaccine induced selective pressure on the virus either by blocking certain viruses from establishing infection or driving escape mutations after infection. Specifically, in an analysis restricted to V1V2, 2 amino acid sites were identified in the V2 region (at positions 169 and 181) that were associated with protective vaccine-induced immune responses, suggesting that the vaccine "blocked" or "sieved" viruses with specific signatures in the V2 region of the envelope. Recent post hoc analyses that focused on a wider range of antibody responses and epitope mapping to the V2 region confirmed a preferential targeting of regions in gp120 identified in the sieve analysis and the correlation with a lower rate of infection in the vaccinees.[32,33]

These data taken together with the correlates analyses and ongoing work pointing to the critical nature of the V2 loop in early viral transmission, mediating ADCC, and neutralization,[32,34–36] further support the hypotheses that antibodies to V2 had a role in the partial protection conferred by the RV144 regimen.[31]

These results have influenced our approach to the next generation of vaccine strategies. For example, vaccine candidates are being screened for their ability to induce IgG antibodies to scaffolded V1V2 of gp120. It is worth noting, however, that given the complex steps in the viral entry, interaction with multiple receptors and an interplay of host and viral factors, it will be important to investigate vaccine strategies that elicit antibodies against other parts of the viral envelope and stimulate effective cellular responses.[37]

CIRCUMVENTING NEUTRALIZING ANTIBODY AND VIRAL DIVERSITY

The RV144 correlates findings dovetail with recent advances in isolating BnAbs from humans. It has been shown that 2–4 years after infection, up to 25% of HIV-1–infected individuals develop BnAbs, creating optimism that a vaccine inducing the "right" antibody could be successful.[38–42] These BnAbs and the epitopes they recognize have been studied extensively to better define targets on the HIV envelope that could be used to design active immunogens with the hope of eliciting antibodies with strong neutralizing potential. Importantly, these antibodies can also be evaluated as passive immunoprophylaxis agents, perhaps in combination with other monoclonal products or with vaccines.[37,43] Other approaches under investigation include using vector-mediated delivery of genes expressing the desired BnAb, an approach that has recently been evaluated in animal models[44] and has the potential advantage of circumventing the need for repeated injections of antibodies.

The enormous diversity of the virus is emblematic of the challenges to HIV vaccine development. Very high number of replication cycles, the error-prone reverse transcription due to lack of proofreading activity, and high rate of recombination between variants within an infected person[45–49] all lead to rapid creation of a large pool of HIV-1 variants in each infected individual. Pressure from host immune cellular and humoral

responses leads to even more viral diversity.[22,31,50–58] As a result, the amount of diversity within an individual can exceed the variability generated over the course of a global influenza epidemic, the latter of which results in the need for modification of the vaccine inserts each year.[59] Most heterosexually infected subjects are infected with a single HIV-1 transmission/founder variant and very few mutations occur in the first 2 months after infection. Focusing on the very early events before establishment of HIV-1 infection and understanding the complex host and viral factors leading to one or few founder viruses getting through are thus critical to circumventing the diversity challenge.[60,61]

Equally critical is understanding of the interplay between early viral evolution from the time of transmission and the development and maturation of BnAbs. It is known that very high level of mutations (somatic mutations) over time are necessary for the evolution of broad and potent anti-HIV antibodies that pose a considerable challenge for vaccine design.[62] Recent investigation into the coevolution of the virus and the BnAb shortly after seroconversion presented an opportunity to map out the pathways that lead to generation of these antibodies.[63] Evidence that certain envelope proteins of the founder virus are more likely to stimulate evolution of BnAbs may present an opportunity to vaccinate with naturally derived viral envelopes that could drive the desired B-cell responses and induce the development of broad and potent antibodies.[64]

CONCLUSIONS

The results of RV144 and correlates analyses that followed were an important milestone for the vaccine field by opening new avenues of research and investigation.[28,37,65] There is, for example, considerable interest in extending the RV144 findings to other populations, HIV-1 subtypes, and risk groups. Plans are underway for phase 2 and 3 studies to explore whether the addition of booster dose of protein or other adjuvants would result in more potent and durable antibody responses over time.

It is more than likely that an efficacious and durable vaccine will need to elicit a balance of responses,[23,66–68] and current prime–boost vaccine strategies aim to elicit a combination of B-cell, $CD4^+$, and $CD8^+$ T-cell responses. For example, vaccine regimens that use DNA and viral vectors (eg, NYVAC and MVA) are under investigation alone or in combination with protein boosts in an attempt to induce durable cellular and humoral responses.

Although the HIV-1 vaccine field has experienced its share of disappointments and challenges with a succession of negative efficacy trials, translational research results from completed and fully analyzed studies generated new critical questions that have advanced the HIV vaccine field in pertinent ways (Table 1). Experience from the past 5 years, and in particular lessons learned from the immune correlates work in RV144, highlight the critical importance of conducting efficacy studies that continue to drive us closer toward a safe and effective preventive vaccine.[69] Moreover, as the biomedical prevention landscape evolves and prevention technologies intersect, opportunities may emerge to evaluate combination strategies to achieve incremental but important reduction in HIV incidence.

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Preventing HIV Among Young People: Research Priorities for the Future

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Objective: To review the current state of knowledge on the prevention of sexual transmission of HIV in adolescents and to highlight the existing gaps and priority areas for future research.

Background: A disproportionate burden of HIV infections falls on adolescents, a developmental stage marked by unique neural, biological, and social transition. Successful interventions are critical to prevent the spread of HIV in this vulnerable population.

Methods: We summarized the current state of research on HIV prevention in adolescents by providing examples of successful interventions and best practices, and highlighting current research gaps.

Results: Adolescent interventions fall into 3 main categories: biomedical, behavioral, and structural. The majority of current research has focused on individual behavior change, whereas promising biomedical and structural interventions have been largely understudied in adolescents. Combination prevention interventions may be particularly valuable to this group.

Conclusions: Adolescents have unique needs with respect to HIV prevention, and, thus, interventions should be designed to most effectively reach out to this population with information and services that will be relevant to them.

Key Words: adolescence, HIV, prevention

(*J Acquir Immune Defic Syndr* 2013;63:S155–S160)

INTRODUCTION

Young people are disproportionately affected by HIV globally; 25% of infected persons are aged between 10 and 24 years.[1] Those aged 15–24 years have 35% of new infections, resulting in 900,000 new infections occurring annually.[2] The greatest burden of HIV among young people is in sub-Saharan Africa. Here, young women have almost 8 times the HIV prevalence as do same-age men,[2] and their annual HIV incidence is an estimated 8%.[3,4] By contrast, in the United States and in Europe, young men who have sex with men are at the greatest risk of developing infection, particularly young men who have sex with men of color.[2] However, in much of Eastern Europe and Central Asia, young injection drug users and their sexual partners have the highest risk.[2] Clearly, adolescents make up a heterogeneous population; risk factors for HIV depend both on individual characteristics and social/environmental contexts. This diversity must be addressed in interventions.

In this article, we highlight the unique needs of adolescents with respect to biomedical, behavioral, and structural interventions that present the greatest promise in preventing sexual transmission of HIV. We also highlight the existing gaps and priority areas for future research. We use the terms "adolescent," "youth," and "young people" synonymously, defining adolescence as the developmental stage between the ages of 13 and 24 years.

WHY ARE ADOLESCENTS A UNIQUE POPULATION?

Adolescence has been described as "a period of momentous social, psychological, economic, and biological transitions."[5] It is a time when substantial brain development

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occurs, including the capacity for complex conceptual thinking.[6] The combination of a heightened responsiveness to rewards coupled with immaturity in the behavioral control areas of the brain may lead to the risky decisions and emotional reactivity that characterize adolescence.[7] The exploration and the formation of identity are considered by many to be the primary developmental goal of adolescence.[8,9] Socially, adolescents are searching for a sense of belonging from peers, who influence their behavior.[10–12] Adolescence is also marked by social transitions such as finishing school, finding employment, independent living, first sexual relationships, pregnancies, and marriage. These milestones occur during a period of decreased adult supervision when young people still have limited knowledge, self-confidence, and life skills, which can lead to engagement in behaviors that heighten HIV risk.

HIV PREVENTION AMONG ADOLESCENTS

Numerous risk and protective factors operate at multiple levels, including the individual, dyad (peer/partner/parent), community (eg, school environment), and societal levels. Identifying the determinants of risk and protective behaviors is necessary to ensure that interventions are appropriate to the population and context where they are delivered. The need for combination HIV prevention strategies, incorporating interventions that address biological, behavioral, and structural factors has been emphasized as being central to impacting the epidemic.[13] Research is needed on selecting and optimizing these combinations for greatest effect, particularly among adolescents. Significant gaps in HIV prevention knowledge for adolescents remain (Table 1).

Biomedical Interventions

Recent successes in HIV prevention have been predominately biomedical and include antiretroviral therapy (ART) for prevention, voluntary medical male circumcision (VMMC), and vaginal microbicides.[14–19] Both treatment as prevention (ART taken by HIV-infected individuals to reduce HIV transmission) and preexposure prophylaxis (PrEP; ART taken by HIV negative individuals to prevent HIV acquisition) demonstrate effectiveness in preventing HIV acquisition or transmission. Although PrEP has been found to be effective in 1 randomized controlled trial (RCT) among men who have sex with men,[18] results from 4 trials among heterosexual individuals have been mixed with 2 trials showing that PrEP was effective[15,20] and 2 trials finding no effect.[21,22]

There are numerous reasons why the results of trials among heterosexual individuals may be conflicting, although adherence is likely one of the most important drivers of efficacy.[23] In fact, in the VOICE trial, adherence, as measured by drug levels in blood, was particularly low (29%) despite the fact that self-reported adherence and pill count suggested good adherence (90%). Being over the age of 25 years was a significant predictor of drug detection in the blood.[22] In contrast, data from the Partners PrEP trial found that daily oral tenofovir (TDF) and emtricitabine/TDF (FTC/TDF) were as efficacious in young women under the age of 30 years as among all women. Specifically, the efficacy of TDF among women

TABLE 1. HIV Prevention Research Gaps for Adolescents

Area	Knowledge Gap
Biomedical	Methods to enhance monitoring and measurement of adherence to biomedical interventions
	Interventions to enhance adherence to biomedical interventions
	Acceptability and safety of biomedical interventions
	How to enhance uptake of biomedical interventions among adolescents who will benefit from them
	How adolescents choose biomedical prevention interventions
	How fertility desires and intentions affect uptake and acceptability of biomedical interventions
	How serostatus of a couple affects the uptake and acceptability of biomedical interventions
	Social marketing of biomedical interventions.
Behavioral	Undertaking formative work to develop culturally appropriate behavioral interventions rather than adapting those based on western psychological models
	Understanding how to maintain intervention effects overtime (durability of effect)
	Understanding sexual relationship patterns (ie, longitudinal partnership formation, types of partners, frequency of sex)
	Methods to obtain valid self-reported risk behaviors and risk perception
	How best to use new technologies and media for prevention and care
	Partner level interventions. Ability to identify main sexual partners and engage in interventions or refer for care
	Adaptation and extension of best-evidence interventions in the United States to high-prevalence settings
Structural	How to effectively and acceptably integrate HIV prevention with other youth-friendly services
	Role of school health in HIV prevention
	Structural barriers to HTC and linkage to care
	HTC models and methodologies
	Integrated sexual and reproductive health packages
	Socioeconomic interventions
	Interventions that address gender inequity/GBV
	Community mobilization to increase uptake of HIV prevention
	Utilization of technology (eg, cell phones or computer) in interventions
Positive prevention	Enhancing linkage and retention to care
	Greater understanding of the treatment cascade in adolescents
	Interventions to assist with disclosure
	Integrated reproductive health services, in particular contraception and PMTCT
	How best to support the transition from pediatric to adult services
	How to tailor clinical services and monitoring for adolescents

(*continued on next page*)

TABLE 1. (*Continued*) HIV Prevention Research Gaps for Adolescents

Area	Knowledge Gap
Ethicolegal	Licensure for biomedicals—efficacy or extrapolation and safety
	Age to roll down to and when in the licensure pathway
	Issues of consent and consent waiver
Crosscutting practice/research	Translating interventions from theory/formative research to practice-implementation science
	Cost effectiveness
	Modeling of effect sizes and potential impact of various interventions
	Combination prevention interventions

<30 years of age was 77% [95% confidence interval (CI), 29 to 92] and the efficacy of FTC/TDF was 72% (95% CI, 25 to 90) compared with all women in whom the efficacy of TDF was 71% (95% CI, 37 to 87) and FTC/TDF was 66% (95% CI, 28 to 84).[24] These discrepant findings in PrEP trials for young women highlight the need for well-designed PrEP pilot studies to better understand discrepancies between self-reported measures of adherence and actual use, best dosing for young women (e.g. daily vs. intermittent), motivations for young women to participate in trials, and appropriate messages and interventions to support adherence and methods that allow participants to accurately report usage and likes and dislikes of products in trial settings. Thus, while promising, questions remain about the scalability and generalizability of ART for prevention in general and in particular to adolescents.

Although adherence to ART is critical for treatment and prevention, taking medication in the long term is challenging. Adolescents with HIV are less likely than are adults to be adherent to ART.[25–29] A literature review examining medication nonadherence among adolescents suggests that simple solutions remain elusive.[30–34] For HIV-uninfected youth, low HIV risk perception may result in a lack of interest in or poor adherence to interventions such as PrEP or microbicides.[35] Furthermore, adolescents are often not in long-term relationships; it is unclear how partnership characteristics affect adherence to prevention interventions. More research is needed among adolescents to understand testing, linkage to and retention in care, and understand factors affecting the uptake of biomedical prevention interventions.

Vaginal and rectal microbicides, applied topically before sex, may be appropriate for young women and men who have sex intermittently. Although 1 trial of coitally dependent vaginal TDF was found to show signs of efficacy among women in South Africa,[19] the use of daily topical TDF was found not to be effective in a second trial in Africa.[22] The explanation for differences in the studies has been attributed to women not using the product, again stressing the fact that adherence is critical to the efficacy of these interventions.[23] Two safety and acceptability trials of a TDF gel-based microbicides in adolescent women are planned in the United States (Kapogianis B. National Institute of Health and Microbicides Trial Network plan safety and acceptability trial of tenofavir gel-based microbicide in adolescent women. 2012. Written personal communication) and in South Africa.[36] A phase 2 trial of rectally applied TDF gel among men and transgendered women will begin enrollment soon and would benefit from bridging studies to adolescents following sufficient safety signals.[37] Research evaluating how best to support uptake, delivery, and adherence will be required to facilitate widespread implementation.

Given the high levels of unplanned pregnancy and unmet need for contraception among many young women in high-prevalence settings, multipurpose technologies, methods that could prevent HIV, other sexually transmitted infections and pregnancy, are urgently needed.[38] Some products are in development, but their acceptability and safety for adolescent girls are unknown. Interventions integrating the provision and uptake of sexual and reproductive health services with HIV prevention need to be evaluated.

VMMC reduces HIV risk by approximately 65% and reduces the risk of sexually transmitted infection acquisition and transmission.[16,17,39] An additional benefit of encouraging early VMMC is that it is almost invariably preceded by HIV testing and counseling (HTC). Given the low uptake of HTC in young men in some settings, there is a need to better link adolescent VMMC with interventions to encourage healthy behaviors including regular HIV testing.

Special Considerations

Most of the research on biomedical interventions has been conducted in adults, partly due to the ethical complexities of research in minors. Although there is increasing recognition of the importance of engaging children and adolescents in research, there remain ethical, legal, and logistical challenges.[40,41] Inclusion of minors in clinical research is governed by ethical principles that vary globally but generally consider need, risk, benefit, and consent.[42,43] Who consents for adolescent involvement is typically governed by the age of the majority by state and/or country with some exceptions. There are also important considerations of the appropriate timing of adolescent involvement in the research of the clinical development of a product or intervention. Excluding adolescents from these studies may delay access to prevention interventions. It is essential that biomedical prevention interventions be implemented with a better understanding of behavioral and contextual factors that impede uptake and adherence. Clearer guidance around safety bridging studies, and when extrapolation to adolescents is acceptable versus when efficacy and/or effectiveness should be demonstrated, is vital for newly developed biomedical interventions.[44]

Behavioral Interventions

Behavioral interventions have been used with the aim of reducing the risk for HIV by delaying sexual debut, promoting condom use, and/or reducing concurrency, partner change, or substance use. Numerous behavioral interventions have been evaluated; however, few have HIV endpoints, and

those that have, have not shown a reduction in HIV incidence.[45–47] The US Centers for Disease Control and Prevention has identified interventions with good or best evidence for HIV risk reduction based on their impact on proximate determinants of incidence.[48] However, there is the need for critical consideration of the role of these interventions in high-prevalence settings. Interventions offered in group settings, such as in schools, may be most feasible in resource-constrained environments.

Schools are often used to deliver behavioral interventions because they reach a large number of youth, often before sexual debut. Of the 3 published adolescent HIV prevention RCTs conducted with HIV incidence endpoints, 2 have been school based.[49–51] None of the studies found an impact on HIV, and results were mixed for sexual behavior. Overall, those with greatest success were curriculum based, adult led, and followed specific guidelines ("Kirby characteristics").[52,53] Combining modalities to deliver biomedical interventions, such as HCT, in schools may lead to a greater program uptake.

Understanding the larger context of behavioral interventions is critical to their success.[54] Many school-based interventions were implemented in settings where massive gender and power inequities may undermine programs' success.[50] Further, issues related to proper intervention implementation and fidelity likely compromised efficacy.[55]

There is increasing emphasis on addressing prevention issues with HIV-infected individuals. Positive health dignity and prevention (PHDP) interventions help people living with HIV to lead complete and healthy lives and reduce HIV transmission. PHDP involves the systematic delivery of a range of combination, behavioral, and sociocultural services within local communities.[56] Although the core components of PHDP have been defined, evidence is required to tailor these for use with adolescents in diverse settings and evaluate cost effectiveness.

Structural/Contextual Interventions

At the structural and contextual levels, important drivers of adolescent risk are poverty, discrimination, gender and power inequities, stigma, and environments that are not youth friendly.[47,57] Few interventions address these structural factors. Given the high prevalence of rape in sub-Saharan Africa,[58] and that HIV transmission in the context of gender-based violence is common,[59] we must examine approaches that tackle HIV prevention within the broader context of gender inequity.

Structural barriers to accessing care need to be addressed for adolescents. Youth-friendly reproductive health services can attract and retain youth in care.[60] Health facilities that are successful in making services more adolescent friendly have consistently included provider training and community activities.[53] Given the central role of HTC and biomedical interventions in the prevention landscape, we need to identify the successes of reproductive health services and adapt and/or integrate HIV prevention in these services. Models for youth-friendly services offering testing have been developed[61–63]; however, adolescents' uptake of HTC is not well understood. Research to explore how to increase HTC uptake, disclosure of serostatus, and linkages to prevention (eg, PrEP) and care (eg, treatment as prevention) is required.

It is critical to address limited education and poverty that increase the risk for HIV infection.[64–67] A recent trial among young women in Malawi showed that cash transfers lowered HIV and HSV-2 prevalence and demonstrated positive changes in the age of the sex partner and frequency of sex acts.[68] Providing cash to young women may have allowed them to change partnership characteristics, reducing their risk of contracting HIV infection; however, the mechanism through which such programs work is still unclear. Several large RCTs examining cash transfers with HIV incidence endpoints are currently underway and may help identify the mechanism of action of such interventions.[69,70] There is a need to explore a range of interventions to reduce poverty and improve the financial independence of young people.

Other structural approaches that change social norms through media campaigns or community mobilization can reach out to a large number of adolescents. Messages that target larger audiences and work to reinforce HIV prevention and care messages play a key role in normalizing HIV testing and in the uptake of newer prevention technologies.[71] The role of community mobilization to increase the uptake of HTC or VMMC is promising, yet it is understudied. Ultimately, interventions combining multiple strategies with sufficient community coverage are likely to have the greatest impact.

Youth are the greatest users of the Internet and mobile devices globally,[72,73] with high usage reported even in developing countries.[74,75] The use of such methods should easily and cost effectively reach a large youth population using this medium and develop tailored programs to make messages relevant to each recipient.[76] Early computer-based interventions showed potential to improve sexual health outcomes for youth.[77–79] Current interventions are harnessing the interactive power of social media sites such as Facebook and Twitter with promising results.[80–82] Mobile phones can also be used as a platform to deliver preventive interventions,[83,84] or to improve adherence to ART.[85] There is a need for rigorously evaluated interventions that effectively link technology to clinic-based efforts to foster safer sexual health behaviors and treatment adherence.[76]

CONCLUSIONS

Despite the high risk of HIV transmission among young people, few rigorously designed prevention interventions with HIV endpoints have been evaluated. Many interventions focus on changing individual-level behaviors rather than on addressing the larger contextual and structural landscape within which young people live. Further, few studies have explored the use of biomedical interventions among young people. Although biomedical prevention offers considerable promise, further research is needed to determine the applicability, safety, and efficacy of these approaches among the youth. The factors affecting HIV risk are complex and will require a combination approach incorporating a supportive behavioral, structural, and/or biomedical intervention.

Developing a prevention menu where adolescents, depending on their phase of transition and sexual activity, may tailor their individual prevention package would represent a major advance in preventing HIV among youth.

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Overcoming Biological, Behavioral, and Structural Vulnerabilities: New Directions in Research to Decrease HIV Transmission in Men Who Have Sex With Men

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Abstract: Men who have sex with men (MSM), including transgender women, comprise a heterogeneous group of individuals whose sexual behaviors and gender identities may vary widely between cultures and among individuals. Their sources of increased vulnerability to HIV are diverse, including the increased efficiency of HIV transmission via unprotected anal intercourse, sexual role versatility, asymptomatic sexually transmitted infections, and behavioral factors that may be associated with condomless sex with multiple partners. Societal stigmatization of homosexual behavior and gender nonconformity may result in internalized negative feelings that lead to depression, other affective disorders, and substance use, which in turn are associated with increased risk-taking behaviors. Social stigma and punitive civil environments may lead to delays in seeking HIV and sexually transmitted disease screening, and later initiation of antiretroviral therapy. The iPrEX study demonstrated that chemoprophylaxis can decrease HIV acquisition in MSM, and the HIV prevention trials network 052 study established the biological plausibility that earlier initiation of highly active antiretroviral therapy can decrease HIV transmission to uninfected partners. Despite these advances, MSM remain among the most significantly HIV-affected population in resource-rich and limited settings. New studies will integrate enhanced understanding of the biology of enhanced rectal transmission of HIV and the focused use of antiretrovirals for prevention with culturally tailored approaches that address the potentiating social and behavioral factors associated with enhanced HIV spread among MSM.

Key Words: men who have sex with men, transgender women, HIV prevention, HIV transmission

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INTRODUCTION

The global HIV/AIDS epidemic was first recognized among men who have sex with men (MSM) in the early 1980s,[1,2] and people who are born male who have sex with other men have remained at high risk for HIV acquisition ever since.[3] Because of the biological susceptibility,[4] a high concomitant sexually transmitted disease (STD) burden, and ongoing risk-taking behavior, in many parts of the world, MSM continue to be one of the populations with the greatest HIV incidence.[3] MSM represent a substantial proportion of those infected with HIV in many resource-constrained environments, including those with generalized epidemics.[5] MSM may be vulnerable to syndemics, the co-occurence of health disparities, which potentiate HIV risk[6] and are exacerbated by societal stigma.[7] The demonstration that antiretroviral chemoprophylaxis decreased HIV incidence among MSM[8] offers new opportunities for HIV prevention. HIV prevention trials network (HPTN) 052 has suggested that early identification of HIV infection and highly active antiretroviral therapy (HAART) initiation could decrease HIV transmission in heterosexuals,[9] which should be relevant for MSM. Reducing HIV incidence in MSM will require multicomponent and culturally tailored interventions integrating scientific insights with community engagement that address their diversity.

BIOLOGICAL AND EPIDEMIOLOGICAL SOURCES OF MSM SUSCEPTIBILITY

Receptive anal intercourse is the most efficient sexual practice transmitting HIV.[4] MSM engaging in insertive anal sex can become HIV infected, particularly if the partner has an STD, is untreated, or is uncircumcised. Because many MSM are sexually versatile, they can acquire HIV as the receptive partner, but after becoming infected, they may transmit to a new partner when they are insertive. Among some sexually active MSM, additional potentiators of transmission are frequent partner exchange, group

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sex, or other traumatic practices. For other MSM, their individual risk practices may involve anal intercourse in the setting of long-term or serial monogamy, but they may have selected a nonmonogamous partner and/or a partner from a subpopulation with high HIV prevalence (eg, black MSM in the United States).[10–12]

SOCIAL AND BEHAVIORAL SOURCES OF VULNERABILITY OF MSM TO HIV

Sequelae of Stigma

Internalized homophobia is associated with an increased risk for HIV acquisition and transmission due in part to increased risk behaviors and decreased engagement in prevention and care.[17,18] Internalized homophobia has been linked to depression, low self-esteem, and feelings of loneliness as well as disregard for partners' and individual's health, leading to unsafe sex.[18,19] Accompanying distress may lead to substance abuse to mask the feelings of shame.[19] The use of alcohol and other recreational drugs has been associated with having multiple partners and sex work, amplifying risks.[20]

Structural factors, such as low education, unemployment, and poverty, may also be related to HIV risk and infection.[10,21,22] Societal rejection and criminalization of homosexuality is a crucial structural factor associated with HIV risk in MSM. In the United States, black MSM who experienced homophobic events were more likely to be HIV infected and to engage in unprotected sex.[23] Experienced discrimination may potentiate the adverse health outcomes.[24] Structural factors may impede MSM access to condoms and HIV/STD testing and to HIV care.[25–28]

Physical and Virtual Venues

MSM socialize and find sexual partners in a variety of places, including bars/clubs, bathhouses, parks, and online.[29] Some studies found sexual risk behaviors more prevalent in specific venues, whereas others did not.[30–36] Social norms may differ by venue. For instance, HIV status disclosure was high among men who met their most recent partner online and lower among men who met their most recent partner in a public place.[32] Some venues, for example, bathhouses, can enhance HIV prevention initiatives,[37] including onsite HIV and STD screening.[38]

Advances in electronic communication may affect HIV prevention in negative and positive ways.[39–41] Social media enhance the ease to meet potential sexual partners, including those who prefer unprotected sex,[42–44] although studies differ in correlating Internet use with unprotected intercourse.[45–48] E-dating seems more prevalent among MSM who live in nonurban areas.[49] Internet sexual behavior seems to be highly correlated with MSM's behavior offline.[50–55] E-technologies also facilitate engagement of hard-to-reach populations in accessing sexual health information[55–57] and can facilitate HIV prevention.[58–61]

RECENT FINDINGS THAT INFORM MSM PREVENTION RESEARCH

Treatment as Prevention

HPTN 052 demonstrated that earlier initiation of HAART in asymptomatic HIV-infected individuals decreased their likelihood of HIV transmission to their uninfected primary partner by 96%.[9] However, only 3% of enrollees were MSM. HIV may be detected in rectal secretions of MSM with undetectable plasma viremia, although the clinical significance of low copy numbers requires further study.[61] Ecological data from areas where treatment access is high and where MSM have constituted the largest numbers of new infections have been mixed, with decreases in HIV incidence seen among MSM in San Francisco[62] but not in London.[63] Observational studies of MSM couples are underway in Europe and Australia. However, other data suggest that "test-and-treat" approaches could decrease HIV incidence in MSM. Individuals who are aware of their HIV status are less likely to engaging in potential transmitting behaviors[64] and successful suppression of plasma viremia with HAART being associated with marked reductions in the detection of seminal HIV.[65,66] Additionally, those who initiated treatment sooner in HPTN 052 had better clinical outcomes,[67] and large observational studies also indicate that earlier treatment results in decreased morbidity.[68] Operational questions remain, given that social stigma may result in delays in accessing testing and treatment services. Earlier HIV identification through self and partner testing[69,70] may enhance prevention efforts.

Chemoprophylaxis

At present, substantial numbers of MSM are unaware of their HIV status. The most optimistic test, link, and treat programs will take years to have an appreciable impact in lowering community viral load for MSM. To have maximal impact, wider expansion of testing and earlier treatment for HIV-infected MSM, accompanied by focused programs of chemoprophylaxis for the riskiest MSM, may be most efficient in arresting HIV spread among MSM.

MSM DIVERSITY

Although MSM engage in similar practices, the term defines a transmission category, without recognizing the diverse identities, behaviors, and social realities that it includes. To address the global AIDS epidemic, an understanding that different MSM subcultures require tailored interventions to achieve "an AIDS-free generation."

MSM in Africa

Although sub-Saharan Africa was long believed to have an exclusively heterosexual epidemic, recent research indicates that the risk of being HIV infected is higher among MSM than among heterosexual African men. HIV prevalence rates of up to 50% have been described,[71–83] with 1 study reporting an incidence of 8.6 per 100-person years in Kenyan MSM.[80] Several studies have reported high rates of bisexual behavior among African MSM, and 1 report noted a high rate of bisexual concurrency (being sexually active with both a man and a woman in the same period) among MSM in Malawi, Namibia, Senegal, and Botswana.[81–85]

MSM in Latin America

Across Latin America, the HIV epidemic is concentrated in MSM with HIV prevalence estimates between 7.9% and 21.2%, 33.3 times higher than that in the general population.[72] Transgender women (TGW) are at an even greater risk of HIV acquisition, with HIV prevalence estimates between 18.8% and 33.5% in Uruguay and Argentina, respectively. Compared to Latin American adults aged 15–49 years, TGW are 50-fold more likely to be HIV infected.[86] Although HIV prevention and treatment efforts have improved, efforts to control the spread of the disease among MSM have been hampered by poverty, inadequate health services, stigma, discrimination, violence, homophobia, and transphobia.[87,88] Modeling data from Peru suggest that earlier treatment initiation and improved treatment adherence must be integrated into comprehensive HIV prevention.[5]

MSM in Asia

HIV in Asia is a concentrated epidemic, with disproportionate rates of HIV infection being found among MSM in virtually all the countries where it has been studied.[89] Social stigmatization of homosexuality and negative effect because of the pressure to have a wife and children has been associated with HIV risk behaviors in several Asian settings.[90–92] Successful social mobilization campaigns like the Avahan initiative in India suggest that community engagement can help to attenuate HIV spread,[93] but recent data from Thailand suggest that high rates of new infections are being noted in younger MSM, often in conjunction with nonparenteral recreational drug use.[91] Asia has perhaps the greatest cultural diversity of same sex identities and social expressions of same sex behavior.[94,95] Many of the traditional categories of gender roles, including the Hijra of south India and the Koetey of southeast Asia, include feminized categories of males who are seen as quite different from gay-identified or homosexual men, and for whom outreach requires targeted and culturally appropriate programs.

Intersectionality

Racial and ethnic minority MSM may experience dual stigmas due to homophobia and racism. For example, black MSM in the United States have the highest HIV concentration of any subpopulation, but they have not been found to engage in higher levels of risk-taking behavior than other MSM.[10] Recent data have found HIV-incidence rates of close 3% annually in a 6-city study of black MSM, with the incidence being higher in younger, gay-identified black MSM.[12]

Adolescent and Young Adult MSM

Self-acceptance of sexual identity leads to healthful outcomes,[96–98] but MSM adolescents may experience rejection, placing them at an increased risk for impaired physical, social, and emotional health.[98] Although attitudes regarding homosexuality have become more supportive in many places, social stigma remains common for young MSM.[99] Coming out can mean risking rejection and loss of support from family.[100] MSM adolescents are more likely than heterosexual peers to experience social isolation, truancy, prostitution, substance abuse, depression, and STDs.[98] Sexual experimentation and perceptions of invincibility may make young MSM at an increased risk for HIV acquisition.[101] Younger MSM had an increased HIV incidence in iPrEX, consistent with decreased adherence.[102,103]

Transgender Men and Women

Transgender persons have been less studied than other sexual and gender minority populations, although TGW (persons born biologically male and expressing female gender identities) have disproportionate HIV burdens. A recent global systematic review and meta-analysis about TGW in 15 countries found a pooled HIV prevalence of 19.1%,[85] indicating an urgent unmet need for HIV prevention and care. There is a paucity of data regarding transgender men (born biologically female and expressing male gender identities) and HIV risks, suggesting a need for further research.

NEW DIRECTIONS IN HIV PREVENTION RESEARCH FOR MSM

Expanding HIV Testing

The engagement of men in HIV testing has been a challenge in many settings. HPTN 043, a randomized controlled trial comparing community-based HIV testing and counseling to clinic-based voluntary testing and counseling, showed considerable efficacy in engaging African and Thai men in HIV testing.[104] Men preferred community-based and mobile voluntary testing and counseling in times and places convenient for working adults and in culturally appropriate settings. Although HPTN 043 had relatively few MSM participants, the implications suggest that expanding testing for MSM will require innovations in how testing is provided, including home testing and in entertainment settings that MSM frequent.

Early Treatment for HIV-Infected MSM

There is a strong biological plausibility for effective ART therapy to reduce sexual transmission of HIV between men. Ecological evidence from San Francisco suggests that early HAART initiation and high levels of treatment coverage may now be having an impact on HIV incidence among MSM at population levels.[65] However, recent epidemiologic and modeling data suggest that in many populations of MSM, primary partnerships may account for substantially smaller proportions among heterosexuals.[89] Sexual networks may be the more relevant social level to assess the impact of ART on HIV incidence among MSM. Such an approach may require community randomized designs but could allow for definitive answers to the important question of the likely role of early ART for HIV prevention for MSM.

Optimizing Chemoprophylaxis

iPrEX demonstrated that antiretroviral preexposure prophylaxis (PrEP) was effective in decreasing HIV incidence in

MSM.[8] However, MSM assigned to take emtricitabine/tenofovir had drug detected only half the time that medication levels were measured.[105] For individuals with episodic risks, pericoital or intermittent fixed interval PrEP dosing is appealing because it could save costs and potentially lower the risks of toxicities. However, 1 early study of the feasibility of intermittent PrEP among MSM and female sex workers in Uganda and Kenya found that postcoital doses were often missed.[106] Studies are underway in the HPTN and research teams in the United Kingdom (Medical Research Council) and France (Agence National de Recherche sur le Sida) to better understand how intermittent PrEP may be optimally deployed (www.hptn.org and www.avac.org). Because anal sex among MSM often entails the use of a lubricating gel and because the CAPRISA 004 study showed that pericoital use of tenofovir gel decreased the incidence in South African women,[107] it is reasonable to postulate that a rectal gel might be acceptable and efficacious. Rectally administered tenofovir gel that did not contain glycerin, which stimulated peristalsis in MTN 006,[108] was found to be acceptable in MTN 007.[109] An expanded multinational safety and acceptability study will evaluate the rectal gel and oral emtricitabine/tenofovir (MTN 017), and it may suggest how future chemoprophylaxis trials may be designed. Finally, although tenofovir-based chemoprophylaxis has been found to be safe, questions about chronic use remain. Others have been interested in using antiretrovirals that are not mainstays of treatment to minimize the likelihood of the selection of drug-resistant mutants that could hamper future treatment scale-up efforts. The first study of new oral regimens for chemoprophylaxis using maraviroc by itself or in combination with emtricitabine or tenofovir is currently enrolling 400 MSM at 12 US sites (HPTN 069/ACTG 5305). Further research evaluating formulations that can be given less often via injection (ie, rilpivirine and newer integrase inhibitors) are underway and could also be relevant for MSM.

Combination Prevention Strategies

Modeling has suggested that combined approaches to the prevention may have the greatest impact in arresting the HIV epidemic among MSM.[110–112] To begin the process of combining evidence approaches into culturally tailored prevention "packages" that may have the widest replicability, the National Institutes of Health has recent funded consortia to develop prevention interventions for MSM in North and South America, China, and Africa. These projects entail a number of key components, including a comprehensive literature review of current HIV prevention interventions for MSM, a modeling exercise to estimate the impact that implementing a combination HIV prevention package will have on HIV transmission, and pilot studies to explore the feasibility and acceptability of the prevention package. The package may will include condom promotion, risk reduction counseling, access to condom-compatible lubricants, linkage to care for HIV care and treatment, expanded HIV testing and counseling, and sexually transmitted infection testing and treatment, but each group will tailor additional components, such as engaging couples and/or networks, use of electronic media, and/or provision of PrEP based on preliminary studies and input from community advisory boards.

Structural Interventions

New biobehavioral HIV interventions for MSM could be enhanced by structural interventions that decrease stigma and promote social integration of MSM. Careful analyses of the impact of changes in laws regarding marriage and other civic enfranchisement in different countries are needed to evaluate whether they are a needed part of local "prevention packages." Interventions that address economic disparities that may potentiate risk taking (eg, conditional cash transfer for male sex workers and other economically disenfranchised MSM subpopulations) also deserve further evaluation.

CONCLUSIONS

Although MSM are disproportionately affected by HIV globally, reduction in incidence will require a diverse set of interventions, based on the understanding of patterns of spread and local norms. Interventions that address stigma and associated sequelae must be culturally tailored and can be augmented with new approaches to increase HIV testing and linkage to care, early initiation of treatment, identification of transmission networks, and chemoprophylaxis. To determine the optimal prevention package, ongoing dialog with key community stakeholders remains essential, given the heterogeneity of MSM cultures and the diverse drivers of risk globally.

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Preventing HIV Infection in Women

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Abstract: Although the number of new infections has declined recently, women still constitute almost half of the world's 34 million people with HIV infection, and HIV remains the leading cause of death among women of reproductive age. Prevention research has made considerable progress during the past few years in addressing the biological, behavioral, and social factors that influence women's vulnerability to HIV infection. Nevertheless, substantial work still must be performed to implement scientific advancements and to resolve many questions that remain. This article highlights some of the recent advances and persistent gaps in HIV prevention research for women and outlines key research and policy priorities.

Key Words: HIV, prevention, women

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INTRODUCTION

Although the number of new HIV infections has declined, as of 2011, women constituted almost half (49%) of the world's 34 million people with HIV infection.[1] Progress in reducing HIV transmission and acquisition among women is, to a great extent, the outcome of robust basic, biomedical, behavioral, and social research and the application of its findings. In this article, we highlight the key advances and gaps in these areas and point to priority areas for research and policy.

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Among women, those aged 15 through 24 years are at highest risk of HIV infection,[2] which remains the leading cause of death among women of reproductive age.[3] Most women acquire HIV through sex with men. The distribution of HIV infection by sex varies considerably by region. In sub-Saharan Africa, women account for 59% of people with HIV, and women aged 15–24 years are 8 times more likely than men of the same age to be infected.[2] In the Caribbean, young women are more than twice as likely to be infected as men. In Eastern Europe and Central Asia, where injecting drug use (IDU) and sex work are the primary drivers of the epidemic, about one third of women with HIV acquired infection by injecting drugs, and an additional 50% likely acquired infection from partners who inject drugs.[2] Latin America's epidemic is predominantly concentrated among men who have sex with men, but >20% of the region's men who have sex with men also report having sex with women.[2] In the United States, marked racial/ethnic disparities in HIV infection rates persist. Although the estimated number of new HIV infections among black women in the United States fell by 21% between 2008 and 2010, black women still accounted for 29% of all infections among black adolescents and adults, with rates 20 times greater than those for US white women[4] and even higher incidence among some subsets of black women.[5] We highlight below some of the core biological, behavioral, and social factors that individually and synergistically contribute to these HIV infection rates among women globally.

THE FEMALE REPRODUCTIVE TRACT AND RISK FOR HIV INFECTION

Research has begun to shed light on the complex interplay between the female reproductive tract, the immune system inflammatory response, and the vaginal microbiome; these interactions may either decrease or increase the tract's vulnerability to HIV infection. The mucosal immune system is unique in its need to balance the functional requirements of protecting the woman from infection while permitting survival of an allogeneic sperm and embryo.[6,7] Sex hormones influence innate immunity in the tract by altering epithelial permeability, microbicide activity, and cytokine and chemokine secretion.[8] The presence of certain immune cells, however, enhances the tract's vulnerability to infection. Investigators recently identified a subset of cervical Th17 $CD4^+$ cells with multiple HIV-enhancing factors, such as CCR5, alpha4beta7, CD69, and interferon-gamma that appear to increase susceptibility to HIV.[9]

Increasing evidence demonstrates the role of genital tract inflammation—whether due to infection, microscopic abrasions that result from sexual activity, douching, or other causes—in increasing women's susceptibility to HIV infection.[10] Seminal fluid introduced during intercourse produces an inflammatory response with induction of proinflammatory cytokines and chemokines and recruitment of leukocytes. Although these events presumably adapt the immune response to promote fertility, they could also affect response to HIV and other infections.[11] Research demonstrates the importance of the vaginal microbiome in maintaining the acidic environment that protects against HIV and suggests mechanisms by which lower genital tract infections can promote HIV acquisition among women.[12,13]

FACTORS THAT AFFECT RISK OF TRANSMISSION TO WOMEN

Estimates of the risk of heterosexual acquisition of HIV vary widely from as low as 1 transmission per 1000 contacts between uninfected and infected individuals to 1 transmission per 3 contacts.[14] Numerous factors, some of which are common in the population, likely increase women's risk and may contribute to the marked variation in these estimates of transmission. These factors include male partner characteristics, such as circumcision status and HIV viral load concentration; sexually transmitted infections (STIs), especially herpes; alterations of vaginal flora, such as bacterial vaginosis; and anal intercourse.[14] Other not yet fully defined factors, such as hormonal contraception[15] and reduced host susceptibility to HIV,[16] may also affect HIV acquisition risk. Common sexual network patterns, such as partners' participation in concurrent sexual partnerships[17] and dissortative sexual mixing by age,[18] increase individual women's risk of acquiring infection and also help spread HIV throughout the population.

WOMEN AND ANAL INTERCOURSE

A substantial proportion of women report anal intercourse, and it appears that the prevalence of heterosexual anal intercourse has increased in recent years.[19,20] One third of women in a national probability sample of US adults surveyed in 2002 and 2003 had ever had anal intercourse.[21] The proportion of women in Britain who reported anal sex during the preceding year rose from 6.5% in 1990 to 11.3% in 2000.[22] Surveys suggest significant prevalence of anal intercourse in other areas of the world as well; 18% of a sample of female sex workers (FSW) in India reported anal intercourse with a client.[23] Although the increased reporting of anal intercourse may be due in part to decreased reluctance to report previously stigmatized behavior, some studies also suggest that increased access to pornography through the Internet may be a contributing factor,[23–25] an observation that attests to the importance of technological advances in influencing behaviors that affect health outcomes.[26]

Anal intercourse not only increases efficiency of HIV transmission,[14] but participation in heterosexual anal sex has been consistently associated with other risk characteristics, such as multiple and concurrent partnerships, drug or alcohol use during sex, and buying or selling sex.[27,28] A result of the underrecognition of the prevalence of anal intercourse is that HIV prevention research and interventions for women have tended to focus almost exclusively on vaginal intercourse. Women are less likely to report condom use during anal intercourse than during vaginal intercourse,[24,25] and some women erroneously perceive that transmission risk is lower for anal than for vaginal sex.[23]

CHANGING PATTERNS IN DRUG TRAFFICKING

While sexual activity remains the primary route of HIV transmission among women globally, in many settings, drug use—particularly IDU—is a substantial contributor.[29] Therefore, the dynamic patterns of drug use and drug trade are relevant to global HIV prevention efforts for women and men. The prevalence of IDU is high in North America, China, Southeast Asia, Russia, Eastern and Central Europe, and Central Asia, and IDU has long been a force in the HIV epidemic in these regions.[30]

Considerably less is known, however, about the prevalence of IDU in Africa,[30] which has emerged as a hub in cocaine and heroin trafficking as these drugs are shipped from and to destinations outside this continent.[31,32] Drug trafficking can introduce drugs to residents of regions where use was previously unknown. IDU is now established in Kenya, Tanzania, Nigeria, Mauritius, and South Africa.[29,30] In Mauritius, for example, IDU accounted for 73% of HIV cases in 2010, and HIV prevalence among IDUs was 47%.[33] In a sample of FSW in that country, 40% reported ever having injected drugs, with respective HIV and hepatitis C virus prevalence among these women of 28.9% and 43.8%, respectively.[33] IDU often results in participation in commercial sex to finance a drug habit, and conversely, sex work may lead to IDU. Thus, drug use and risky sex emerge as synergistic modes of HIV acquisition for women. Moreover, anecdotal reports note exceptionally unsafe practices, such as blood sharing,[34] which exacerbate the already increased risks faced by women who inject drugs.[35] Therefore, there is considerable concern about the potential for IDU to fuel HIV transmission among women and men in regions of the world where IDU had not previously been a major problem.

SEXUAL VIOLENCE

History of trauma, especially sexual abuse, is another significant risk factor for HIV infection among women.[36,37] Gender-based violence inside and outside the context of intimate partner relationships is a common experience for women worldwide and increases their risk for HIV acquisition through several biological, behavioral, and social mechanisms: by causing genital injury as a result of forced intercourse with an infected partner; by limiting women's ability to negotiate safer sexual behaviors; and by creating a pattern of sexual risk taking among women who experienced abuse during childhood or adolescence.[38] War and conflict situations especially heighten women's risk of experiencing sexual violence, including rape.[39] The intersection between sexual violence, anogenital injury, and HIV infection may be a critical factor in HIV's disproportionate impact on women and girls in some regions of the world with generalized

epidemics.[40] Researchers have therefore recently called for a multidisciplinary focus on 3 key areas: sexual violence perpetrated against adolescent women, sexual violence in conflict-affected areas, and effects of such violence on the HIV epidemic.[40]

INTERVENTIONS FOR PREVENTING HIV INFECTION AMONG WOMEN

Using Antiretrovirals for HIV Prevention

Research has demonstrated that administering effective antiretroviral therapy to HIV-infected individuals can reduce sexual HIV transmission within serodiscordant partnerships by 96%.[41] This finding suggests that widespread implementation of diagnosis and treatment of HIV-infected individuals ("treatment as prevention") is likely to be a highly effective means of preventing HIV infection among both men and women. But treatment for prevention has yet to be fully implemented in any country. Moreover, because women remain at risk of acquiring HIV from partners who are unaware of their infection or who lack access to or do not wish to take antiretroviral therapy, there remains a need for effective strategies that uninfected women can use to protect themselves from HIV acquisition.

Preexposure prophylaxis (PrEP) for HIV-uninfected individuals is one such potential strategy. Five studies that included women have reported the results of trials using topical or oral tenofovir with or without emtricitabine to prevent HIV acquisition: 3 demonstrated efficacy,[42–44] and 2 did not.[45,46] The US Food and Drug Administration approved tenofovir/emtricitabine for use as oral PrEP in July 2012.[47] These PrEP efficacy trials were conducted in countries where HIV incidence is high. A number of questions remain about women's use of PrEP, not only because of conflicting efficacy results but also because in many countries lower HIV incidence in the general population may decrease the risk/benefit ratio of long-term systemic drug use to prevent infection. For example, some studies have shown changes in bone mineral density associated with tenofovir use[43,48] and higher rates of adverse effects.[43,45] Moreover, exposure to tenofovir/emtricitabine and its active metabolites varies widely in different mucosal tissues, with substantially lower concentrations of tenofovir's active metabolite in vaginal and cervical tissue than in the rectum,[49] suggesting that tenofovir/emtricitabine use will be less forgiving of lapses in adherence for women exposed to HIV through vaginal intercourse than for individuals whose risk of HIV infection is primarily through anal intercourse.

Despite documentation of variable adherence,[45,46] PrEPs acceptability has generally been high when studied among trial participants, such as FSW in Kenya[50] and women in Uganda, South Africa, and the United States.[51] Other studies of hypothetical use among people not participating in trials have reported willingness to use oral PrEP among young urban African American men and women,[52] although a substantial proportion (40%) of male and female emergency room patients in 2 New York City hospitals indicated that they were unlikely to use it.[53] Among FSW in China, willingness to use PrEP correlated with interpersonal factors, such as level of trust in physicians.[54]

Focus groups among men and women in the United States revealed that interest in PrEP will likely depend on its effectiveness, cost, and ease of access.[52,55] However, the best way to market PrEP to women is unclear and is likely to vary *between* countries and among women at risk *within* countries. Preferences for vaginal gel versus tablets for PrEP, for example, varied somewhat among clinical trial participants by region, with US women preferring tablets, whereas African women were divided in their preference for gel or tablets.[51] The study's authors note that a potential advantage of a gel over a pill or condom is that the increased lubrication afforded by the gel may allow its promotion as a sexual health benefit that improves sex and partner satisfaction rather than simply as a disease prevention device that may raise questions of infidelity.[51] Further research is needed to better define the efficacy of PrEP in women, identify new drugs for PrEP, and enhance adherence.

Female Condoms

The excitement and enthusiasm about recent biomedical advances for HIV prevention may have diverted attention from other existing methods of prevention, such as the female condom.[56] Widespread use of this method has been limited due to its cost, clinicians' and patients' lack of awareness of the existence of the product and how to obtain it, and aesthetic concerns that decreased acceptability among some users.[56,57] Nevertheless, the female condom is acceptable to some women at high risk of HIV acquisition and affords several advantages.[54,57] It is free of systemic side effects, protects women from STIs at least to a similar extent as male condoms,[56] prevents pregnancy,[58] and requires less male cooperation than the male condom. In 2005, a second-generation nitrile version of the female condom was released whose mass production is cheaper than the original polyurethane model. Studies in Brazil, South Africa, and Washington, DC, suggest that expanded distribution would be cost-effective in preventing HIV infection in those settings.[59,60]

Structural Interventions

Structural interventions for HIV prevention have received increasing attention in recent years—in part because of the increasing recognition that interventions that change social determinants of health have potential for the greatest population impact.[61] These interventions typically attempt to change the environment in which people engage in health-related behaviors—often by enacting policy or legislation, empowering communities and groups, enabling environmental changes; shifting harmful social norms; or catalyzing social and political change.[62,63] Earlier structural interventions that used community mobilization strategies and government policy initiatives have been associated with increased condom use and decreased STI rates.[64–66] More recently, investigators in India used community mobilization strategies to reduce violence, harassment, stigma, and discrimination against sex workers to reduce this population's vulnerability to HIV and other STIs.[67] A randomized controlled trial of cash payment for adolescent girls in Malawi for staying in school demonstrated decreased

prevalence of HIV and herpes simplex virus-2 infections.[68] The intervention's effect appeared to operate partly by shifting participants from older partners to younger partners with whom they had less frequent sexual activity.[68] The ongoing HIV Prevention Trials Network Study 068 is evaluating the effects on HIV incidence among young women in South Africa of a cash transfer that is conditional on school attendance. Finally, the Affordable Care Act, enacted in the United States in 2010, is a structural intervention that could markedly decrease the currently large number of women and men in the United States whose lack of health insurance hinders their access to HIV prevention and treatment interventions.

OUTSTANDING QUESTIONS

Although significant progress has been made in understanding and addressing the biological, behavioral, and social factors that affect HIV infection among women, numerous research questions persist and cry out for attention; these include the need to:

1. Develop safe, effective, acceptable, and affordable methods that women can use to prevent their acquisition of HIV. These methods should require minimal adherence, be controlled by the woman, and not require a partner's cooperation.
2. Resolve the persistent questions concerning the effect of hormonal contraception—especially depot medroxyprogesterone acetate—on women's risk of acquiring and transmitting HIV.[15,69–71]
3. Determine how best to use rapidly changing new media and other communication technologies for prevention tasks, such as increasing medication adherence and marketing prevention products and services to women and providers.[72–76]
4. Identify and implement interventions that eliminate stigma and discrimination. Societies have made little headway in combating stigma, despite the longstanding recognition that stigma undermines HIV prevention efforts, and considerable gaps remain in the HIV-related stigma literature. Prevention studies should include research to define, measure, and eliminate stigma toward those living with and those at increased risk for HIV infection, such as sex workers and homosexual and bisexual men.[77]
5. Identify and work to change laws, policies, and other structural arrangements that increase women's vulnerability to HIV infection, such as inheritance laws and property rights violations, and educational, occupational, and income factors that drive women into sex work for economic survival.[78,79]

In addition, a key and pressing research question is how to determine the efficacy of interventions in settings where the HIV incidence among women is low. In many settings where HIV incidence is low, new infections are still occurring, underscoring the need for effective prevention interventions; this situation makes the conduct of clinical trials with HIV incidence outcomes difficult because the low incidence requires prohibitively large sample sizes. One potential approach is to assume that biological efficacy does not vary by country and to restrict studies in lower incidence countries to determination of safety of new interventions or the conduct of implementation studies to refine uptake, acceptability, and adherence in these settings, issues that are likely to be influenced by context and culture. Thus, it is not always reasonable to assume that a biomedical intervention that requires adherence will have the same efficacy in one cultural setting that it has in another. This situation is particularly important for women in industrialized countries, such as the United States, where a marked racial disparity exists in HIV infection rates in women in the context of overall low HIV incidence and demands the conduct of further intervention studies.

CONCLUSIONS

Although the recent decline in HIV incidence in some settings is encouraging, important biomedical, behavioral, and social science questions remain concerning how best to prevent HIV infection among women globally. Women need safe, effective, acceptable, accessible, and affordable methods, whose use they can control themselves without requiring a partner's cooperation. Ideally, new methods should require infrequent dosing and have minimal adherence requirements. Like contraception, women need a variety of HIV prevention methods that can be used with different partners and/or at different stages of their lives. Some methods should prevent both HIV infection and pregnancy, whereas others should prevent HIV infection without affecting ability to conceive.

Research has yielded substantial progress in preventing HIV infection among women. Further gains will require pursuing and resolving remaining research questions and fully implementing the many advances that have been made. To achieve the goal of an "AIDS-free generation," researchers, clinicians, public health practitioners, and advocacy groups must convince the public, funders, and policy makers that continued support for HIV prevention research and implementation of effective high-impact prevention programs for women is critical.

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Not Just the Needle: The State of HIV-Prevention Science Among Substance Users and Future Directions

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Abstract: Efforts to prevent HIV transmission among substance-using populations have focused primarily among injection drug users, which have produced measurable reductions in HIV incidence and prevalence. By contrast, the majority of substances used worldwide are administered by noninjectable means, and there is a dearth of HIV prevention interventions that target noninjecting substance users. Increased surveillance of trends in substance use, especially cocaine (including crack) and methamphetamine, in addition to new and emerging substances (eg, synthetic cannabinoids, cathinones, and other amphetamine analogs) are needed to develop and scale up effective and robust interventions for populations at risk for HIV transmission via sexual behaviors related to noninjection substance use. Strategies are needed that address unique challenges to HIV prevention for substance users who are HIV infected and those who are HIV uninfected and are at high risk. We propose a research agenda that prioritizes (1) combination HIV-prevention strategies in substance users; (2) behavioral HIV prevention programs that reduce sexual transmission behaviors in nontreatment seeking individuals; (3) medical and/or behavioral treatments for substance abuse that reduce/eliminate substance-related sexual transmission behaviors; and (4) structural interventions to reduce HIV incidence.

Key Words: substance users, HIV prevention

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INTRODUCTION

HIV-prevention research on substance-using populations has focused primarily on people who inject drugs (PWIDs). Scale-up of proven combination HIV-prevention strategies that include syringe exchange programs (SEPs) and opioid substitution therapies (OSTs) effectively and significantly curtail HIV incidence among PWIDs. Around the world, however, most substances of use and abuse (eg, cocaine/crack, heroin, prescription medications, amphetamine-like stimulants, amyl nitrites, cannabis, alcohol, and tobacco) are administered through routes of administration other than injection (eg, snorting, smoking, inhaling, ingesting, and rectal insertion). These forms of substance use apply to a much larger proportion of the general population than injection drug use does, affecting virtually all HIV-risk groups and all regions of the world. These licit and illicit substances of use and abuse make up a dynamic part of the world economy and are available in even the most conservative societies.

NOT JUST THE NEEDLE

Strategies for HIV prevention among PWIDs do not translate well to noninjectors. First, the most important HIV transmission route among noninjectors is sexual and is not linked to the route of drug administration. Second, because the nature and the frequency of substance use among noninjectors vary widely (eg, sporadic use, binging, and daily use), they may not identify as "substance users" and may not be reached by venue-based HIV-prevention interventions that typically target PWIDs, such as SEPs and OST. Moreover, noninjection substance use occurs in various contexts that confer HIV transmission risks and involves unique subgroups (eg, lesbian, gay, bisexual, or transgender; street youth; sex workers; and low-income migrant workers), which complicates omnibus prevention efforts. Adding complexity, both injection and noninjection substance users who are HIV positive can transmit infection, which among nonsubstance users can be prevented using antiretroviral therapy (ART).[1] Data are needed to inform whether this strategy is viable for active substance users who may have a difficulty in adhering to ART regimens. Finally, policymakers, leaders in civil societies, and even some substance users debate whether noninjection substance use warrants focus in HIV prevention above and beyond evidence-based interventions used by all persons at risk. We present the literature regarding this

issue and advocate for a research agenda to guide HIV-prevention efforts among all populations of substance users, including noninjectors.

NONINJECTION SUBSTANCE USE AND TRANSMISSION OF HIV AND OTHER SEXUALLY TRANSMITTED INFECTION

Some forms of noninjection substance use, particularly stimulant use, confer elevated rates of HIV transmission, due to their association with high-risk sexual behaviors.[2] Cocaine and amphetamine-like stimulants can increase sexual arousal[3,4] and promote high-risk sexual behaviors among users.[3] Stimulants are frequently a drug of choice among men who have sex with men (MSM)[5] and female sex workers. Other noninjected substances also associated with sexual HIV transmission include alcohol,[6] volatile nitrates, and some prescription drugs.[7] Due to its worldwide availability, alcohol misuse is increasingly recognized as a significant factor associated with HIV sexual risk behaviors in both MSM[8] and heterosexuals.[9] There are no studies showing independent associations between cannabis use and elevated HIV transmission risks.[10]

TOOLS FOR PREVENTING HIV TRANSMISSION IN NONINJECTING SUBSTANCE USE

Epidemiology and Surveillance

There is a compelling need for better data on HIV incidence attributable to noninjection substance use. Substance use often involves ≥2 substances that may be coadministered (ie, polypharmacy)[11] or used within the same time frame, which complicates measurement and an understanding of contextual influences of substance-related HIV risks. These realities underscore the need for event-level data and surveillance approaches that are flexible and time sensitive. Studies that focus on HIV risks related to noninjection substance use often rely on estimates of relative risks. By contrast, little attention has been focused on attributable risks at the individual and population levels, which would yield the number of HIV infections that could be averted if specific forms of substance use were reduced or eliminated (ie, etiologic fractions). Such studies require prospective data collected from large samples reporting varying levels and types of substance use. For example, in Project EXPLORE and the Multisite AIDS Cohort Study, both large studies of MSM, substance use, particularly stimulant use, was shown to account for 28% and 33%[12,13] of new HIV infections, respectively.

Interventions

HIV-prevention science has overwhelmingly focused on behavioral interventions to reduce HIV-transmission behaviors. Behavioral interventions, often consisting of brief individual or multisession group interventions, have shown efficacy in reducing drug and/or sexual transmission behaviors compared with the standard of care or to baseline risk behaviors.[14] Substance users are less likely, however, to reduce sexual risk behaviors compared with drug risk behaviors.[14] The lack of evidence-based programs for sexual behaviors related to noninjection substance use is striking. Notable exceptions exist for female crack cocaine users,[15] or heterosexual[16] and MSM methamphetamine users.[17] Interventions are especially needed that reduce substance use–related HIV risks in groups that have high HIV prevalence (eg, MSM, sex workers, street youth, and migrant workers).

Behavioral drug treatments including contingency management and cognitive behavioral therapies have shown reductions in sexual risks and methamphetamine use among MSM in outpatient treatment.[18] No medications are approved to treat stimulant dependence, which is unfortunate. Among individuals who inject opioids, treatment using OST can reduce HIV incidence.[19] Although medications are approved for alcohol dependence, none show efficacy in reducing sexual HIV risk behaviors. Future HIV-prevention strategies should consider Screening, Brief interventions, and Referral to drug Treatment in venues that high-risk substance users frequently attend, such as sexually transmitted disease clinics.[20]

Recent advances offer new biomedical approaches to HIV prevention, such as HIV treatment as prevention (TasP) and as a prevention strategy for HIV-uninfected populations as preexposure prophylaxis (PrEP)[21] or postexposure prophylaxis (PEP). With the potential use of these new therapies, there are concerns about adherence to ART,[5,22] engagement in care, and continued risk behaviors among substance users that dampen the political will for assessing these strategies. Yet the effect of stigma is significant and measurable: in the United States and Canada, injection *and* noninjection drug users were less likely than were nondrug users to have access to ART.[23] One recent study found that offering PEP in combination with contingency management was feasible and acceptable among methamphetamine-using MSM.[24] Overall, little research has evaluated acceptability, feasibility, and efficacy of TasP, PrEP, or PEP with substances users, independent of needle use. Surveillance studies rarely include biomarkers of HIV disease status or substance use among substance users, which leads to underestimates of prevalence.

Noninjection substance users, particularly stimulant users, often encounter multilevel risk environments that prevent access to HIV and drug treatment. These include gender inequalities, intimate partner violence,[25] stigma, discrimination, incarceration, homelessness, lack of health insurance, and coerced treatment. Effective structural interventions are also needed to address these substance-related HIV risks that range in scope and unit of analysis. These include changes in drug possession laws, increased access to drug treatment, and interventions at the venue-level (eg, safer inhalation facilities, prison settings) and community-level (eg, school-based interventions). The need for research on the influence of regional drug policies (eg, supply control efforts, criminal sanctions on drug possession and use, and prescription monitoring systems) is palpable. Drug policies differ according to the needs, resources, and culture of the region, whereas most were created with the intention of enhancing public good[26]; these often carry major unintended consequences to the public health.[27] Research into structural level changes within the health care

system also is of high priority. In the US President's National HIV/AIDS Strategy, HIV prevention is organized at the system level to optimally influence the outcomes toward HIV prevention among HIV-positive individuals, including substance users (seek, test, treat, and retain).

NEW SUBSTANCES AND EMERGING GROUPS AT RISK

Shifting patterns of substance use and the ways and contexts in which they are used present a moving target for HIV prevention. In countries where the HIV incidence among PWIDs has declined, HIV transmissions among substance users have shifted from injection to sexual behaviors. In Brazil and the southern cone of Latin America, cocaine injection was prevalent in the late 1980s and in the early 1990s but subsequently declined with a rise in crack use.[28] In Thailand, since the late 1990s, declining heroin injection has been replaced by widespread methamphetamine smoking.[29] South Africa is also experiencing a methamphetamine epidemic, with most users reporting noninjection routes of administration.[30] Other countries in sub-Saharan Africa have witnessed emerging epidemics of heroin and cocaine use, and their impact on HIV incidence within the context of high HIV prevalence in the general population is unknown.[31] Changes in the ways in which substance use influences HIV transmission behaviors across broad geographic areas underscore the vital need for rapid surveillance assessment and response, with an increased use of biomarkers that target HIV subtypes and medication resistance.

New compounds are being derived from parent substances of abuse, altered sufficiently to avoid laws on drug possession and distribution.[32] Their use is on the rise.[33] These include synthetic cannabinoids, cathinones (eg, "bath salts"), and other amphetamine analogs, which are marketed to the youth. Whether these substances are associated with elevated HIV transmission risks is unknown. Among noninjection substance–using youth, engagement in HIV-risk behaviors is high, especially among those who are MSM and street involved.[34] Evidence is accruing that shows school attendance is protective against HIV[35] and substance use.[36] Little is known about substance-related risks or their mitigation in youth who drop out of school, are orphaned, or who do not work.

GAPS IN KNOWLEDGE

- Can HIV-positive substance users adhere to ART and experience the TasP benefit? When offered as part of HIV prevention, ART can prevent HIV transmission in HIV serodiscordant couples when started early[1] and reduces HIV transmission in HIV-negative MSM.[21] Yet, substance users were systematically excluded from "proof-of-concept" trials that established the initial efficacy of combination HIV-prevention strategies due to concerns over potential medication adherence problems.
- What data exist on HIV in high-risk subgroups of substance users, including users of noninjection substances, from racial/ethnic groups and in regions where substance use, homosexuality, or sex-work are illegal that can guide high-impact prevention studies? There is a compelling need for data from low- and middle-income countries that have ongoing generalized HIV epidemics (eg, Sub-Saharan Africa and South and Southeast Asia) or emerging epidemics (eg, Central Asia).
- What medications or behavioral therapies are effective for treating substance use that might reduce HIV-related transmission behaviors? In contrast to OST, effective medications for alcoholism have modest effect sizes, and there are no medications for stimulant drugs. As more effective medications are developed, efforts to assess these for reducing drug-related sexual risk behaviors should be prioritized.[37]
- What structural interventions can be implemented to reduce HIV transmissions among users of injection and noninjection substances within settings of criminal justice or of primary care services?

THE WAY FORWARD

An evidence-informed strategy to guide HIV prevention in noninjection substance users draws heavily from the successes of combination HIV prevention in nonsubstance users and from declines in HIV transmission among PWIDs from using the combination of SEPs, OSTs, and ART.

We propose a rational plan of HIV-prevention research for substance users addressing the following:

Epidemiology

In most high-income countries, links between noninjection substance use and HIV transmission behaviors are well described. There is a need for evidence describing associations between these factors, particularly in regions where cultural and religious sanctions exist against substance use, homosexual behaviors, street youth, and women. An increased emphasis on biomarkers of HIV incidence and substance use is vital.

Combination Prevention Approaches in Noninjection Substance Users

There is a crucial need to conduct studies that advise implementation of combination prevention approaches (eg, PrEP, TasP, and PEP) in substance users. Strategies of TasP remain unproven among injection and noninjection substance users who are HIV positive, which is of the highest priority. Combination HIV-prevention strategies of PrEP and PEP in HIV-negative substance users at high risk also merit consideration. Recognizing that no medication can be effective if it remains in the bottle, efforts to quantify and address potential problems with medication adherence in substance users, including structural and behavioral approaches, are important. Testing of depot formulations of ART medications specifically in noninjection substance use would carry a high impact. There is a concomitant need for combination HIV-prevention research that addresses co-occurring infections in substance

users, particularly hepatitis C, tuberculosis, and sexually transmitted infections.

Substance Use–Related Risk Reduction Strategies

Sexual behaviors are the principal risk for HIV transmission among noninjection substance users, and studies that develop potent substance-use reduction tools, including medication and behavioral approaches, can reduce risk behavior. However, it is unknown as to what extent HIV incidence can be reduced.

FUTURE DIRECTIONS

To significantly reduce HIV incidence among individuals who engage in noninjection substance use and sexual risk behaviors, scientists and policymakers need to set aside personal biases about substance use, sexual behaviors, and cultural attitudes that promote abstinence as the only goal, recognizing that even modest decreases in substance use and related sexual risks may reduce harms and hence be associated with impressive etiologic fractions. Although condoms are effective against HIV transmission, rising HIV incidence in high-risk subgroups of substance users are unlikely to be reversed without additional prevention strategies, such as combination prevention, structural interventions, and interventions to reduce substance use. In prior work,[38] we noted the need to overcome "addictophobia" to continue gains in HIV prevention with PWIDs. Future success in HIV prevention for noninjection substance users will rely on the ability to marshal the scientific and political will to allocate resources to reduce HIV transmissions in groups whose sexual risk behaviors are associated with substance use—and not just with the needle.

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An Expanded Behavioral Paradigm for Prevention and Treatment of HIV-1 Infection

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Abstract: This article addresses behavioral and social research priorities for prevention and treatment of HIV-1 infection. The approach used to define these priorities is based on 3 premises: (1) Behavioral interventions for prevention and treatment are necessary but not sufficient for producing reductions in transmission or advances in treatment; the same is true of biomedical interventions, and by themselves, they cannot maximally impact the health of communities. (2) Combination prevention and treatment strategies should include optimal combinations of behavioral and biomedical strategies but also must include the varieties of the behaviors of individuals, communities, and systems needed to ensure effective treatment and prevention. (3) And it is no longer useful, given scientific advances in understanding how treatment contributes to prevention, to discuss prevention without incorporating treatment and vice versa. This redefinition of behavioral approaches in combination prevention and treatment provides a new paradigm for defining behavioral research in HIV-1 disease. No longer is it sufficient to focus on single behavior (eg, high-risk sexual behavior, adherence to antiretroviral medications) of individuals in a vertical way. Rather, the behavioral agenda not only need to expand to encompass traditional investigations of single behaviors but also need to include the behavior of many actors and systems that are essential in facilitating reductions in transmission and improvements in treatment outcomes. In addition, there is the need for expanded implementation research agenda to encompass the study of methods to achieve high coverage, acceptability, and effectiveness of available menu of interventions.

Key Words: HIV prevention, behavior, combination prevention strategies

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Clinical trials demonstrating the efficacy of the use of antiretroviral medications for prevention (eg, chemoprophylaxis, prevention of mother-to-child transmission) improved treatment for HIV-1–infected individuals, and reducing transmission to others rightfully attract the admiration of those in treatment and prevention science and bring hope to those working in the field and to patients with the disease. But although those advances make important contributions to the scientific literature and attract excitement from the public at large, implementing them in ways that affect widespread benefit are considerably more complicated.[1]

Some have expressed concern that these important advances in treatment and prevention of HIV-1, especially those based in the use of antiretroviral therapy, have greatly reduced or even completely eliminated the need for behavioral or social strategies in HIV-1 prevention.[2] After years of HIV-1 prevention clinical trials—using a variety of strategies including treatment of sexually transmitted infections including herpes simplex virus 2 and behavioral counseling—success in preventing transmission of HIV-1 was achieved through male circumcision[3–5] and the use of antiretroviral therapies for chemoprophylaxis[6] and to prevent transmission from individuals infected with HIV-1 to uninfected individuals in discordant couples,[7,8] including prevention of transmission from mothers infected with HIV-1 to their infants during pregnancy and breastfeeding periods.[9] Prior research has demonstrated the prevention potential of treating individuals for substance abuse and providing clean needles and syringes to those continuing to use them.[10–12]

Others and we have advanced the position that behavioral and social strategies are necessary, but not sufficient, for preventing and treating HIV-1 disease.[13] All of the evidence points to the importance of behavioral and social strategies to reduce HIV-1 transmission and to treat those with the disease. Examples abound with adherence to HIV-1 medications being one of the greatest barriers to efficacy when antiretroviral medications are used for chemoprophylaxis (whether in pill or gel form[6]) and prevention of mother-to-child transmission programs are dependent upon individual and system variables.[9] The same is true for those infected with HIV-1; the "cascade of treatment" typically shows that 20%–30% of these infected individuals in most jurisdictions in the United States know that they are infected with HIV-1 and are in treatment effective enough to reduce viral load to undetectable levels.[13]

Our first premise is that biomedical, like behavioral, interventions are necessary but not sufficient for prevention and treatment of HIV-1. Biomedical interventions are similar to behavioral strategies: the biomedical strategies cannot work, nor will they have widespread effectiveness if the conditions for their use are not optimized and if individuals fail to use them in ways that are necessary to ensure that they work and achieve their intended effect.

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A NEW FRAMEWORK FOR COMBINATION PREVENTION AND TREATMENT

Our analysis of combination prevention and treatment is based on a second premise, specifically expanding the understanding of "combination prevention and treatment" and of "behavior." Combination prevention and treatment most frequently is used to define the optimal ways of combining biomedical and behavioral (and sometimes social and structural) and biomedical interventions to prevent or treat the disease.[12] We not only incorporate these elements into our definition of combination prevention and treatment but also expand the concept to address the varieties of behaviors—on the part of individuals and larger systems—needed to ensure effective treatment and prevention. Behavior refers to the actions of the individual and the behavior of systems (eg, family or health care systems), those working in those systems, and entire communities.[1] Often when behavior is discussed, the emphasis is placed on strategies directed to the individual that aim, for example, to help that person get tested, adhere to treatment or prevention regimens, and/or reduce risk behavior. Undoubtedly, such strategies can play a role in the overall promotion of prevention and treatment. But strategies focused only on the individual are time and labor intensive, although having an effect on reported risk behaviors, have had limited efficacy on HIV acquisition, and may have limited reach and therefore limited efficacy in the community at large.[14]

The model of HIV-1 prevention and treatment presented in Figure 1 demonstrates this broadened use of behavior. Community awareness and mobilization are essential for ensuring that the services are designed to appeal to the needs of the population and that the individuals for whom the services are designed know about them and are motivated to use them. After mobilization, HIV diagnosis is essential so that infected and uninfected individuals can receive appropriate services. The next phase involves appropriate triage so that those who do not have HIV-1 infection can be counseled in how to avoid it and so that they can access specialized services (eg, male circumcision, drug or mental health treatment, chemoprophylaxis, if available). Those who are infected also need to be counseled in how to avoid spreading HIV-1 to others, how to access specialized treatments if necessary (eg, drug or mental health treatment), and the importance of and linkage to care for their HIV disease not only for their own health benefits but also for the public health.[7,8] Adherence is essential for both uninfected and infected individuals, and community support may be essential for adherence at levels needed to ensure that the prevention and treatment strategies can work.[1,6]

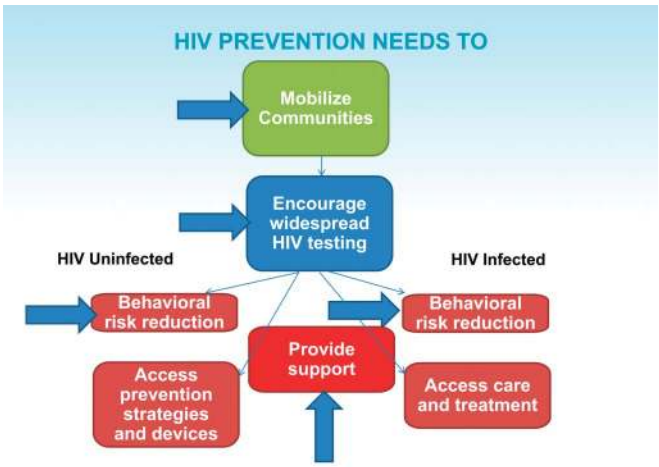

FIGURE 1. An expanded model for the prevention and treatment of HIV-1.

WHAT IS NEEDED TO SUCCESSFULLY CONFRONT THE HIV EPIDEMIC?

An effective HIV-1 prevention and treatment service system in the low-, middle-, and high-income countries needs to incorporate all of the elements necessary for successful deployment of prevention activities and efficacious management of HIV-1 disease. A comprehensive system must include useful prevention activities, early identification of HIV-1–infected individuals in need of care, linkage to care, appropriate initial and continued counseling and other forms of support for continued risk reduction and management of HIV-1 disease, assessment of HIV-1 disease stage, treatment with antiretroviral medications for those who qualify, monitoring while on treatment to ensure efficacy, adherence support, and provision of sexual and reproductive health services.[1] All of this would ideally be structured in ways that make access easily available and affordable and that do not require extensive travel, lengthy wait times, loss of income to the individuals being served, and that is done in ways that respect and recognize the dignity of the patients.

Table 1 lists the full range of activities needed to implement this complex agenda. Easy-to-access services have become the priority for many HIV-1 prevention and treatment systems, as the goal is not only to increase the number of persons on treatment but also to maintain them in prevention and treatment services.

Effective management of prevention and treatment services involves skills and behaviors that have been little studied or addressed in the HIV-1 prevention or treatment literature. The focus of behavioral research has been on the outcome: do individuals engage in behaviors to reduce the chances of acquiring or spreading HIV or optimizing treatment. This narrow perspective has led to studies—most often using strategies targeted at the individual—to reduce certain behaviors (eg, high-risk sexual behavior) or increase others (eg, adherence to medications). The expanded paradigm presented here retains that focus, as ultimately, it is the behavior of individuals that has a large influence on disease outcomes. But the expanded paradigm also widens that focus to recognize that those specific outcomes are influenced strongly by the behavior of systems (eg, systems of prevention and care that facilitate easy access for consumers), other individuals (eg, health care providers), and services offered (eg, all of the tools in the "prevention toolbox," strategies for diagnosing HIV-1 infection and linking individuals to care, strategies for maintaining standards of prevention and care).[1]

There is increasing recognition that the behavior of managers and management systems are essential for the

TABLE 1. Essential Elements of Community-Wide Implementation of HIV-1 Prevention and Treatment Programs

Easily accessible services
Close to home
Affordable
Avoiding lengthy wait times
Avoid loss of income to individuals
Effective management
Transparent personnel systems
Prudent use of finances and resources
Uninterrupted flow of supplies and medications
Initial training and ongoing mentoring of health care providers
Community-wide support systems
Motivate testing
Provide pre- and posttesting support services
Address educational and other barriers to use of prevention and treatment technologies
Support adherence to prevention and treatment technologies
Adequate prevention programs
Makes full use of the "prevention toolbox"
Early identification of HIV-1–infected individuals
Employs a variety of community-wide testing strategies to encourage maximum testing coverage (eg, routine HCT, home-based HCT, community-based HCT, workplace-based HCT)
Appropriate initial and continued counseling
Risk reduction
Adherence
Other specialized needs
Linkage to and maintenance in care
Maintaining treatment and prevention standard of care
Assessment of HIV-1 disease stage
Treatment of HIV-1 infection
Prevention and treatment of opportunistic infections
Monitoring while on treatment or prophylaxis to ensure efficacy
Regimen modification as necessary
Sexual and reproductive health services

HCT, HIV counseling and testing coverage.

effective application of behavioral and biomedical prevention and treatment strategies.[15] If those in charge do not appreciate the importance of how to manage personnel in a transparent and fair manner, then those personnel will be disenchanted and unmotivated and that attitude will undoubtedly affect their interactions with patients. If resources are not well utilized and essential supplies are not well managed, then interruptions in service are inevitable, thereby not only affecting the health of clientele but also causing people to lose faith in the health system. Patients will receive less than adequate service if frontline health care providers are not skilled: both medically and interpersonally.

There has been recognition of the increasing importance of community-wide support systems to motivate testing, address educational barriers, and support behavioral risk reduction and adherence needs of community members.[16] A variety of evidence-based strategies have been identified to maximize testing coverage and diagnosis and linkage to care of persons infected with HIV-1, and considerable emphasis has been placed on effective initial and ongoing counseling.

Linkage to and maintenance in care remain a work in progress, and most often, using community health workers to walk individuals through systems and follow-up with them when they fail to return. No doubt, other health system behaviors such as easy access and culturally appropriate care are essential as well. Monitoring and maintaining quality of services, especially in low- and middle-income countries, remains a challenge, especially with turnover of staff and difficult working conditions. Maintaining high quality of services remains a challenge, especially as the goal is to expand availability of new biomedical technologies and to continue efforts at task shifting and task sharing, so that diverse types of providers can prescribe and monitor the use of antiretroviral therapies and other efficacious interventions.

RESEARCH PRIORITIES

The approach to behavior presented in Figure 1 and developed in Table 1 changes the research agenda from a focus on specific behaviors (eg, reductions in sexual risk behaviors; adherence to antiretroviral medications) to a focus on the broader "Essential Elements of Community-Wide Implementation of HIV-1 Prevention and Treatment Programs." Examples of a broadened research agenda that are inclusive of implementation research questions are presented in Table 2. It is hoped that this expanded paradigm, and the research examples derived from it and presented in Table 2, will provide a stimulus to broaden thinking about the kinds of questions

TABLE 2. Behavioral Research Priorities to Address Essential Elements of Community-Wide Implementation of HIV-1 Prevention and Treatment Programs

Access to services
Example of research priority: Constrained resources may not make it possible to address all issues that provide easy access to services. Which variables (eg, proximity, waiting times, cost) are most influential in promoting access to and satisfaction with prevention and treatment services?
Effective management
Example of research priority: Which management skills are essential for ensuring effective prevention and treatment services? How are these best taught and maintained? How can quality of management be monitored and maintained?
Community-wide support systems
Example of research priority: What configurations of community support systems maximize testing, reduce risk behaviors, and maintain adherence?
Adequate prevention programs
Example of research priority: What strategies can be used to motivate policy makers and program planners to make full use of the prevention toolbox?
Early identification of HIV-1–infected individuals
Example of research priority: What testing strategies are the most cost effective for identifying HIV-1–infected individuals and ensuring their entry into and maintenance in care? What enhances linkage to care?
Appropriate and continued counseling
Example of research priority: What counseling strategies most cost effectively reduce risk and maintain adherence?
Maintaining prevention and treatment standard of care
Example of research priority: How can health care providers, especially with task shifting, establish and maintain prevention and treatment standard of care

asked in research and the kinds of programmatic interventions developed, to maximize at the individual and societal level the benefits that advances in prevention and treatment science have delivered to us thus far. A planned study, HIV Prevention Trials Network 071 (PopART), aims to take a broad approach to the challenge of preventing HIV transmission at the community level. In the latter study, interventions to be studied include community mobilization, house-to-house HIV testing, use of community health workers to promote linkage and adherence, combined with use of treatment as prevention and referral for male circumcision, promotion of prevention of mother-to-child transmission, and widescale provision of condoms.

CONCLUSIONS

There is no question that biomedical advances in HIV prevention and care are transformative and life saving. We now have tools that we did not have only a few years ago. But these technologies can have little effect if they are not used the way that they need to be in order to make a real difference in confronting the epidemic. In this way, efficacy and effectiveness all come back to behavior: of individuals and systems. Simply put, these advances will have little benefit without individual behavior and an understanding and reformation of systems responsible for attracting people to services and keeping them there for the long term.

These optimal packages will cost money, and those funds are difficult to find in these tight economic times. But there is also no doubt that the strategies proven so efficacious in clinical trials will fail to have impact on epidemics in communities, regions, or countries unless the complexity of their implementation is addressed. Vermund and Hayes[17] put it eloquently: "Yet as we have more tools for HIV prevention, 'HIV fatigue' in donor nations combined with concern from economic downturns form 2008 onwards may result in HIV programs. Past experience suggests, however, that failures in HIV prevention or early treatment will simply cost society more in the long run, given the high direct costs of illness and indirect costs of disability, suffering and death."

Prevention and treatment programs that incorporate the complexity of behaviors necessary for success are a good investment. They will promote health and productivity among individuals and protect society from further disease.

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Preparing for the Unexpected: The Pivotal Role of Social and Behavioral Sciences in Trials of Biomedical HIV Prevention Interventions

Beryl A. Koblin, PhD, Michele Andrasik, PhD,† and Judy Austin, MPhil‡*

Abstract: A range of efficacies have been reported for biomedical HIV prevention interventions, including antiretroviral treatment, male circumcision, preexposure prophylaxis, microbicides, and preventive vaccines. This range of efficacies probably results from the influence of multiple inputs and processes during trials, including the strength and target of the intervention, host factors, target population characteristics, level of HIV exposure, and intervention dose. Expertise in social and behavioral sciences, in conjunction with basic science, clinical research, epidemiology, biostatistics, and community, is needed to understand the influence of these inputs and processes on intervention efficacy, improve trial design and implementation, and enable interpretation of trial results. In particular, social and behavioral sciences provide the means for investigating and identifying populations suitable for recruitment into and retention in trials and for developing and improving measures of HIV exposure and intervention dose, all within the larger sociocultural context. Integration of social and behavioral sciences early in idea generation and study design is imperative for the successful conduct of biomedical trials and for ensuring optimal data collection approaches necessary for the interpretation of findings, particularly in cases of unexpected results.

Key Words: biomedical interventions, HIV, populations, adherence, social science, behavioral science

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HIV prevention strategies have expanded significantly with the demonstrated success of several biomedical interventions for reducing HIV incidence in randomized clinical trials. Early initiation of antiretroviral treatment by HIV-infected individuals in serodiscordant partnerships reduced HIV transmission by 96%, an unprecedented level of efficacy in HIV prevention research.[1] Male circumcision reduced HIV infection among heterosexual men in Uganda, Kenya, and South Africa by 51%–60%.[2–4] Daily oral preexposure prophylaxis (PrEP) with tenofovir or tenofovir/emtricitabine reduced HIV infection by 44% among men who have sex with men (MSM) in multiple countries and 67%–75% among serodiscordant heterosexual couples in Kenya and Uganda.[5,6] A more modest effect (39%) was observed for event-related application of tenofovir vaginal microbicide among heterosexual women in South Africa.[7] Similarly, a recombinant canarypox vector vaccine prime with a recombinant glycoprotein 120 (rgp120) subunit vaccine boost showed modest efficacy (31%) in a general population sample in Thailand.[8]

Conversely, several interventions have failed to find significant effects on HIV acquisition. Four vaccine efficacy trials, 2 using an rgp120 subunit vaccine alone,[9,10] 1 using a recombinant adenovirus type 5 (Ad5) vector vaccine (Step Study),[11] and 1 using a DNA-based vaccine prime and recombinant Ad5 vector vaccine boost (HVTN 505),[12] did not demonstrate protective effects. Furthermore, the Step Study showed a higher HIV incidence among MSM vaccinees who were uncircumcised and had Ad5 neutralizing antibodies at enrollment.[11] HSV-2 suppression with acyclovir did not reduce HIV acquisition or transmission among HSV-2 seropositive men and women.[13,14] No reduction in HIV acquisition was evident for daily oral tenofovir/emtricitabine among heterosexual women in Kenya, South Africa, and Tanzania.[15] The VOICE Study among women in South Africa, Uganda, and Zimbabwe tested 3 products, tenofovir gel, oral tenofovir, and oral tenofovir/emtricitabine, and none were found to be effective in reducing HIV acquisition.[16]

The range of reported efficacies probably results from the array of social and structural agents, actors, and contexts interacting within a dynamic system, as illustrated in Figure 1. Joint efforts within basic science, clinical research, epidemiology, biostatistics, community, and social and behavioral sciences are needed to understand the potential influence of these factors on intervention efficacy, to improve trial design and implementation to maximize the probability of identifying efficacious interventions, and to facilitate interpretation of trial results, which are often not straightforward.[11,16–18]

SOCIAL AND BEHAVIORAL SCIENCES IN THE CONTEXT OF HIV PREVENTION TRIALS

In the conduct of HIV prevention trials, social and behavioral sciences provide the framework and tools[19] for

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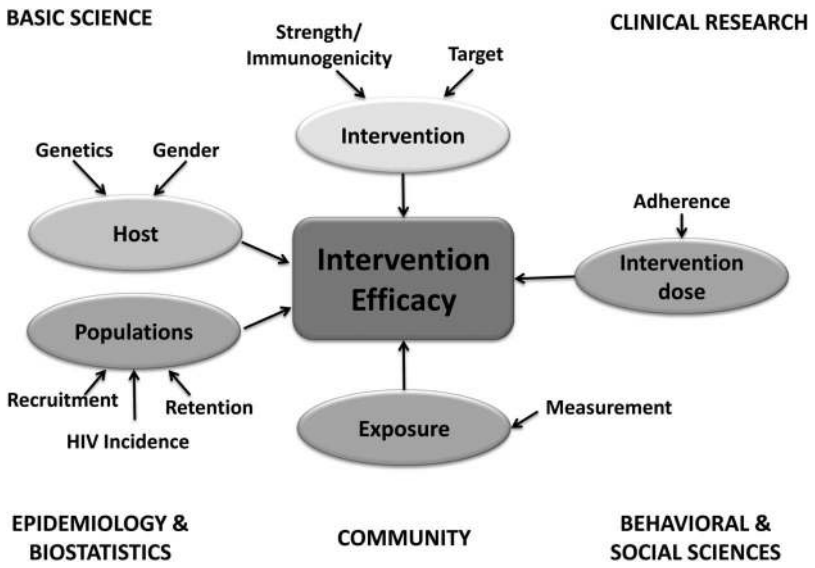

FIGURE 1. Role of scientific disciplines in trials of biomedical HIV prevention interventions.

investigating factors that may have an effect on observed intervention efficacies. Social and behavioral science disciplines provide a wealth of theoretical and empirical evidence with which to inform HIV prevention trials. For example, social science encompasses the broader dynamic cultural, geographic, economic, and social systems within which individual and group HIV risk behavior is embedded. Psychology informs our knowledge of the cognitive processes used in responding to behavioral risk questions[20] and the differential impact of environment on behavior.[21] Anthropology informs our knowledge of social patterns and practices across culture underscoring the need to attend to race, sexuality, class, gender, and nationality.[22] Insight into the most at-risk populations and the factors that disproportionately impact the health of these populations is gained from the field of sociology.[23] In the varied contexts in which multicenter trials are conducted, an awareness of and appropriate response to the perspectives, practices, and expectations of diverse target groups allows researchers to anticipate participation and retention rates, adherence, HIV exposure, and likely dissemination and uptake of efficacious interventions. Using a conceptual framework for social and behavior sciences in HIV prevention trial research[19] can assist in the integration and concurrent conduct of biomedical and social and behavioral science research in the context of trials. Below we discuss 3 factors: potential study populations to include and retain in trials, quantifying HIV exposure, and documenting intervention dose (Fig. 1).

Populations

Efficacy testing of biomedical HIV prevention interventions requires recruitment of participants who remain at high risk despite receiving known prevention interventions and who can be expected to adhere to study protocol and complete follow-up visits. Numerous preparedness studies have been conducted to identify populations and regions suitable for hosting trials with an HIV infection endpoint.[24–30] Beyond providing HIV incidence estimates, this work has incorporated assessment of recruitment and retention strategies, and facilitators and barriers to participation, prompting the development of appropriate educational and counseling materials.[31] Preparedness studies do not guarantee ultimate trial participation[32] or accrual of samples with adequate HIV incidence rates.[33,34] Consequently, within a dynamic research environment, investigation into the shifting drivers of community engagement, enrollment, recruitment, and retention is needed, not only in preparation for each new trial but also throughout ongoing follow-up, if successful study participation is to be assured.

For example, recent work within the HIV Vaccine Trials Network (HVTN) provided valuable insight into factors affecting recruitment of MSM and transgender women into HVTN 505. Survey and focus group data on MSM from 6 US cities indicated that although >70% were prepared to consider participation, lack of knowledge and information about HIV vaccine trials was a major deterrent. Additional barriers included concerns about side effects, privacy, being perceived as "risky," and vaccine-induced seropositivity. Participation facilitators included perceived safety, helping to end the epidemic, and potential protection from HIV.[35] Consequently, dissemination of community-level information on vaccine research, side effects, and steps to address social impacts were undertaken. Efforts also are underway to understand, share, and improve individuals' experiences as trial participants.

HIV Exposure

A critical aspect of biomedical prevention trials is the assumed equivalence of HIV exposure across study arms. Randomization and blinding are used to eliminate imbalances,[36,37] but the potential for a differential shift in risk during follow-up remains. Unblinding or "perceived treatment assignment" while blinded may prompt changes in risk behaviors, with concomitant changes in exposure to HIV.[38] Differential HIV exposure by treatment arm may undermine investigators' ability to detect efficacious interventions. Thus, exposure to HIV must be adequately documented if valid

conclusions are to be drawn. Furthermore, HIV exposure could be an effect modifier of biomedical intervention efficacy and thus measurement approaches must adequately distinguish exposure levels.

Yet, valid measurement of HIV exposure constitutes an ongoing challenge. One step removed is measurement of unprotected sexual activity, markers of which include pregnancy[39] and sexually transmitted infections.[40] However, their distal location from the behavior of interest, and ambiguity with respect to scale, negate their usefulness as indicators of exposure. More proximal measures, such as seminal plasma detection (eg, testing for prostate-specific antigen) or biomarkers of spermatozoa, confirm recent sexual activity (eg, within 48 hours) but give little indication of overall HIV exposure.[41–43]

In the absence of a viable biological tool, self-report has served as the method of choice and can be used to better understand trial results. For example, detailed analysis of behavioral data among MSM in the Step Study indicated that the increased HIV rates among subgroups of vaccinees were not explained by differences in HIV exposure.[17] Furthermore, the potential of a biological mechanism to explain the increased HIV rates among uncircumcised men was supported by the behavioral data showing that men reporting unprotected insertive anal sex at baseline, that is, close to vaccine administration, demonstrated an increased risk of infection associated with vaccine.[17] In post hoc secondary analysis of the RV144 HIV vaccine trial, greater vaccine efficacy was observed among participants categorized as low-risk, suggesting an interaction between level of HIV exposure and vaccine efficacy.[44] For both studies, finer gradations of sexual risk behaviors may have revealed more subtle differences. The need for effective, sensitive risk behavior measures, permitting a thorough examination of efficacy findings, cannot be overstated.

Intervention Dose

Intervention dose is another critical component of biomedical efficacy trials. Insufficient dosing levels resulting from low adherence have been proposed as the mechanism accounting for the range of efficacies reported in PrEP studies.[6,15,18] Microbicide trials have been similarly challenged with self-report overestimating adherence. In MTN-001, the 94% self-reported adherence contrasted sharply with the 35% to 65% nonadherence estimates derived from blood tenofovir levels.[45] In CAPRISA 004, using adherence rates derived from gel applicators returned, a tenofovir vaginal gel proved to be 54% effective with high adherence (>80%) but only 28% effective when adherence was low (<50%).[7]

The lack of standardized adherence measures also hinders the understanding of the relationship between adherence and protection.[18] Without a gold standard for adherence, triangulation of prospective objective measures [eg, electronic devices (Wisepill, MEMS), unannounced product counts, returned applicator testing] with biological markers (eg, drug levels) and participant self-report provides the best possible estimate of true adherence. Accurate interpretation of future study outcomes requires a combination of adherence measures, ideally including real-time measures,[46] permitting targeted interventions for participants experiencing adherence lapses. At the same time, movement toward interventions less dependent on daily adherence is a critical step.[47]

MOVING FORWARD

The overarching principal proposed here is the early integration of social and behavioral science expertise—during the idea generation and study design phases—to improve the success of biomedical trials and for ensuring the collection of data necessary to interpret findings, particularly given the potential for unexpected results.

With regard to study populations, the importance of preparation for large-scale trials and ongoing research during trial conduct to correct lagging recruitment or poor retention rates should not be underestimated. Furthermore, nimble protocols able to assess uptake of newly developed interventions (eg, PrEP, self HIV testing) among enrolled study participants must be designed.

Although considerable research exists on self-reported risk behaviors, large-scale biomedical trials provide a unique opportunity to examine self-reported risk behaviors in direct relationship to HIV incidence. Thus, specific research questions about self-report methods (eg, optimal recall period, event-specific vs. global measures of risk behaviors) can be answered within this context.

Recent work on self-report measures of adherence using rigorous cognitive testing to define ideal questions (taking vs. missing doses), response sets, and reference periods to improve the psychometric properties of adherence tools ultimately identified 3 items that yielded the most reliable and valid data.[48] Triangulation of improved self-reports with objective adherence measures can serve to monitor use and identify participants needing support and inform adherence interventions where feasible.[18,46]

In era of combination prevention approaches, the issues of populations, HIV exposure, and adherence measurement will complicate trial design, conduct, and analyses. The integration of basic science, clinical research, epidemiology, biostatistics, community, and social and behavioral sciences will be essential to meet forthcoming challenges.

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The Detection and Management of Early HIV Infection: A Clinical and Public Health Emergency

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Abstract: This review considers the detection and management of early HIV infection (EHI), defined here as the first 6 months of infection. This phase is clinically important because a reservoir of infected cells formed in the individual renders HIV incurable, and the magnitude of viremia at the end of this period predicts the natural history of disease. Epidemiologically, it is critical because the very high viral load that typically accompanies early infection also makes infected individuals maximally contagious to their sexual partners. Future efforts to prevent HIV transmission with expanded testing and treatment may be compromised by elevated transmission risk earlier in the course of HIV infection, although the extent of this impact is yet unknown. Treatment as prevention efforts will nevertheless need to develop strategies to address testing, linkage to care, and treatment of EHI. Cost-effective and efficient identification of more persons with early HIV will depend on advancements in diagnostic technology and strengthened symptom-based screening strategies. Treatment for persons with EHI must balance individual health benefits and reduction of the risk of onward viral transmission. An increasing body of evidence supports the use of immediate antiretroviral therapy to treat EHI to maintain CD4 count and functionality, limit the size of the HIV reservoir, and reduce the risk of onward viral transmission. Although we can anticipate considerable challenges in identifying and linking to care persons in the earliest phases of HIV infection, there are many reasons to pursue this strategy.

Key Words: early/acute HIV infection, HIV transmission, treatment as prevention, antiretroviral therapy

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INTRODUCTION

The goals of immediate antiretroviral therapy (ART) for individuals presenting with early HIV infection (EHI) are twofold: first, for the health benefits of the individual and second to reduce the risk of onward viral transmission. Use of ART to control the HIV epidemic has garnered considerable interest at the population level. The extent to which elevated transmission during EHI[1]—if not reached by treatment—might compromise the preventive effect is a matter of debate.[2–5]

The evidence to date about the feasibility of treatment as prevention targeting persons with EHI are summarized in Table 1. This review synthesizes the existing evidence on the individual-level effects of early treatment and its potential role in using ART to prevent HIV transmission. Specifically, we consider the significance of early treatment in 3 areas: the challenges of finding early infection, in moderating essential behavior change in these individuals, and considerations for treatment of those with EHI.

EARLY HIV INFECTION

Sexual transmission of HIV generally involves only 1 or a small number of viral variants infecting receptive cells.[6,7] The earliest days of infection are marked by HIV replication in the mucosa, submucosa, and lymphoreticular tissues, during which viral markers can only be detected in the affected tissues but not in the plasma.[8] Once HIV RNA concentration increases to 1–5 copies per milliliter in plasma, nucleic acid amplification can be used to qualitatively detect HIV, after which the sequential appearance of various viral makers define the stages of EHI for which different quantitative clinical assays can be used to monitor viral load.[9] At the same time, the initial immune response includes a "cytokine storm" that in a substantial number of newly infected people produces acute retroviral syndrome[10] and that can be used to mark the stages of acute infection.[11]

Gut T-cell depletion[12] and rapid growth in the HIV DNA reservoir size[13,14] take place in the earliest (first ~25 days) after infection.[15] However, elevated risk of transmissions has

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TABLE 1. Evidence to Date on the Feasibility of Treatment as Prevention Targeting Persons With EHI

Things for Which There Is Some Evidence	Unknowns
ART at CD4 > 350 cells/mL reduces infectiousness by 96% in stable serodiscordant couples	How well ART can reduce infectiousness in persons with EHI, particularly in the preseroconversion phase
The extent to which EHI may contribute to ongoing transmission	How likely we are to be able to identify and treat a large enough portion of EHI to impact the efficacy of treatment as prevention within a population
Early ART can suppress viral load in individuals with EHI	The long-term safety of early ART, and the durability of the suppressive effect
Some regimens may be more effective at reducing viral load	The tolerability (toxicity) and the long-term safety of these regimens, although this may not be significantly different from those affecting the general population starting ART in chronic infection
Early ART has some short-term health benefits for the individual	Long-term health benefits of early ART for the individual
Adherence to short course is generally good	Feasibility of good adherence in the event of uninterrupted therapy
Resource poor areas have limited capacity to screen acutes or to provide routine viral load testing	The extent to which new technologies will be able to overcome these constraints

been shown to persist for up to 6 months after seroconversion.[16] "Early HIV infection" here will therefore refer to all stages of acute infection including seroconversion and up until the establishment of early chronic infection, approximately 3–6 months after HIV acquisition.

This stage of infection is critical both clinically and epidemiologically because (1) the reservoir of infected cells is formed in the individual that render HIV incurable; (2) the magnitude of viremia at set point predicts the natural history of disease,[17] and (3) the very high viral load that typically accompanies acute infection—combined with specific characteristics of recently transmitted viral variants[18]—can make acutely infected individuals maximally contagious to their sexual partners.[9]

HIV AND THE SPREAD OF INFECTION

The biological plausibility of elevated HIV transmission risk during EHI is based on the heightened viral load of persons with early infection—often on the order of 10^6 log copies per milliliter[19]—which is also mirrored in high levels of virus in the genital tract.[19–21] In addition, characteristics of the transmitted virus,[18] concomitant sexually transmitted infections,[22] and patterns of sexual behavior among recently infected individuals[23] who may be unaware of their status[24] may all factor into the role that EHI plays in the spread of HIV. However, the extent to which HIV treatment as prevention programs must account for transmission during EHI is a matter of some debate.[5,25]

The biological plausibility that EHI may enhance transmission risk is supported in some risk groups by the findings of phylogenetic methods to define transmission clusters[22,26–28] or reconstruct transmission events during EHI[29] using viral sequences from recently infected persons. Results suggest that HIV transmission from persons with EHI may account for 25%–50% of all viral transmissions within certain populations.[16,26,29] Some posit, however, that the failure of these methods to consider other risk factors for transmission or to distinguish between new and chronic infection may lead them to overestimate the portion of new infections attributable to EHI.[30]

Mathematical models also provide insight into the role of EHI in HIV epidemiology. As we have summarized previously,[9,31] model estimates of the contribution of EHI to population-level transmission have varied widely, with estimates of the portion of new cases attributable to EHI ranging from 1% to 82% (Table 2), depending on epidemic stage, model structure, assumptions about sexual contact rates and patterns, and the assumed duration of high infectiousness associated with EHI. We are aware of only one model to date that has formally assessed the potential impact of prevention interventions during EHI,[25] the results of which suggest that transmission prevention during both EHI and chronic infection are needed for maximal impact.

IDENTIFYING EHI

Successful use of ART during EHI to control the HIV epidemic will depend greatly on our ability to effectively

TABLE 2. Proportion of New Infection Attributed to Early EHI

Author	Population/Setting	Proportion of New Infections Attributed to EHI (%)
Jacquez et al[32]	MSM (United States)	25 to 51
Pinkerton and Abramson[33]	MSM (United States)	25 to 90*
Koopman et al[34]	MSM (United States)	20 to 47*
Kretzschmar and Dietz[35]	Hypothetical (United States)	65 to 82*‡
Coutinho et al[36]	Mixed	2 to 89
Xiridou et al[37]	MSM (Europe)	<1 to 39
Pinkerton[38]	Mixed (United States)	3 to 17
Prabhu et al[39]	Mixed (United States)	11
Goodreau et al[40]	Heterosexuals (SSA)	20 to 25
Hayes and White[41]	Heterosexuals (SSA)	23 to 41†
Eaton et al[42]	Heterosexuals (SSA)	16 to 28*
Pinkerton[43]	Heterosexuals (SSA)	85 to 93†
Abu-Raddad and Longini[44]	Heterosexuals (SSA)	~7 to ~15‡
Salomon and Hogan[45]	Heterosexuals (SSA)	~20 to 40†
Hollingsworth et al[46]	Heterosexuals (SSA)	9 to 31
Powers et al[25]	Heterosexuals (SSA)	19 to 52‡

MSM, men who have sex with men; SSA, sub-Saharan Africa.

*Transmission probabilities were drawn from the listed population, but the reported proportion of new infections attributed to EHI result from a range of hypothetical sexual behavior parameters that do not necessarily reflect those of the same subpopulation.

†Range of estimates reflect the estimated proportion of transmissions during an HIV infected person's entire infectious period that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI at the population level will depend on the epidemic phase and sexual contact patterns.

‡The range of estimates shown was extracted from the endemic-phase portion of graphs showing the time-course of the proportion due to EHI.

screen and identify these individuals to target for intervention, although this is not yet part of routine testing strategies. Such efforts will likely demand more frequent testing, particularly among those believed to be at greater risk of HIV infection and with the use of novel tools such as self-administered HIV tests—where legally sanctioned[47]—paired with open access to care. The acute phase of EHI when antibodies are not yet present will remain undetected by traditional antibody tests,[48–50] when diagnosis must rely on direct detection of virus using nucleic acid amplification tests or viral antigen such as p24. Give the financial, technical, and logistical barriers to widespread use of nucleic acid amplification tests, third- and fourth-generation indirect enzyme immunoassays have emerged as a strong alternative. The sensitivity of these tests to HIV antibody isotypes that emerge earlier in the course of infection (IgM and IgG), and in the case of fourth generation to p24 antigen, allow detection earlier in the course of infection with relatively good sensitivity.[3–5,49,51] However, limited availability of fourth-generation enzyme immunoassays in resource poor settings and low sensitivity for detecting HIV infection before seroconversion limits their utility in many settings with high EHI prevalence.[52,53]

Pooling samples for batched RNA screening may be a cost-effective alternative for EHI detection in places with higher prevalence of persons with EHI,[6,7,49,54–58] but laboratory-based assays remain costly, necessitate people attending for testing venipuncture, and require patient follow-up. Field evaluations of available point-of-care tests to date have reported disappointingly high false-positive and false-negative rates.[1,9,59,60]

In light of these shortcomings, symptom-based screening—particularly those that incorporate targeted screening—must be developed as a cornerstone of field efforts to identify persons with EHI. Candidate populations include those presenting with symptoms indicative of sexually transmitted infections[2–5,61,62] or with reported high-risk behavior.[6,7,11,50,62] A strengthened symptom-based screening strategy will also require retraining of clinicians and community health workers, paired with routinized point-of-care viral load testing.[63]

PREVENTION IN PERSONS WITH EHI

Beyond the limitations of timely and adequate identification of acutely infected individuals are the unique challenges of preventing the HIV transmission in these individuals. Behavioral interventions will demand swift and decisive strategies to reduce risk behaviors, including notification of current sexual partners, limitation of new partner acquisition, condom use, and, possibly, abstinence during the acute phase. Seeking behavior change is the most constant theme in HIV prevention, but the limited evidence available on behavior change during EHI[9,64,65] bode less well for future interventions in persons with EHI.

Following the biological plausibility of reduced viremia leading to reduced HIV transmission risk,[66,67] we expect that treated persons with EHI will be less likely to transmit to their partners. In the absence of a mechanism to directly observe this effect, the phylogenetic cluster study by Rieder et al on transmission dynamics in gay men in Switzerland suggests that at least 5 reconstructed transmission events were attributable to presumed transmitters who ceased early therapy.[68] Although discouraging from a disease control standpoint, these findings also underscore the need for new ways to modify and measure the impact of early ART on HIV transmission in persons with EHI.

THERAPEUTIC EFFECTS OF EARLY ART

The rationale for treating individuals with EHI is based on the suppressive effect of ART on patient viral load, which consistent of 4 elements: (1) alleviation of symptoms of early infection, (2) preservation of immune function, (3) reduction in the viral reservoirs, and (4) reduction of HIV transmission during EHI.

Until more recent evidence to the contrary,[15,69] early exposure to ART was considered something best avoided or at least be administered intermittently so as to minimize cumulative side effects or the development of drug resistance.[16,70] Here, we summarize findings from the body of literature reporting treatment effects of ART—defined as 1 to 4 antiretroviral drugs in a regimen—administered as either consistent or intermittent courses—during all phases of EHI (Table 3).

Early ART Alleviates Acute Syndrome Symptoms

Acute retroviral syndrome can manifest within days to weeks after exposure, as mildly as a viral syndrome or as severely as multisystem dysfunction.[18,116–118] By reducing viral levels in treated patients, ART can modify both the direct viral effect and the host immune response to the virus, thereby alleviating symptoms of acute infection.[9,27,68,96] Treatment for the sole purpose of reducing these symptoms was included as an indication for treatment for individuals with EHI in a recent set of treatment guidelines in the United Kingdom.[63]

Effect of ART in EHI on Immune Function

There is little debate about the role of immediate ART for individuals presenting with very low initial CD4 counts or who are severely unwell,[19–21,119] but there is some uncertainty about appropriate courses for those identified in EHI with only minor symptoms and high CD4 counts. Known immunological benefits of ART initiated during EHI to date fall into 2 general categories: slower disease progression and near-term improvements in HIV-specific immunological responses.

Regarding disease progression, numerous observational studies and 7 randomized clinical trials have identified associations between early ART and the slowing of the depletion of $CD4^+$ T cells[77,83–86,90–92,99,102,106,107] as well as with the facilitation of immune cell restoration.[22,80,92,94] Preservation of immune cell function has also been reported[23,95,100,108,112] but not universally.[24,115] In many of these studies, ART exposure was very brief and longitudinal follow-up time relatively short, limiting the strength of inferences that can be drawn about early treatment.

ART during EHI has also been associated with improved HIV-specific T-cell function,[5,25,73,89,96,100,110] although starting ART too early may possibly interfere with the initial HIV-specific humoral response.[115] Persistent

TABLE 3. Summary of Studies of the Virological or Immunological Effects of ART Administered During EHI (≤6 Months After Seroconversion)

Author	Setting	Cohort Name/Study Design	N	Comparator Group
Ananworanich et al[15]	Asia	Open-label treatment 2-arm trial	30	15 HIV+ ART naive
Archin et al[71]	NA	CHAVI/STAT	27	—
Bacchus et al[72]	ER	VISCOTI	12 (all control HIV after interruption)	—
Cellerai et al[73]	ER	Retrospective clinical	20	15 HIV+ ART naive long-term nonprogressors
Desquilbet et al[74]	ER	PRIMO (SERECO controls)	58	116 HIV+ ART naive
Evering et al[75]	NA	Clinical	3	2
Fidler et al[76]	ER	Clinical	79	—
Fidler et al[77]	ER	Clinical (CASCADE controls)	89	179 HIV+ ART naive
Gay et al[78]	NA	UNC Duke Acute HIV Infection Consortium	51	92 HIV+ ART naive
Gianella et al[79]	ER	Clinical (Swiss HIV Cohort Study controls)	32	89 HIV+ ART naive with recent EDI
Goujard et al[80]	ER	RCT: ANRS-112 INTERPRIM 3-arm Trial	30: ART; 31: ART-STI; 30: ART-STI-IFN	—
Goujard et al[81]	ER	ANRS PRIMO	164	—
Grijsen et al[82]	ER	PRIMO-SHM substudy	84	28 HIV+ ART naive
Grijsen et al[83]	ER	RCT: PRIMO-SHM 3-arm trial	38: 24 wk cART 38: 60 wk cART	36: no (deferred) ART
Hecht et al[84]	NA	AIEDRP cohort	13 acute 45 early	337 HIV+ ART naive
Hocquelox et al[85]	ER	Retrospective clinical	32	—
Hoen et al[86]	ER, NA	QUEST GW	148	—
Hogan et al[87]	NA	RCT: ACTG 5217 (set point)	66	63: no (deferred) ART
Jain et al[88]	NA	UCSF Options Project	32	34 HIV+, ART initiated later (unknown N of HIV− controls)
Jansen et al[89]	ER	Clinical	11	6 HIV+ ART naive
Kaufman et al[90]	NA	Single-arm open-label	14	—
Kinloch-de Loes et al and Koegl et al[91,92]	ER	RCT	39	38: placebo
Koegl et al[92]	ER	Clinical AHI/PHI cohorts	100	56 HIV+ ART naive
Lampe et al[93]	ER	QUEST (CASCADE controls)	79	358 HIV+ ART naive
Le et al[94]	NA	San Diego Primary Infection Cohort	213	136 HIV+ ART naive
Lodi et al[95]	ER, NA, AUS	CASCADE	m	—
Markowitz et al[96]	NA	Clinical	16 (11 of whom also part of a vaccine trial)	—
Mehandru et al[97]	NA	Clinical	54	18 uninfected controls
Moir et al[98]	NA	Clinical	43: early 50:chronic	35 HIV−
Niu et al[99]	NA	RCT: DAIDS Treatment Initiative	13	15: placebo
Oxenius et al[100]	ER	Clinical	8	—
Pantazis et al[101]	ER, NA, AUS	CASCADE	1023	—
Prazuck et al[102]	ER	Clinical	20	18 HIV+ ART naive
Reider et al[68]	ER	Zurich Primary HIV cohort and Swiss HIV Cohort Study	111	—
Rosenberg et al[103]	NA	Clinical	18	6 AHI ART naive
Rosenberg et al[104]	NA	RCT: ACTG A5187 Study	20	—
Saez-Cirion et al[105]	ER	VISCONTI	14	Untreated HIV controllers, viremics, and treated chronics

TABLE 3. (*Continued*) Summary of Studies of the Virological or Immunological Effects of ART Administered During EHI (≤6 Months After Seroconversion)

Author	Setting	Cohort Name/Study Design	N	Comparator Group
Seng et al[106]	ER	ANRS PRIMO and SEROCO	293	—
SPARTAC Trial Investigators[107]	Multicountry	RCT: SPARTAC Trial	120: 12 wk ART 118: 48 wk ART	124 standard of care (no ART)
Steingrover et al[108]	ER	Clinical (TRIESTAN study controls)	26	46 HIV+ controls; initiated ART during chronic infection
Steingrover et al[109]	ER	Dutch HIV Monitoring Foundation Cohort/Amsterdam Cohort Studies	32	250 HIV+ late ART initiators
Stekler et al[50]	NA	Seattle Primary Infection Cohort (historical controls)	157	27 historical + 60 contemporary controls
Streeck et al[110]	ER	Clinical	12	8
Tilling et al[111]	ER, AUS	Quest Study	—	—
Vinikoor et al[112]	NA	Open-label treatment trial	31	30 HIV− controls
Volberding et al[113]	NA	ACTG 371 single-arm trial	28	45 "recent" HIV infections (versus acute)
Wyl et al[114]	ER	Zurich Primary HIV cohort (Swiss HIV Cohort Study controls)	33	79 chronic HIV, ART naive
Younes et al[115]	NA	Clinical	39	—

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Ananworanich et al[15]	3 arms of elective ART: 5 class "megaHAART" versus 3 class regimen initiated within 3 d of enrollment for 24 wk	AHI: M	$CD4^+CCR5^+$ gut T cells increased from 41% at baseline to 64% at 24 wk	<50 copies achieved in 14/15 patients in blood and 13/13 in gut. Total blood HIV DNA at 0 wk predicted reservoir size at 24 wk
Archin et al[71]	ART within 45 d of EDI	AHI: B and F	Degree of resting cell infection is directly related to the availability of $CD4^+$ T cells susceptible to HIV, regardless of whether viremia is controlled by the immune response and/or ART	Success of early ART may depend to a certain extent on whether or not infected resting $CD4^+$ T cells are stable
Bacchus et al[72]	ART initiated 10 wk postinfection for 3 yrs	—	—	HIV DNA reservoir distributed large in short-lived memory $CD4^+$ T cells
Cellerai et al[73]	ART initiation within 13 d of seroconversion	SC: (A and B) and/or (C and/or F)	Early ART results in levels of highly polyfunctional HIV-1–specific $CD4^+$ and $CD8^+$ T cells as in long-term nonprogressors	—
Desquilbet et al[74]	17 m	RI: F or [B or (A and B)] or E PHI: G	—	No difference in viral set point 12 mo after treatment discontinuation in the treatment group compared with matched controls
Evering et al[75]	ART started within 72 h of flexible sigmoidoscopy	AHI: M	ART may halt measurable evolution of HIV-1 quasi-species derived from the gastrointestinal tract; meaning immune activation in the gut may persist whether or not there is viral replication	—
Fidler et al[76]	3 arms of elective short course: 4 drug, 3 drug, PI only	AHI: G or F or (A and B) or L	No differences in rate of CD4 recovery by arm	Faster VL decline in patients on 4 drug regimen compared with 3 drug or PI-containing ART

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TABLE 3. (*Continued*) Summary of Studies of the Virological or Immunological Effects of ART Administered During EHI (≤6 Months After Seroconversion)

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Fidler et al[77]	Elective 3 mth short course at PHI	PHI: E or F or L	Rate of CD4 decline slower in treated group over 3 yrs	No difference in mean VL at 2 yrs
Gay et al[78]	NNRTI-based 3 drug regimen initiated during AHI	AHI: A and B	Relatively high median baseline activation level of $CD8^+CD38^+HLA\text{-}DR^+$ T cells	More rapid viral decline in treated AHI patients than controls
Gianella et al[79]	Elective standard 1st line within 120 d of EDI; option to stop after 1 yr of suppression	AHI: G and [D and (B and/or H)] RI: I or (B and J) and (F or I) or K	—	Early ART associated with lower plasma and cell RNA as compared with late starters and ART naive for >1 yr after ART cessation
Goujard et al[80]	ART = continuous therapy; ART-STI = 36 wk ART with three 4 wk interruptions; ART-STI-IFN = same as ART-STI group with addition of peg-IFN	AHI: B and D PHI: D	$CD4^+$ T-cell counts and $CD4^+/CD8^+$ T cell ratios similar between groups after 6 mth interruption; HIV-specific responses didn't differ across arms. interruption didn't have deleterious impact; all regimens show sustained immunological benefit after cessation	87% of the patients achieved undetectable RNA at 32 wk; but RNA and HIV DNA levels were same after 6 mth interruption
Goujard et al[81]	Standard therapy according to national guidelines within 3 mth of EDI who interrupted and stayed in follow-up ≥ 12 mth	PHI: (B and D) or E	Controllers had lower levels of specific $CD8^+$ T-cell frequency and $CD8^+$ T-cell activation	14/164 patients controlled VL for median 4.5 yrs
Grijsen et al[82]	Forty-five 24 wk SCART; thirty-nine 60 wk SCART; both triple class regimen	PHI: (B and D) or (A and J within 180 days)	—	—
Grijsen et al[83]	3 class regimen for 24 or 60 wk; changed if DR or poor tolerance	PHI: (A and B) or (A and J within 180 d)	Time to reinitiation of therapy longer in both ART arms	ART lowered viral set point (plasma VL at 36 wk after interruption)
Hecht et al[84]	Elective ART for ≥12 wk within 6 mth of seroconversion; subsequently interrupted	EHI/PHI: (A and B) or E or (A and F)	$CD4^+$ T-cell counts higher in early group at 24 and 72 wk	Differences in RNA levels across groups at 24 wk gone by 72 wk
Hocquelox et al[85]	ART within 3 mo of PHI, interruption after ≥3 mth with/ ≥24 mth follow-up	PHI: (D and H) and/or E	Controllers had more stable $CD4^+$ counts over time	5/32 controlled VL for med 6.25 yrs
Hoen et al[86]	Randomized to 1/4 regimen types	PHI: (A and B) and G	Median increase in $CD4^+$ 147 cells/mL by 48 wk	Median decrease in VL −5.4 log copies by 48 wk. Baseline $CD8^+/CD38^{++}$ T-cell count predictive of suppression
Hogan et al[87]	ART for 36 wk	RI: F or (A and/or D within 180 d)	Trial stopped by DSMB due to higher-than expected disease progression in delayed treatment arm	—
Jain et al[88]	—	AHI/EHI: "within 6 mo of infection"	Delayed ART group had higher levels of $CD4^+$ and $CD8^+$ T-cell activation	Delayed therapy associated with higher proviral and plasma DNA. % of activated $CD4^+$ and $CD8^+$ T cells associated with size of reservoir

TABLE 3. (*Continued*) Summary of Studies of the Virological or Immunological Effects of ART Administered During EHI (≤6 Months After Seroconversion)

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Jansen et al[89]	Intensive 5-class regimen initiated "within weeks of EDI"	AHI: D or G	ART associated with more HIV-specific $CD4^+$ T cells but this wasn't associated with ability to control VL post-ART	ART associated with lower VL; 1/5 interrupters controlled VL up to 2 yrs later.
Kaufman et al[90]	Standard 1st line with supervised treatment interruption (STI) protocol	AHI: (A and B) or (C and D) EHI: G or F	Gradual decrease in $CD4^+$ and viremia levels over time after interruption; baseline HIV-specific immune activation did not predict duration of viral control	
Kinloch-de Loes et al and Koegl et al[91,92]	Daily zidovudine	PHI: (G and K) or (H and A and B)	CD4 cell counts differed across arms by 6 mth	—
Koegl et al[92]	3 or 4 class regimen as determined by physician, discontinued at median of 9.5 min	PHI: (A and B) or E	Treated group experienced increase in CD4 count; untreated group CD4 fell. Time to CD4 < 3350 significantly shorter in untreated group	Med VL in ART group lower 6 mth post cessation, difference gone by 12 mth
Lampe et al[93]	3 or 4 class regimen as part of vaccine trial; interruption optional	PHI: (G and K) or (H and A and B)	—	Unsuppressed VL prevalence at 3 yrs higher in untreated, but effect of transient ART on long-term VL is likely modest
Le et al[94]	97 initiated within 4 mth post-EDI; 116 initiated after 4 mth EDI	PHI: K	Earlier ART initiation was associated with larger portion of and faster pace of $CD4^+$ T-cell recovery	No association between VL at ART initiation and $CD4^+$ T-cell recovery
Lodi et al[95]	ART initiated within 3 mth of seroconversion for ≤3 mth	SC: (A and B) and/or E	—	95.8% experienced virological rebound within median 1.7 mth after treatment interruption
Markowitz et al[96]	ART initiated during EHI; voluntarily discontinued after mean 3.2 yrs	RI: B and L	$CD4^+$ and $CD8^+$ cell–mediated HIV-specific immune responses increased	Posttreatment viral rebound present in all subjects after mean 26 d, followed by a significant but transient (mean 1 yr) suppression in all but 1 subject
Mehandru et al[97]	ART initiated during acute/early infection. Range 1–7 yrs of ART	AHI: M	ART during AHI/EHI does not lead to complete immune reconstitution in the GI mucosa despite immune reconstitution in the peripheral blood	—
Moir et al[98]	ART	EHI: "within 6 mth of providing baseline samples"	Early ART associated with better B-cell function recovery against HIV and non-HIV antigens	—
Niu et al[99]	Daily high-dose zidovudine	AHI: (H and A and B) or K	Significantly higher CD4 in treated subjects after 6 mth of therapy	No difference across 2 arms in plasma VL after 6 mth
Oxenius et al[100]	3 class regimen initiated either at seroconversion or 6 mth after	AHI: G and K	ART during PHI preserves HIV-specific $CD4^+$ and $CD8^+$ T cell physically and functionally (HIV-specific immunity), even when ART is intermittent	—
Pantazis et al[101]	Early (N = 675) treated within 6 mth of seroconversion for ≥30 d; deferred (n = 348) treated after 6 mth	AHI: E or (A and B) or L	CD4 cells lost rapidly after cessation but subsequent loss rate equal to untreated	No difference in VL set points, defined as mean of all available VL measures post-ART

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TABLE 3. (*Continued*) Summary of Studies of the Virological or Immunological Effects of ART Administered During EHI (≤6 Months After Seroconversion)

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Prazuck et al[102]	Elective ART initiated within 10 wk of symptomatic AHI; at least 12 mth before interruption	AHI: (A and B) or (D and H)	Early ART associated with higher CD4 2.8 yr after cessation	25% of treated group controlled RNA 2.8 yr after cessation
Reider et al[68]	93 elected to initiate ART early; approximately 51% stopped after 1-yr suppression	AHI: G and [D and (H and/or B)] RI: G and (B and J) and I	Phylogenetic cluster study to examine transmission dynamics identified 20 clusters; 5 inferred transmissions occurred during chronic stage among presumed transmitters >3 m after cessation.	
Rosenberg et al[103]	3 class regime, most within 72 h of diagnosis with STI if VL exceeded 5000 copies	AHI: A and B and D	Increased HIV-specific T cells and stable T helper cells responses, suggesting a functional immune responses can be augmented in chronic infection	Despite rebound in viremia, all subjects were able to achieve at least a transient steady state off therapy with viral load below 5000 RNA copies per milliliter
Rosenberg et al[104]	ART initiated during acute/early infection, interrupted at 30 wk; 1:1 randomization of vaccine versus placebo	AHI: B and D	All subjects had "relatively healthy CD4" counts	Med viral set points (defined as average of all measured VL after ART) lower in all subjects as compared with historical controls (MACS)
Saez-Cirion et al[105]	ART initiated within 10 wk of PHI	PHI: D and (H or B) and or E	—	HIV suppressive capacity of $CD4^+$ cells and T-cell activation status lower in posttreatment patients than HIV controllers
Seng et al[106]	ART initiated during PHI for ≥6 m; interrupted for ≥3 m (PRIMO); 35% given monotherpay, rest combo-ART	PHI: D or ((B or H) and B) or E	Rapid CD4 decline in first 5 m after cessation, more slowly thereafter. More rapid gains in CD4 during ART associated with greater loss after cessation	—
SPARTAC Trial Investigators[107]	3 class regimen as determined by physician	PHI: E or (A and B) or F or L or (G and J)	Time to $CD4^+$ count <350 was 65 wk longer with 48-wk course versus SOC	48-wk course conferred lower RNA levels 36 wk after cessation versus SOC
Steingrover et al[108]	3 or 4 class regimen, simplified 1 yr after initiation; subsequent interruption	PHI: (D and (B or H)) or E	Significantly greater drop in $CD4^+$ cell count in later initiators within first 4 wk; no difference after 4 wk	Time to viral rebound (50–500–5000 copies) significantly longer in earlier ART initiators
Steingrover et al[109]	3 or more class regimens; early initiation within 180 d with early interruption	PHI: [(A and D) and (B or H)] or E	No significant difference in rate of CD4 decline between 2 groups	Early transient ART associated with a initial but transient lowering of viral set point, defined as 7 wk after seroconversion or 7 wk after ART interruption
Stekler et al[50]	40: ART <30 d; 82: ART 31–180 d; 35: ART >180 d	AHI: A and B EHI: D and F	—	—
Streeck et al[110]	ART for 24 wk during AHI	AHI: G and K and [B and (C or D)]	Treatment associated with increased CD4+ cell count, enhanced differentiation of HIV-specific $CD8^+$ T cells from effector memory to effector cells at week 24, and higher virus-specific interferon-g+ $CD8^+$ T-cell responses after viral rebound at 48 wk. But by 6 m no difference in CD4 count	Treatment resulted in suppression of viremia at 48 wk but no difference at 6 mth after termination

TABLE 3. (*Continued*) Summary of Studies of the Virological or Immunological Effects of ART Administered During EHI (≤6 Months After Seroconversion)

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Tilling et al[111]	4 class regimen during PHI	PHI: B and [A and/or (C and D)]	Rapid decline and normalization of $CD8^+/CD38^{++}$ cell counts within 2 wk of ART and continued to fall in suppressed patients	80% suppressed on therapy, most of whom (67%) continued to have falling $CD8^+/CD38^{++}$ cell counts
Vinikoor et al[112]	ART initiation within 45 d of AHI diagnosis; for those suppressed for 96 wk	AHI: A and B	% of $CD8^+$ cells with $CD38^{++}HLA\text{-}DR^+$ decreased from 72.6% to 15.6% in 96 wk but was higher than HIV− controls	Shorter time to suppression predicted lower activation at 96 wk
Volberding et al[113]	4 class regimen in acute or recent HIV with interruption after 52 wk of suppression until viral rebound	AHI: B and [A or (C and D)] or (D and E) RI: ((C and D) and (A and B)) or (C and F)	Baseline percentages of activated $CD8^+$ T cells, naive and memory CD4þ and CD8þ T cells, and absolute CD4þ and CD8þ T-cell counts were not associated with primary end point success	End point of viral suppression for 24 wk postinterruption achieved at same rate in both arms
Wyl et al[114]	Elective std 1st line; option to stop after 1 yr of suppression	AHI: E and [C and (G and/or B)] RI: E and (B and I) and H	—	VL (both plasma and cell associated) lower in treated versus untreated controls 1 yr after ART cessation, but no difference by 3 yrs
Younes et al[115]	1 yr of ART initiated at 5 different time points up to 18 mth postseroconversion	SC: (A and B) or G or D or F and K	Earlier ART inhibits generation of significant frequencies of HIV-specific Tm cells. Later ART limits HIV-specific CD4 T -cell responses. ART initiation between 3–18 m show brisk and broad HIV-specific CD4 T-cell responses	—

A, enzyme immunoassay (EIA) negative; AUS, Australia; AHI, acute HIV infection; B, detectable plasma HIV RNA; C, EIA positive; D, Western blot negative or indeterminate; E, negative and positive EIA result within 12 months; ER, Europe; F, detuned nonreactive EIA; G, acute retroviral syndrome symptoms, most commonly including fever, malaise, headache, lethargy, and malaise; H, detectable p24 antigen; I, negative gp120 avidity; J, Western Blot positive; K, duration from estimated date of infection based on at least one of the following (1) onset of ARS symptoms, (2) a documented high-risk exposure, or (3) estimated date of infection determined by laboratory methods; L, evolving titer-positive HIV antibody test; M, Fiebig acute HIV staging (<30 days postinfection); NA, North America; PHI, primary HIV infection; RI, recent infection; SC, seroconversion.

immune activation has been identified among early ART initiators,[29,75,81,112,113] possibly to a lesser extent than persons starting ART during chronic infection.[16,26,29,88]

Taken together, these data suggest that immediate use of ART irrespective of CD4 count could be expected to confer health benefits to patients with HIV. However, the durability and magnitude of these effects are yet unknown, limiting their immediate application to clinical decisions regarding optimal management of persons with EHI. Future research efforts must take note that increasingly higher CD4 thresholds for ART initiation in guidelines will continue to narrow the gap between early and delayed therapy, necessarily limiting our ability to decisively attribute observed health effects to early therapy.[30,48–50,95]

Effect of ART in EHI on Virological Outcomes

In addition to improvements in surrogate markers of clinical progression, studies report potential benefits of ART during EHI on virological outcomes. The potential effect of ART on the viral set point—the level at which a patient's viral load stabilizes after seroconversion—is of great interest given its strong association with the course of disease progression.[120] Two observational studies[101,109] and several trials[83,87,104] have examined this issue, all but one[101] reporting lower viral set points among patients treated during EHI versus those who were not. The variable definitions of viral set point across these studies, defined as the viral load at points in time ranging from 7 to 72 weeks after ART cessation, and the noncomparability of controls may contribute to the inconsistency of results across observational studies.[87,104,109] Nevertheless, the fact that 3 randomized clinical trials[87,104,107] all demonstrated some reduction in viral set point between ART-treated and control participants suggest the presence of a substantive effect.

Although some report no effect of transient therapy on virological indicators after cessation,[92,101,113] most identify a significant difference in the viral loads of the early treatment groups[74,77,80,84,95,96,99,107,110,114] versus their comparators. Interruption of ART almost invariably leads to the reemergence of

detectable viral replication and the progression of HIV infection, a result of the establishment of inaccessible viral reservoirs.[121]

Finally, very early treatment may impact the size of the latent reservoir that is established early after infection. Research in this area may be critical for future work on HIV cure,[71,105] the key barrier to which is eradication of the latent pool of inaccessible reservoir cells.[122] To date, results of 4 separate study groups provide the most insight. The RV254/SEARCH 010 Study Group has reported that ART during EHI may play a key role in immune restoration and preventing the seeding of the HIV reservoir in the gut mucosal tissue of 20 Thai participants.[15] These findings are supported by other groups who also report reduction in the sizes of viral reservoirs—measured as levels of cell-associated HIV DNA—among individuals with EHI receiving immediate ART compared with deferred therapy,[75,85,88,123] in some cases even to levels comparable with those of documented elite controllers.[124] Examining perhaps the most rigorous measure of the persistent HIV reservoir, resting CD4 cell infection with replication competent virus, Archin et al observed a strong correlation between the extent of viral replication before suppressive ART and the size of the resting cell reservoir.[71] The Virological and Immunological Studies in Controllers after Treatment Interruption group demonstrated that early ART could also enhance viral control of therapy irrespective of HLA type and CCR5 genotype in a subset of patients treated intermittently during early infection.[72,81,125] This group showed that immediate ART initiated within 12 weeks of diagnosis and maintained for a minimum of 3.5 years before discontinuing was associated with a higher proportion of viral controllers several years after stopping ART compared with the proportion of controllers described in untreated chronic infection (from $<$1% to 15.6%).

These findings together with the successful elimination of HIV from 1 patient[126] and the functional cure reported in an infant treated at birth[127] give cautious hope to the concept of strategic use of ART to limit establishment or reestablishment of the viral reservoir and work toward HIV cure.

Other Considerations of Early ART

A successful strategy to carry out early ART for prevention purposes must address a complex interplay of factors likely to mediate its impact. The acceptability of such a strategy must, for example, help patients faithfully confront the reality of lifelong adherence from an earlier stage in the course of disease, with which we have limited experience. Our understanding of the toxicity of prolonged exposure to antivirals for even longer duration is also limited.[86]

The choice of ART regimens will also determine the success of treatment as prevention strategies targeting persons with EHI. Current regimens are designed for simplicity, reduced cost, tolerance, patient and clinician preference, and the genotype of transmitted virus. However, for persons with EHI, treatment choices may be informed by patients' desires to initiate therapy as soon as possible—often before resistance data are available—and the inclusion of agents known to achieve rapid decreases in plasma viral load. Selecting drugs that concentrate in the genital or gastrointestinal tracts, such as integrase inhibitors, may protect lymphocytes in these compartments that are especially vulnerable to the adverse effects of EHI and also present clear prevention advantages. Evidence that intensive drug regimens of up to 5 agents may confer benefit over standard triple therapy for individuals with EHI is still formative.[96]

The potential risks of earlier initiation of ART can be, in part, anticipated, given the anticipated risks of lifelong treatment for all patients with HIV. Early ART may present new challenges for effective delivery of patient care, but may also have positive impacts on patient quality of life[82] and retention in care.[128] But the relatively short follow-up periods, transient nature of the treatment exposure, and small sample sizes limit insight and underscore the need for further research into comparative treatment outcomes.[129] Furthermore, interruption of therapy has been associated with major cardiovascular, renal, and hepatitic disease,[69] outcomes that must be considered when bearing risks versus benefits of sustained therapy.

Finally, as with all treatment as prevention efforts, feasibility of future programs must anticipate logistical challenges such as drug stock-outs or unavailability of second-line regimens.[130]

SUMMARY AND CONCLUSIONS

The formative nature of research into ART during EHI is reflected in the lack of consensus surrounding treatment guidelines for these persons. The United States and United Kingdom are the only 2 countries known to date with specific guidelines for clinical management of disease in persons with EHI.[63,130–132] In both cases, treatment is recommended, though both note caveats about the strength of evidence.

However, an increasing body of evidence supports the role of immediate ART among individuals identified with EHI to facilitate immune function, limit the size of the HIV reservoir, and reduce the risk of onward viral transmission. We and others have anticipated the considerable difficulty in finding subjects in the earliest phases of HIV infection given the added demands of repeat HIV testing, limitations of detection using currently available technologies, and the need for enhanced provider and patient awareness of the clinical and prevention significance of EHI. These considerations notwithstanding, future HIV control efforts will need to emphasize novel and targeted methods to identify patients with EHI and provide unequivocal support for treatment to improve their quality of life and limit onward transmission of HIV.

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Antiretroviral Therapy for Prevention of HIV and Tuberculosis: A Promising Intervention but Not a Panacea

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Abstract: The demonstration of the efficacy of antiretroviral therapy (ART) for HIV prevention in heterosexual HIV serodiscordant couples has resulted in the call for widespread implementation of "Treatment as Prevention" (TasP) to confront the challenge of continued transmission of HIV. In addition, evidence of the possible effect of use of ART on decreasing the incidence of tuberculosis (TB) in persons living with HIV has also contributed further enthusiasm. Mathematical modeling studies evaluating the potential impact of TasP on the trajectory of the HIV and TB epidemics have inspired discussions about a possible future without AIDS. We present the evidence regarding the effect of ART on the incidence of HIV and TB, benefits and risks associated with embracing TasP, and the need for multicomponent prevention strategies and for further research to generate empiric data on the effect of TasP on HIV and TB at a population level.

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INTRODUCTION

The demonstration of the efficacy of antiretroviral therapy (ART) in preventing HIV transmission offers promise for controlling the HIV epidemic.[1–4] The HIV Prevention Trials Network (HPTN) 052 study demonstrated the efficacy of ART when used by HIV-infected persons for the prevention of HIV transmission in serodiscordant heterosexual couples.[1] This clinical trial, in conjunction with a number of ecological, observational, and mathematical modeling studies, provides support for the concept of "Treatment as Prevention" (TasP). Other evidence from ecological and observational studies provides support for the potential role of ART for prevention of tuberculosis (TB).[5,6] The potential for ART to prevent HIV transmission has resulted in advocacy for widespread implementation of TasP and has inspired discussions about a future AIDS-free generation.[7] Mathematical modeling studies have also assessed the impact of TasP in conjunction with other prevention interventions on the HIV epidemic[8] and its impact on the incidence of HIV-associated TB.[9] In this article, we present the evidence regarding the use of ART for prevention of both HIV and TB and summarize key issues that need to be addressed to appropriately situate this intervention within the context of other available prevention interventions. We also highlight the need for further research to provide empiric data on the effect of ART for individual health and its effects on the trajectory of the HIV and TB epidemics at population level.

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EFFECT OF ART ON HIV INCIDENCE

The HPTN 052 study was a randomized-controlled trial that compared early versus delayed initiation of ART in 1763 serodiscordant heterosexual couples in 9 countries.[1] HIV-infected partners with $CD4^+$ counts between 350 and 550 cells/μL were randomized to receive early therapy (ie, immediate ART) or delayed therapy at $CD4^+$ count of 200–250 cells/μL or onset of HIV-related symptoms. A total of 39 HIV-1 transmissions were observed, of which 28 were virologically linked to the infected partner. Of the linked transmissions, only 1 occurred in the early therapy group (hazard ratio [HR]: 0.04, 95% confidence interval [CI]: 0.01 to 0.27) with evidence of 96% protection. In terms of overall transmission, ART had a protective effect of 89%.

There have been a series of ecological, observational, and mathematical modeling studies supporting TasP. Ecological studies from San Francisco, South Africa, Taiwan, and Canada suggested that expansion of ART use was associated with a reduction in the number of new HIV infections or expected HIV cases.[10–14] In the study from San Francisco, an association between expansion of ART use and decreases in community viral load was reported, measured as the sum of the most recent viral loads in HIV-infected individuals, over the period between 2004 and 2008 in conjunction with a decrease in number of new infections.[11] Data from the British Columbia, Canada, revealed a significant inverse association between the number of individuals on ART and the number of individuals newly testing HIV positive per year.[12] Similarly, a recent study from South Africa demonstrated that increase in coverage of ART use in 1 region was associated with a decrease in HIV incidence.[14] In the latter study, an HIV-uninfected individual living in a community with high ART coverage, defined as 30%–40% of persons with HIV infection on ART, was 38% less likely to acquire HIV than an individual living in a community with ART coverage of less than 10%.

Observational studies supporting an association between ART use and decrease in HIV transmissibility have largely been derived from studies that included HIV serodiscordant couples. The earliest study reporting such an association was with use of zidovudine monotherapy,[15] followed by further studies that included the use of combination ART in HIV-discordant couples.[16–20] Only 1 study failed to demonstrate association between use of ART and decrease in transmission,

the latter including a limited number of discordant couples from China.[21] A 2011 review of 7 observational studies and 1 randomized-controlled trial collectively identified 464 episodes of HIV transmission among serodiscordant couples, of which 72 episodes occurred among couples in which the HIV-infected partner was on ART and 392 occurred in couples in the absence of ART.[22] The rate ratio of HIV transmission for these studies was 0.34 (95% CI: 0.13 to 0.92)—ie, there was an estimated 66% decrease in risk of HIV transmission with ART use by the HIV-infected partner.

In a more recent study from China, the effect of ART on HIV transmission among 38,862 heterosexual serodiscordant couples was reported from national HIV epidemiology and treatment databases between 2003 and 2011.[19] A total of 1,613 HIV transmissions were identified, with an overall transmission rate of 1.6/100 person-years (95% CI: 1.5 to 1.7). The rate of transmission for the treated couples was 1.3/100 person-years (95% CI: 1.2 to 1.3), which was significantly lower than the rate in the ART-naive cohort (2.6/100 person-years [95% CI: 2.4 to 2.8]; adjusted HR: 0.74 [95% CI: 0.65 to 0.84]). This study's findings are particularly important as they demonstrate the efficacy of this intervention outside of the context of a research study. A key limitation of both the ecological and observational studies is that they cannot support causal association between use of ART and decrease in HIV infections, as the latter effect may have been caused by other factors.

Evidence supporting ART for prevention is also derived from mathematical modeling studies. In a study by Granich et al,[23] which was based on optimistic assumptions of ART coverage and adherence and used data from the South African epidemic, expansion of use of ART for all individuals identified with HIV infection was shown to have the potential to lead to HIV elimination, defined as HIV incidence less than 0.1%, in 50 years. A meta-analysis of 12 modeling studies regarding the HIV epidemic in South Africa found that TasP could substantially reduce new infections under similarly optimistic assumptions of annual voluntary testing, followed by greater than 90% linkage to care with immediate ART initiation and 85% of patients remaining on treatment over 3 years.[24] The HIV Modeling Consortium raised several priority issues for future modeling studies of ART for prevention including the need to report on the impact of decisions over both the short and long term, to estimate the impact of current programs rather than radically different future programs, and to use real-life assumptions about testing, linkage to and retention in care, and medication adherence.[25–27] The authors also encouraged future models to examine negative outcomes of expanded treatment programs, including their potential influence on risk behaviors by individuals living with HIV.

EFFECT OF ART ON TB INCIDENCE

HIV-infected individuals have 20–37 times the risk of developing TB compared with HIV-uninfected individuals.[28] The case-fatality rates among HIV-infected persons are several-fold higher than those without HIV infection and are strongly associated with the degree of immunodeficiency.[29,30] Data from clinical trials and observational studies have shown that initiation of ART in patients with TB is associated with a reduction in mortality.[31–34] In addition, data from clinical trials, cohort studies, ecological studies, and mathematical modeling suggest that use of ART has the potential to reduce the risk of TB in patients with HIV infection.[1,35–41]

A recent meta-analysis of 3 randomized-controlled trials and 8 cohort studies from resource-limited countries that compared TB incidence by ART use in HIV-infected adults demonstrated that ART was strongly associated with a reduction in TB incidence (HR: 0.35, 95% CI: 0.28 to 0.44).[5] This association was significant across all baseline $CD4^+$ count strata: less than 200 cells/μL (HR: 0.16, 95% CI: 0.07 to 0.36), 200–350 cells/μL (HR: 0.34, 95% CI: 0.19 to 0.60), and greater than 350 cells/μL (HR: 0.43, 95% CI: 0.30 to 0.63), without evidence of HR modification with respect to baseline $CD4^+$ count. Clinical trial data demonstrated nearly identical reductions in TB incidence when initiating ART at $CD4^+$ count 200–350 cells/μL (HR: 0.50, 95% CI: 0.28 to 0.83) compared with <200 cells/μL[42] and at greater than 350 cells/μL (incidence rate ratio: 0.51, 95% CI: 0.28 to 0.91) when compared with $CD4^+$ count of 200–250 cells/μL.[1] A reduction in TB incidence was also demonstrated in high-income countries following ART initiation in adults with $CD4^+$ counts greater than 350 cells/μL.[6] However, it is important to note that the absolute reduction in TB rates is greatest at lower $CD4^+$ strata, and no evidence is available for the effect of use of ART at $CD4^+$ count >500 cells/μL on the incidence of TB. Surprisingly, findings from HPTN 052 did not show a decrease in pulmonary TB incidence in individuals who initiated ART at $CD4^+$ count between 350 and 550 cells/μL versus those who initiated ART at $CD4^+$ 200–250 cells/μL, whereas there were fewer episodes of extrapulmonary TB, largely presumptive in nature, with early use of ART.[1] Of note, a trial conducted in Botswana found that reductions in TB incidence with ART use at $CD4^+$ counts <200 cells/μl were similar among HIV-infected adults receiving 6 months of isoniazid preventive therapy (IPT) with either positive or negative tuberculin skin tests,[38] suggesting that ART impacts risk of TB following either endogenous reactivation or exogenous exposure.[43]

Studies evaluating the impact of ART on TB incidence at a population level are more limited. An ecological study from a high HIV and TB burden community of approximately 15,000 persons in South Africa demonstrated an association between implementation of an ART program using criteria based on prevailing national guidelines and TB notification rates. Between 2002 and 2008, as ART coverage increased from 0% to 21% of the HIV-infected population, adult TB notification rates increased to a maximum of 2,500 cases per 100,000 population between 2002 and 2005, then decreased by an average of 202 cases/100,000/yr, reaching 2,000 cases per 100,000 population in 2008.[44] Notably, the decline in new TB notifications was observed exclusively among the HIV-infected population receiving ART. Furthermore, 2 cross-sectional surveys performed in the same community showed a significant reduction in TB prevalence among a randomly selected HIV-infected population sample, from 9.2% in 2005 to 3.6% in 2008 (adjusted $P = 0.013$), whereas the prevalence among HIV-negative individuals remained unchanged.[45] Similar findings were reported in a retrospective descriptive study in which ART scale-up between 2005 and 2009 in a rural district in Malawi was associated with a 33% (95% CI: 27 to 39%) reduction in new TB cases and

a 25% (95% CI: 9 to 49%) reduction in recurrent cases.[39] It is also important to note that, in these 2 studies, ART was initiated at advanced stages of HIV disease, largely at $CD4^+$ count of <200 cells/μL. Given the observational nature of these studies, they are unable to demonstrate a causal relationship between use of ART and reduction in TB incidence/prevalence. The observed trends may have been confounded by high mortality before case diagnosis, provision of IPT (in Malawi), or changes in TB case detection efficiency. It is likely that TB case finding was increased in the ART programs, which may have led to a reduction in TB transmission because of undiagnosed, untreated TB.

Mathematical modeling using data from 9 countries in sub-Saharan Africa suggested that widespread implementation of annual HIV testing and ART initiation early in the course of HIV infection regardless of $CD4^+$ count would lead to rapid reduction in HIV-associated TB at the population level.[41] Assuming that coverage increases to 95% by 2015, initiating ART within 5 years of HIV seroconversion would reduce the incidence of HIV-related TB in 2015 by 48% (range: 37%–55%).[41] The reduction would be greater if ART is started within 2 years of HIV seroconversion (63%; range: 52%–72%). More substantial reductions would be anticipated if the intervention is sustained until 2050: if ART is started 5 or 2 years after HIV seroconversion, the incidence in 2050 will be reduced by 66% (range: 57%–80%) and 95% (range: 93%–96%), respectively.

TasP: WHO SHOULD BE PRIORITIZED?

Much of the ongoing discussion regarding TasP has centered on initiation of ART for individuals with higher $CD4^+$ count who would otherwise not be eligible for ART for their own health. Expansion of ART to individuals with higher $CD4^+$ counts has been noted to be associated with certain challenges. Studies have shown that HIV-infected individuals with higher $CD4^+$ counts are at higher risk for loss to follow-up both during the pre-ART phase and when they receive ART.[46] In addition, there remains uncertainty with regard to the balance of benefits versus risks of ART for the health of HIV-infected individuals at higher $CD4^+$ counts.[47,48]

It is also ironic that, although substantial attention has been given to initiation of ART at a higher $CD4^+$ count, largely for the purpose of prevention of HIV transmission, there remains a gap in coverage for individuals who are in urgent need of ART for their own health and where use of ART will also have substantial prevention effects.[49] In most resource-rich and resource-limited countries, ART initiation is occurring at advanced stages of HIV disease, significantly below the recommended $CD4^+$ count thresholds.[42,50,51] A recent study of 36,411 adult patients who started ART between 2005 and 2009 in Mozambique reported that the proportion of patients with late ART initiation, defined as initiation at a $CD4^+$ count $<$ 100 cells/μL or WHO clinical stage IV, decreased from 46% to 27% during 2005–2007 but remained constant at more than 33% during the period between 2007 and 2009.[50] Globally, it is estimated that only 47% (range: 44%–50%) of adults and children in low- and middle-income countries who were eligible for ART for their own health have access to such treatment.[52] Thus, there is a huge need for the expansion of ART access to those who need ART for their own health (at $CD4^+$ count $<$ 350 cells/μL) and for prevention of transmission to others, the latter a benefit of treatment not appreciated in this population. Importantly, data from 1 discordant couples study demonstrated that the risk of HIV transmission follows a gradient with HIV-infected individuals with lower $CD4^+$ counts at higher risk of transmission to their sexual partner.[16] Indeed, it is important to note that the weight of evidence in support of TasP from ecological and observational studies is based largely on the effect of ART initiation at lower $CD4^+$ counts, ie, when the HIV-infected partner was eligible for ART based on their own health needs, as indicated earlier (Table 1).[10–14,17–19,53] In only 2 discordant couples studies, an observational study and HPTN 052, was ART initiated in HIV-infected individuals for the purpose of HIV prevention, ie, when the HIV-infected partners were not yet eligible for ART for their own health.[1,16] Similarly, the evidence in support of the effect of ART use on HIV incidence is derived from use of ART in HIV-infected individuals with low $CD4^+$ count.

Thus, expansion of treatment for those who need it for their own health is likely to have substantial benefit for them in terms of prevention of HIV and TB-related morbidity and mortality and decreased HIV incidence among their HIV-uninfected partners and potentially protecting their families, households, and communities from risk of TB. Clearly, expansion of TasP to those at earlier stages of HIV disease is an important frontier for further research and implementation.

TasP: AN UNLIKELY PANACEA

Enthusiasm for TasP must be tempered by acknowledging that it is not a panacea but rather its success is dependent on a multiplicity of other complementary and necessary interventions.[54] Behavioral, biomedical, and structural interventions are required to ensure that various components of the HIV care cascade are optimized to achieve the ultimate goal of TasP. Achieving higher coverage with ART for those in need will require expansion of HIV testing, using innovative approaches such as provider-initiated testing and counseling, household testing, and community-focused approaches.[55,56] It will also require attention to maximize every step of the HIV care cascade from linkage of those found to be HIV positive to retention in care, prompt determination of ART eligibility, and initiation of ART with provision of adherence support.[54] Without attention to the HIV care cascade, the promise of TasP as an intervention for both HIV treatment and HIV prevention will fail to be realized[57] (Figure 1). Two meta-analyses from sub-Saharan Africa demonstrated that less than a third of persons testing HIV positive remain in care until ART initiation.[58,59] Results are similar in the United States, where 19%–29% of persons with HIV infection are estimated to achieve viral load suppression.[60–62]

In reality, it may be difficult to achieve the magnitude of coverage with ART for all individuals with HIV in a community as presumed in many of the modeling studies, supporting the need for other HIV and TB prevention interventions. As noted in Figure 1, HIV testing is the foundation of all prevention interventions. Although, for those individuals found to be HIV infected, TasP is an important prevention intervention when combined with supportive interventions, those found

TABLE 1. Summary of Cited Studies of ART for Prevention of HIV Transmission

Author of Study	Type of Study	Population	Location	Criteria for ART Use	Effect of ART
Tanser et al[14]	Ecological	General	KwaZulu Natal, South Africa	South African Guidelines[79] Study period: 2004–2011 -2004–2010: CD4 < 200 or WHO Stage IV -April 2010: CD4 < 350 pregnant women and TB patients -Aug 2010: CD4 < 350	Estimated 38% reduced chance of acquiring HIV if individual living in community of high ART coverage (30–40%) as compared with low coverage (<10%)
Das et al[11]	Ecological	Largely MSM	San Francisco, United States	Prevailing guidelines[80] Study period: 2004–2008 -2004–2006: CD4 < 200, symptomatic disease -2007–2008: CD4 < 350, symptomatic disease	Mean and total community viral load decreased from 2004 to 2008 in association with decreases in new HIV infections (798 in 2004 to 434 in 2008)
Porco et al[10]	Ecological	Largely MSM	San Francisco, United States	Prevailing guidelines[80] Study period: 1994–1999 -1994–1998: Provider opinion -1998–1989: CD4 < 500, symptomatic disease	Estimated 60% decline in HIV infectivity from 0.120 before widespread use of ART to 0.048 after widespread use of ART ($P = 0.028$)
Fang et al[13]	Ecological	General	Taiwan	Prevailing guidelines[81,82] Study period: 1997–2002 -1997: CD4 < 200, symptomatic disease -1998–1999: CD4 < 500, symptomatic disease -2000–2001: CD4 < 350, symptomatic disease -2002–2007: CD4 < 200, symptomatic disease -2008–2009: CD4< 350, symptomatic disease	Estimated HIV transmission rate decreased by 53% (0.391 versus 0.184 new cases/prevalent case-year; 95% CI: 31 to 65)
Montaner et al[12]	Ecological	General	British Columbia, Canada	Prevailing guidelines[81,83–85] Study period: 1996–2009 -1996–1998: CD4 < 200, symptomatic disease -1998–1999: CD4 < 500, symptomatic disease -2000–2001: CD4 < 350, symptomatic disease -2002–2007: CD4 < 200, symptomatic disease -2008–2009: CD4 < 350, symptomatic disease	Overall correlation between number of individuals on ART and number newly testing HIV+ per year was −0.89 ($P < 0.001$)
Lu et al[21]	Observational	Discordant couples (N = 1,927)	China	Prevailing guidelines[86] Study period: 2006–2008 2006–2008: CD4 < 200, symptomatic disease	No statistically significant difference in seroconversion rates between couples in whom the index partner was on ART (4.8%) and couples in whom index partner was not on ART (3.2%; $P = 0.12$)
Sullivan et al[20]	Observational	Discordant couples (N = 2,993)	Rwanda, Zambia	Prevailing guidelines[86] Study period: 2002–2008 -CD4 < 200 or WHO Stage III/IV	Eight linked seroconversions among 647 couples where index partner was taking ART as compared with 171 seroconversions in 6062 couples where index partner was not taking ART (RR 0.32, 95% CI: 0.14 to 0.73)

(*continued on next page*)

TABLE 1. (*Continued*) Summary of Cited Studies of ART for Prevention of HIV Transmission

Author of Study	Type of Study	Population	Location	Criteria for ART Use	Effect of ART
Del Romero et al[17]	Observational	Discordant couples (N = 424)	Spain	Prevailing guidelines[81,83–85] Study period: 1989–2008 -1989–1996: Provider practice -1996–1998: CD4 < 200, symptomatic disease -1998–1999: CD4 < 500, symptomatic disease -2000–2001: CD4 < 350, symptomatic disease -2002–2007: CD4 < 200, symptomatic disease -2008–2009: CD4 < 350, symptomatic disease	No HIV conversions in 144 couples where the index partner was taking combination ART as compared with 5 seroconversions in 341 couples were the index partner was not taking ART
Melo et al[18]	Observational	Discordant couples (N = 93)	Brazil	Study period: 2000–2006 33 cases where index partner on ART for pregnancy 8 cases where index partner on ART for CD4 < 350 cells/μL	No seroconversions among couples in whom index partner was on ART as compared with 6 seroconversions in 52 couples where index partner was not on ART (incidence 6.45; 95% CI: 2.65 to 12.93)
Jia et al[19]	Observational	Discordant couples (N = 38,862)	China	Study period: 2003–2011 Chinese national treatment criteria -2003–2008: CD4 < 200 or WHO Stage III/IV -2008–2011: CD4 < 350	26% relative risk reduction in HIV transmission (adjusted HR 0.74, 95% CI: 0.65 to 0.84) in couples with the index partner on ART
Donnell et al[16]	Observational	Discordant couples (N = 3,381)	7 African countries	Study Period: 2004–2007 CD4 > 250 and at the time of study did not meet national guidelines for ART	92% reduction in HIV transmission in couples in whom the index partner was on ART (adjusted incidence rate ratio 0.08, 95% CI: 0.00 to 0.57, $P = 0.004$).
Cohen et al, HTPN 052[1]	Randomized controlled trial	Discordant couples (N = 1,763)	African countries, Brazil, India, Thailand, United States	Study Period: 2007–2010 -Early initiation: CD4 350–550 -Delayed initiation: CD4 200–250	96% reduction in linked transmissions 89% reduction in all transmissions

to be HIV-uninfected should also be candidates for HIV prevention interventions. They need to be linked to appropriate prevention interventions such as voluntary medical male circumcision (VMMC) and preexposure prophylaxis (PrEP), with ongoing counseling and adherence support, as needed, and repeat HIV testing. Despite substantial evidence in support of the efficacy of VMMC for prevention of HIV transmission,[63–65] its implementation and scale-up has been suboptimal in some

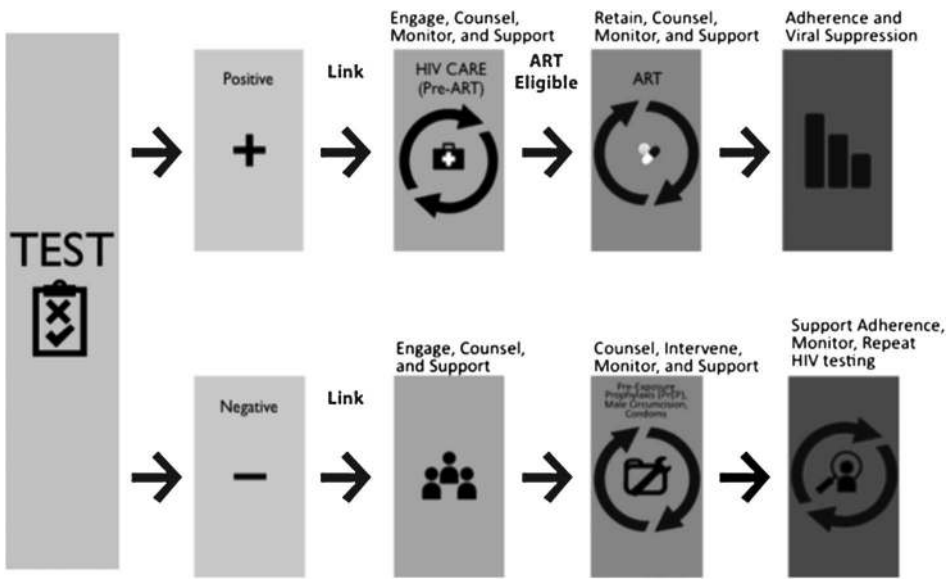

FIGURE 1. Cascade for comprehensive prevention strategies for individuals with and without HIV infection.

settings.[66] Availability of new nonoperative methods for male circumcision that do not require anesthesia and can be performed by nurses holds great promise.[67,68] A recent study demonstrated that expansion of VMMC is cost effective and may have a substantial effect on decreasing the number of new HIV infections in the short term, with TasP demonstrating substantial effect in the long term.[8] PrEP using antiretroviral drugs in HIV-uninfected individuals is also a promising intervention shown to be efficacious in several studies,[2,4] whereas conflicting results have been noted in other studies where adherence with PrEP was compromised.[69,70] That a significant proportion of transmissions in couples in HPTN 052 and other discordant couple studies were unlinked highlights the potential importance of PrEP if monogamy among couples is not assured. PrEP may also be appropriate for individuals at high risk who are unaware of their partner's HIV status or in settings where an HIV-infected partner is unwilling or unable to take ART for prevention.

Enthusiasm for the potential effect of ART on TB incidence should not divert resources from other TB control strategies, including the "three I's," ie, intensified case finding, IPT, and infection control, in addition assuring provision of directly observed therapy for those diagnosed with TB.[71,72] A comprehensive public health approach that includes these strategies is needed to control the TB epidemic, particularly among HIV-infected individuals. HIV-infected individuals on ART remain at an increased risk for TB when compared with HIV-uninfected individuals, even when their $CD4^+$ counts are high.[73,74] With the increase in survival associated with ART, the lifetime risk of TB in HIV-infected persons in the absence of other interventions is likely to remain high. IPT and ART prevent TB via complementary mechanisms,[75] and evidence supports an additive protective benefit from concomitant IPT use among individuals on ART.[36,37] To provide IPT safely, it must be implemented in the context of intensified case finding, to prevent the development of drug resistance from inadvertently prescribing monotherapy to individuals with undiagnosed TB. Implementation of infection control measures is also essential to prevent nosocomial transmission of TB in health care settings where ART is provided.

RESEARCH GAPS

There is an urgent need for empiric data to evaluate the effectiveness of TasP at a population level. Two studies are planned to address this question, the HPTN 071 (PopART) Study in South Africa and Zambia and the Mochudi Study in Botswana.[76] In addition, there is a paucity of data regarding whether ART use will be an efficacious intervention for prevention of HIV transmission in key populations, particularly among men who have sex with men and injection drug users.[49]

There is also an urgent need to obtain empiric data to assess the potential benefits and risks associated with use of ART for individuals at higher $CD4^+$ counts, who are largely the target group of current considerations for TasP.[77] Few data exist with regard to this issue in patients with $CD4^+$ count >350 cell/μL from resource-limited settings, supporting the need for clinical trials to inform this question.[47] The ongoing START study is aiming to address this question largely in developed countries,[78] whereas the TEMPRANO study in Cote d'Ivoire (ANRS12136) may provide some insights on this question. However, neither study will provide definitive answers to the question of the benefits and risks of early versus deferred ART in terms of key outcomes including mortality, TB incidence, and hospitalizations in resource-limited countries.[47]

There is the need for implementation research that aims at examining the "how" with regard to implementation of TasP and its scale-up, if found to be effective at population level.

CONCLUSIONS

Expanded use of ART holds great promise for saving lives and enhancing the health and well being of persons living with HIV and for the prevention of HIV and TB. The evidence for TasP should serve to further energize efforts to reach all those who need ART for their own health as an important priority. Aspiration for TasP should not distract attention from the quality of HIV programming, the effectiveness of the HIV care cascade, and the need for inclusion of other HIV prevention interventions and other TB prevention measures. Important questions that remain to be answered include which population to prioritize, what other interventions to use, how to integrate TasP in the health system, how best to use ART for the benefit of individuals and society, and how to measure its effectiveness and impact at population level.

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Can We Achieve an AIDS-Free Generation? Perspectives on the Global Campaign to Eliminate New Pediatric HIV Infections

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Abstract: Efforts to prevent the mother-to-child transmission (PMTCT) of HIV infection have encountered remarkable successes and considerable challenges around the globe. The reductions in vertical HIV transmission observed in Europe and North America have helped raise the possibility of the virtual elimination of new pediatric HIV infections and in turn an "AIDS-free generation". Yet in many resource-limited settings, preventable new pediatric infections continue to occur daily. Here, we consider what will be required to reach an end to the global pediatric HIV epidemic, and what we can hope for in the context of resurgent international interest. The science of PMTCT has advanced dramatically since the first evidence for the use of antiretroviral (ARV) drugs for PMTCT in 1994. The timing and causes of vertical transmission are now well understood, and this knowledge has led directly to highly efficacious PMTCT interventions based on the use of combination ARV regimens. The application of these interventions around the world has been uneven, however. Several African countries report good access to and uptake of PMTCT services and corresponding low rates of early mother-to-child transmission. However, limited population coverage of PMTCT programs with continued use of suboptimal ARV regimens still hamper prevention efforts in many other countries. Looking forward, reaching ambitious international targets to reduce pediatric HIV infections will require a combination of increased access to efficacious ARV regimens and strengthened health systems for maternal and child health, supported by continued strong political will and international attention.

Key Words: PMTCT, mother-to-child transmission, pediatric HIV

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INTRODUCTION

Over the last 30 years, since the first cases of pediatric AIDS were reported, the field of perinatal HIV has met with remarkable successes and considerable challenges.[1] Global efforts by scientists and clinicians have resulted in a nuanced understanding of the mechanisms of mother-to-child HIV transmission (MTCT) and optimal approaches for its prevention.[2–4] In the United States, Europe, and a handful of other countries, scientific advances have been rapidly translated into policy, antiretroviral (ARV) therapy for prevention of mother-to-child transmission (PMTCT) is routine, and new pediatric infections are increasingly rare.[5–8]

By comparison, in less well-resourced parts of the world, efforts to prevent new pediatric infections have been far less effective. It is estimated that there are more than 900 new infections daily in children less than 15 years of age, 90% attributable to MTCT and 90% occurring in sub-Saharan Africa.[9] In 2011, there were approximately 330,000 new pediatric HIV infections, bringing the total number to more than 3.3 million children worldwide since the beginning of the epidemic.[10] In response to these global challenges, there is a renewed global dialog around PMTCT and new exciting expectations that successes achieved in wealthy countries can be extended to sub-Saharan Africa. A global plan toward elimination of new HIV infections among children, developed by a task team convened by UNAIDS and the President's Emergency Plan For AIDS Relief (PEPFAR), has been set in motion resulting in multilateral efforts to accelerate perinatal prevention efforts.[11] This article will consider what it will take to reach an end to the pediatric HIV epidemic and what we can hope for in the context of resurgent global interest.

THE SCIENCE OF PREVENTING PEDIATRIC HIV INFECTION

The findings of the Pediatric AIDS Clinical Trials Group 076 Trial, published in 1994, heralded the first major breakthrough in the field of perinatal prevention.[12] The study demonstrated that zidovudine, the only approved ARV medication at the time the study was designed, when given to the woman during pregnancy, labor and delivery, and to the infant during the first 6 weeks of life, was safe and provided substantial protection to the baby, lowering MTCT risk by almost two thirds. Over the next 2 decades, multiple studies were conducted examining a variety of drug regimens, building on the lessons of 076, and seeking to identify optimal strategies to safely reduce transmission risk.[13] Early trials in sub-Saharan Africa focused on identifying short-course simplified regimens that were inexpensive and easy to implement

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in low-resource settings. The HIV Prevention Trials Network 012 trial demonstrated a 48% reduction in early MTCT by giving a single dose of nevirapine to both the laboring mother and to infant at birth.[14] This was another landmark study that led to the establishment of the first programs using ARVs for PMTCT in sub-Saharan Africa and many other parts of the world.[15]

Clinical trials in tandem with cohort and laboratory studies have also elucidated the mechanisms of HIV-1 transmission. Understanding the timing and risks of MTCT has informed new interventions while failure to fully consider these issues has contributed to the limited impact of many PMTCT programs in high HIV prevalence settings. Three critical considerations are apparent. First, transmission can occur at any point during pregnancy, labor and delivery, and breastfeeding, highlighting the need for ARV protection throughout the long period of exposure.[16] Second, women with advanced HIV disease and high viral loads are at highest risk for MTCT and disease progression. Effective treatment for antiretroviral therapy (ART)-eligible pregnant and lactating women will improve maternal health and prevent the vast majority of infant infections.[17,18] Third, avoidance of breastfeeding, one of the key components of PMTCT in high-resource countries, can result in substantial morbidity and mortality in settings where breastfeeding is a key child survival intervention.[19,20] A series of clinical trials have now demonstrated the efficacy of providing ARVs to the mother and/or infant during breastfeeding to prevent HIV transmission while preserving overall child health.[21–25]

THE PRACTICE OF PREVENTING PEDIATRIC HIV INFECTION

It is estimated that more than 100,000 pediatric infections were averted through PMTCT programs between 2003 and 2010[9] and a number of countries in sub-Saharan Africa have demonstrated substantial success. Botswana, Rwanda, and South Africa report good access to and uptake of PMTCT services and low rates of early MTCT.[26–28] In a national survey conducted at 580 facilities in 9 South African provinces, caregiver–infant pairs were tested for HIV at the first immunization visit.[28] The prevalence of HIV exposure among infants was 32.3% (95% CI: 30.7% to 33.6%) and the national perinatal MTCT rate at 4–8 weeks postpartum was 2.7% (85% CI: 2.1% to 3.2%).[28] Similar population-wide data from other African countries do not exist, however, and it is likely that the majority of high HIV prevalence countries have less effective PMTCT programs.

Shortcomings in current approaches to PMTCT exist on multiple fronts. There is a high burden of unintended pregnancy among HIV-infected women in many countries[29,30] and an urgent need for access to family planning services as a basic part of PMTCT programs. Availability of PMTCT services remains a concern because only 4 countries in sub-Saharan Africa report greater than 90% coverage of PMTCT services.[9] Many countries continue to rely on less efficacious ARV short-course regimens and face major challenges in identifying and adequately treating pregnant and lactating women eligible for ART for their own health who are also at highest risk for MTCT.[31,32] Moreover, few programs, even those in countries reporting successful outcomes, retain mothers and their infants in long-term follow-up to ensure ARV coverage throughout the duration of breastfeeding, final determination of infant infection status at weaning, and transfer of the HIV-positive mother into HIV care and treatment services. And with evidence that women's risk of HIV acquisition may increase during pregnancy,[33–35] there is growing concern around incident HIV infection during pregnancy or breastfeeding as an important cause of vertical HIV transmission.[36,37]

These issues facing PMTCT services are rooted in broader challenges facing maternal and child health (MCH) services. In most countries, PMTCT programs have been built on the fragile infrastructure of MCH services that generally provide only the most basic pediatric and reproductive health services and are ill-prepared to deliver the more complex continuous care, and therapies required for successful perinatal prevention. Although there is an increasing awareness within ART programs that retention in care is critical to ensure good long-term health outcomes,[38,39] PMTCT has been implemented as a short-term health intervention with limited focus on long-term engagement.

REACHING ELIMINATION TARGETS—WHAT WILL IT TAKE?

There are ambitious international aims to reduce the number of new HIV infections among children by 90% and the number of maternal AIDS-related deaths by 50% by 2015.[11] These goals are both inspirational and daunting, aiming to see fewer than 40,000 new pediatric infections, which represent an 88% reduction compared with 2011. To achieve these targets, a rapid expansion of the breadth and depth of PMTCT services will be needed to reach significantly more women in countries where HIV is prevalent and to provide them with effective ARV interventions to prevent infant infections and protect maternal health.

Availability of and access to PMTCT services is the necessary first step to prevent new pediatric HIV infections. If HIV testing during pregnancy can be used as a proxy for access to PMTCT, in 2010, only 35% of pregnant women in low- and middle-income countries received an HIV test.[10] Nine of the 22 countries with the highest number of new pediatric infections reported testing rates of less than 50% including the Democratic Republic of Congo (11%) and Nigeria (14%). The challenge of increasing access is considerable if PMTCT services are to reach women where they obtain antenatal care that, in most settings, is often decentralized to rural and distant communities. Although several countries have expanded PMTCT services, effective scale-up has been elusive in many lower prevalence settings where the diagnosis and treatment of HIV infection during pregnancy are less common.[9] As a more fundamental barrier, some of the most affected countries are challenged by low rates of attendance in antenatal care. For instance, in Ethiopia, the majority of pregnant women do not access MCH services during pregnancy thwarting traditional

PMTCT efforts.[40] Novel approaches are urgently needed to reach beyond health facilities to identify HIV-positive pregnant women in their communities and engage them in both PMTCT and MCH services.

To reach international elimination targets, the depth of PMTCT services will also need to be "scaled-up." Effective PMTCT requires, at a minimum, therapeutic treatment for ART-eligible women, estimated to be approximately 40% of those entering care.[41] Historically, PMTCT programs have provided ARV prophylaxis but have had limited ability to identify, engage, and treat ART-eligible women. In 2011, only 57% of all HIV-positive pregnant women received efficacious ARV regimens (other than single-dose nevirapine) and of among women receiving any prophylaxis, only 45% were assessed for ART eligibility. Availability of infant testing is limited but is critical for identifying HIV-infected infants and linking them to early treatment; in 2011, only 28% of HIV-exposed babies had early infant diagnostic testing within the first 2 months of life.[10]

Access to timely CD4 testing is critical to distinguish ART-eligible pregnant women but is often poor in the MCH setting. And despite the vast scale-up of ART services in sub-Saharan Africa access to treatment is generally restricted to ART centers where it is prescribed by physicians and specially trained nurses. For example, in the Kagera region of Tanzania, ICAP, a PEPFAR implementing partner, works with the Ministry of Health to implement HIV services. Between 2008 and 2011, there was an expansion of both PMTCT and ART services: PMTCT services sites increased from 22 to 228 health care facilities and ART service site increased from 9 to 59 facilities.[42] At the 59 ART facilities, PMTCT services were also available and PMTCT clients could access on-site ART. By comparison, the vast majority of facilities offering PMTCT were unable to provide ART for eligible women. In this case, scaling up effective PMTCT would require expansion of ART services to as many as 169 additional facilities in the region.

Several innovations are poised to address these implementation challenges, and if successful could lead to substantially more pregnant women initiating treatment. Point of care technology for CD4 testing is now increasingly available allowing on-site, same day determination of ART eligibility. Introduction of point of care CD4 testing has resulted in higher rates of ART initiation and retention in nonpregnant adults,[43] but there are few evaluations from PMTCT settings. Furthermore, initiatives to train and certify nurses and midwives to prescribe ART have been highly effective in a number of countries and critical to efforts to decentralize ART services.[44,45] Coupled with increased availability of CD4 testing, determination of ART eligibility and initiation of treatment can be accomplished by existing staff in antenatal clinics. However, it should be noted that MCH services are chronically underresourced and adding new skills and responsibilities to existing staff provides only a partial solution. More extensive efforts to address the human resource for health crisis in sub-Saharan Africa are urgently needed to reach the Millennium Development Goals (MDG) and these elimination targets.

Although these innovations are likely to lead to incremental improvements in PMTCT services, "Option B +," which recommends initiation of lifelong treatment for all HIV-positive pregnant and lactating women, may be a game changer, transforming the framework of perinatal prevention and dramatically improving MCH outcomes.[46,47] World Health Organization 2010 guidelines offer 2 options for PMTCT both of which prioritize the identification and treatment of ART-eligible pregnant women. For women not eligible for ART Option A provides zidovudine prophylaxis during pregnancy coupled with daily nevirapine to the infant during breastfeeding, whereas Option B offers triple drug prophylaxis to the mother during pregnancy and breastfeeding.[48] In contrast to these approaches, Option B+ replaces "CD4 count" with "pregnancy status" to determine ART eligibility so that all pregnant and breastfeeding women are recommended to initiate lifelong ART. Option B+ shifts the paradigm of ART initiation from disease status to transmission risk, not dissimilar to the recommendation for discordant couples.[49] This new approach, Option B+, recognizes that pregnancy is a critical entry point for HIV-positive women to engage in lifelong HIV care and treatment services.

The country of Malawi began implementing Option B+ more than a year ago and has seen a dramatic increase in the number of pregnant women initiating ART.[47] Early reports of retention in care for women initiating ART during pregnancy are similar to rates reported among nonpregnant adults. Many critical questions remain to be answered to determine if this approach is safe for mother and child and acceptable to women and communities. It also remains to be determined whether this approach improves ARV adherence, retention of mothers and children across the PMTCT cascade, and whether it is effective at keeping mothers healthy and protecting infants from acquiring HIV infection. Option B+ has now been adopted by a number of other countries in sub-Saharan Africa. Coupled with other simplification strategies such as use of once-daily fixed dose combination ART regimens, Option B+, has the potential to jumpstart the elimination campaign and propel perinatal prevention efforts forward.

It should be noted, however, that although expansion of PMTCT and ART coverage among pregnant and postpartum women is at the core of the global elimination campaign, without ongoing prevention efforts treatment alone will be insufficient to achieve an AIDS-free generation. Prevention of new HIV infections among women and unwanted pregnancies among HIV-positive women are central components of PMTCT and are critical to achieving elimination targets.[50] Not surprisingly, only by combining prevention and treatment efforts will substantial progress be made.

CAN WE ACHIEVE AN AIDS-FREE GENERATION?

The campaign to eliminate new pediatric infections and keep mothers alive is well under way: governments and communities are being engaged; financial resources are being mobilized; new strategies are being employed, and early reports suggest that increasing numbers of women and children are being reached with PMTCT services. These are important achievements that set the tone for a rapid and robust

scale-up of PMTCT programs. However, it seems unlikely that elimination targets will be reached by 2015, which may be unsurprising given that similar accomplishments that took several decades to achieve in developed countries with well-resourced health systems. Experience with other health campaigns may further temper expectations. In a recent assessment of progress in developing countries toward MDG 4 and 5, to reduce under-5 mortality by two thirds and maternal mortality by three quarters, respectively, between 1990 and 2015, it was estimated that only 31 countries will achieve MDG 4, 13 MDG 5, and 9 countries will achieve both.[51] Twenty-three countries in sub-Saharan Africa are not expected to reach MDG 4 before 2040.

Elimination targets may be out of reach by 2015, but expectations for the campaign should remain high. Renewed attention to the health of women and children, particularly those affected by HIV, is long overdue as is a shift in the PMTCT model of care from one that focuses on short-term prophylaxis to one that embraces PMTCT as an entry point into comprehensive HIV services able to address the health needs of the HIV-positive women, her infant and family. Furthermore, efforts to strengthen health systems and address the human resource for health crisis in sub-Saharan Africa and other parts of the world where children are highly vulnerable to a variety of severe health threats will likely do more than prevent new pediatric HIV infections. In synergy with other global health initiatives, the campaign to eliminate new pediatric infections and keep mothers alive should lead to substantial and measurable improvements in health outcomes for women and children worldwide. We can expect and demand nothing less.

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Integrated Strategies for Combination HIV Prevention: Principles and Examples for Men Who Have Sex With Men in the Americas and Heterosexual African Populations

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Abstract: Combination HIV prevention is of high priority for increasing the impact of partially efficacious HIV prevention interventions for specific populations and settings. Developing the package requires critical review of local epidemiology of HIV infection regarding most-impacted populations and those at high risk of HIV transmission and acquisition, drivers of HIV infection, and available interventions to address these risk factors. Interventions should be considered in terms of the evidence basis for efficacy, potential synergies, and feasibility of delivery at scale, which is important to achieve high coverage and impact, coupled with high acceptability to populations, which will impact uptake, adherence, and retention. Evaluation requires process measures of uptake, adherence, retention, and outcome measures of reduction in HIV infectiousness and acquisition. Three examples of combination prevention concepts are summarized for men who have sex with men in the Americas, young women in sub-Saharan Africa, and HIV serodiscordant couples.

Key Words: combination HIV prevention, integrated prevention, men who have sex with men, young women in Africa, HIV serodiscordant couples

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INTRODUCTION

Control of HIV will require integrating a combination of evidence-based HIV prevention interventions, developed based on the understanding of local epidemic patterns, including local HIV prevalence, incidence, and epidemic factors and important risk factors among key populations. A growing number of interventions have shown partial efficacy in reducing HIV infectiousness and susceptibility, including knowledge of HIV serostatus, which leads to behavioral risk reduction particularly among those learning HIV-infected persons, condom use, medical male circumcision (MC) for HIV-uninfected men, and antiretrovirals when used as therapy (ART) by HIV-infected persons and preexposure prophylaxis (PrEP) by HIV-uninfected persons. However, no single HIV prevention strategy will have complete uptake or perfect adherence, thus will have $<100\%$ effectiveness, making the rational packaging of partially effective interventions into integrated programs one of the most critical research and implementation questions for HIV prevention for the near future.

THINKING ABOUT COMBINATION HIV PREVENTION

Making combination prevention work requires careful selection of component interventions and objectivity in reviewing data about key risk factors, most affected populations, and efficacy of individual interventions. Parsimony in selecting possible interventions is important because scale, coverage, affordability, and impact could be compromised with more complex combination packages. Pilot work is important to determine the acceptability and feasibility of scaling these interventions to achieve high coverage by prioritizing the subset of the population at high risk of HIV transmission or acquisition, and acceptability of interventions to those populations.

A key first principle for choosing the components of a combination intervention package is synergy—ideally that the effect of a combination of interventions is at least the sum of the parts, if not greater. Just like combination ART is most effective when the components are active against different parts of the viral life cycle, a combination of prevention interventions directed at different risk factors and avenues of HIV transmission may have the greatest combined impact. An example of targeting different paths for transmission among heterosexuals in a generalized heterosexual epidemic would be a combination strategy that includes (1) MC for HIV-uninfected men, (2) ART roll out in HIV-infected persons, and (3) behavior change interventions that reduce risk and increase uptake and adherence to these interventions. Interventions that seek to reduce infectivity in HIV-infected individuals are likely to be most synergistic with interventions that reduce susceptibility among HIV-uninfected individuals.[1] Mathematical models can be used to identify situations where interventions may

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have a "superadditive" effect by reducing the basic reproductive number (Ro) of an infection below a critical threshold.[2]

A second principle of combination HIV prevention is coverage, which is a function of access to the interventions and willingness of persons prioritized based on the risk to utilize the interventions. A fundamental initial step toward achieving high coverage of HIV prevention interventions is HIV testing and knowledge of HIV serostatus, which is needed for targeting interventions to reduce HIV susceptibility or infectiousness. For HIV-infected persons, in order to have high coverage of ART for HIV prevention benefits, prevention coverage entails breaking down the multiple steps in the cascade from HIV testing to linkage to care: clinic referral, ART eligibility assessment, pre-ART retention, ART initiation for those who are eligible, and sufficient adherence to achieve sustained viral suppression,[3] particularly among those most likely to transmit. Similarly, there is a cascade for "HIV prevention" for persons who are HIV uninfected: learning one's HIV status, uptake, and adherence to evidence-based prevention services (such as MC) and more user-dependent interventions such as PrEP, coupled with prevention counseling. Achieving high coverage requires addressing the multiple steps in these "cascades" beginning with the knowledge of serostatus, demand stimulation (to increase awareness of HIV risk, benefits of, and access to interventions), linkage, adherence, and retention.

Economic analyses are important for estimating the cost–benefit of intervention packages in terms of HIV infections averted and lives saved. As an example, economic analyses of the impact of scaling up ART showed that at high ART coverage, over time, the intervention costs incurred are balanced by reduced costs of HIV-associated morbidity, mortality, and incident HIV cases averted.[4,5] Economic analyses can estimate the initial cost outlay and time to "break even" in costs based on infections prevented with a universal "test-and-treat" scenario,[4] or scaling up ART coverage at different CD4 levels.[5] In assessing the health economic impact of combination prevention, the principles of synergy and coverage also apply. Interventions that reduce susceptibility, such as PrEP and MC, are cost-effective additions to ART for the prevention through the synergistic effect of reducing HIV incidence at costs that, relative to lifelong ART, are less.[6,7] Nonetheless, costs for prevention can plateau over time. If strategies to reduce infectiousness and susceptibility are not adequately scaled up, then the number of new infections may remain constant rather than decreasing, thus increasing the overall costs in the long term.[4] One challenge for health economic analyses is to incorporate heterogeneity in costs, in addition to heterogeneity in disease modeling because as programs are scaled up, smaller programs may have increased costs.[8] For HIV prevention interventions to be cost-effective over time, economic analyses support combining highly effective strategies, widespread coverage for ART, synergistic interventions that reduce susceptibility, and identification of efficiencies in the delivery of services throughout the cascade from testing, linkages to, and retention in care.[6]

We describe 3 populations and relevant considerations in developing and testing possible strategies for combination HIV prevention in these populations to illustrate the differences in the populations to be reached, risk factors for new HIV infections, and interventions to be considered for combination HIV prevention packages.

HIV AMONG MEN WHO HAVE SEX WITH MEN AND TRANSGENDER WOMEN

Men who have sex with men (MSM) account for the majority of new HIV infections throughout North and South America. In the United States, MSM comprised nearly two thirds of new HIV infections in 2010; they are the only group in whom new infections are increasing. Black MSM aged 13–24 years had more than 3-fold the number of new HIV infections as white and Latino MSM and increased the most from 2007 to 2010. Transgender women (people assigned "male" at birth but identify as female and/or transgender) have extremely elevated infection rates in both North and South America.[9–12] Although HIV infection rates are high in Asia and Africa as well, less is known about drivers of infection in these populations; research is ongoing to determine the feasibility of reaching MSM in Asia and Africa,[13] which will guide future HIV prevention efforts.

Recent modeling on the epidemiology of new infections in MSM in the Americans suggests that more than one third of new infections occur within main partnerships, and approximately two thirds of those infections occur within partnerships that are not known to be serodiscordant.[14] To address the major risk factors of HIV infection in MSM populations in the America, several approaches are being currently piloted individually; those with high uptake and adherence will be combined to test their ability to achieve synergistic reductions in infections (Table 1).

1. Personalized risk calculators can reduce risk behaviors and improve outcomes including HIV risk behaviors,[15] control of dyslipidemia,[16] bone mineral density,[17,18] dietary behavior,[18] and alcohol abuse.[19,20] Online tools, including education and videos can reduce risk, lower delivery costs, increase intervention fidelity, and maximize dissemination.[21] An online tool is being piloted to determine if it is useful for MSM to assess their risk and set goals for improving sexual health, similar to diet and exercise Web sites. This Web site will then direct men to interventions, described below.
2. Daily oral emtricitabine (FTC)-tenofovir (TDF) PrEP significantly reduces the risk of HIV in MSM[22]; efficacy is related to adherence.[23] Interventions shown to be effective in increasing adherence to ART in HIV-positive persons or preventive medications in healthy individuals (eg, malaria prophylaxis, HIV postexposure prophylaxis, osteoporosis prevention) include SMS strategies,[24,25] client-centered counseling,[26] cognitive behavioral therapy,[27] and providing clinical feedback[28]; these approaches have been utilized to support PrEP adherence and are currently being piloted in PrEP studies and demonstration projects.[29,30]
3. HIV testing in sexual partnerships with emphasis on linkages to HIV care for HIV-infected men. A substantial proportion of transmissions are occurring from MSM who are unaware of their HIV infection, including those in relationships that are believed to be seroconcordant negative. Rates of HIV testing and the proportion of HIV-infected persons identified[31] are significantly higher when "recruitment" occurs through social and sexual networks, particularly in young and African American MSM[32]; these approaches are being

TABLE 1. MSM in the Americans: Risk Factors, Considerations for Interventions to Include in a Combination Prevention Package, and Prioritization and Delivery Questions

Risk factors
Receptive anal sex accounts for 4 out of 5 of the new infections in North America and 2 out of 3 in South America[14]
A substantial minority of infections are occurring in main partnerships, including between men who believe they are both HIV negative
Substantial proportion of infections coming from those undiagnosed, diagnosed but untreated, or not fully suppressed
Young African America and Latino men account for a disproportionate number of new HIV infections in North America
Prevention interventions considered for combination prevention package for MSM
Novel strategies for HIV testing are needed to reach young minority MSM
An online, confidential tool might help MSM assess their risk and develop sexual health goals
Focus on testing and linkage to care for HIV-infected male partners
PrEP can help reduce the risk for MSM; given dependence of efficacy on adherence to daily oral PrEP, risk assessment, motivations to take PrEP, and adherence support are needed
Couples-based counseling may be useful in helping reducing risk among MSM couples
MC would not substantially alter new infection rates because the preponderance MSM engage in both insertive and receptive anal sex
Prioritization and combination prevention delivery questions
Will MSM use an online risk assessment tool and will it help them use prevention interventions that meet their needs?
How to most effectively incorporate linkage to care and prevention into novel testing strategies?

piloted in combination with home self-testing. SMS reminders also increase testing rates.[33]

4. Brief couples HIV testing[34] and online strategies are being piloted, given data that indicate a substantial minority of infections occur in stable partnerships.
5. Strategies to increase linkage to care for HIV-infected MSM are being evaluated in a number of programs to reduce the drop-off in the HIV care cascade and to achieve viral suppression in the majority.[35]

Synergies for prevention in this population could be achieved by (1) addressing multiple components of the "transmission chain" (eg, reducing per-act risk transmission through PrEP and reducing partner change rate through behavioral interventions) and (2) targeting populations with minimal overlap (eg, PrEP for HIV-uninfected men, HIV testing, and linkage to ART to suppress viral load in HIV-infected partners). The individual components of the proposed package are being piloted (Table 1) to determine which are desirable, scalable, culturally appropriate, potentially cost-effective, and have plausibility for having an impact on HIV seroincidence in both North and South America. Once the package is finalized, the integrated strategy will be tested in a 2-stage process: a "vanguard" pilot study of the entire package and if the combination impacts intermediate measures (eg, uptake of and adherence to components and synergistic combinations), an efficacy trial.

YOUNG WOMEN IN SUB-SAHARAN AFRICA

One of the highest priorities for delivery and evaluation of integrated strategies for HIV prevention is young women in sub-Saharan Africa.[36] The magnitude of the HIV epidemic in heavily impacted areas such as KwaZulu-Natal province in South Africa is staggering, where a study of women attending family planning and sexually transmitted disease clinics from 2004 to 2007 found an HIV prevalence of 35.7% among young women whose median age was 22 years and an HIV incidence of 6.5/100 person-years.[37] Data from the Africa Center in KwaZulu-Natal showed highest HIV incidence (6.6/100 person-years) among women at 24 years of age and a peak HIV incidence of 4.1% among men 5 years later (ie, age 29).[38]

Drivers of HIV risk among young African women include unprotected sex, sexually transmitted infections in some populations, and age differences. Older partners have higher HIV prevalence, and gender power disparities are greater, making it harder for women to negotiate safer sex.[39–41] Gender-based violence may be an important driver in these settings, as indicated by the alarming rape statistics from parts of Africa. However, evidence-based interventions are not available for some of the social and behavioral drivers of infection among young women in Africa. Young African women also are at risk for unwanted pregnancy[42,43] among HIV-infected and HIV-uninfected women and require addressing cultural underpinnings and system access.[44,45] Social norms often dictate that young women should not engage in sex and thus influence provider attitudes about contraception can be a barrier to young women's access to prevention services, condoms, contraceptive services, sexual and reproductive health services, treatment of sexually transmitted infections, and HIV testing,[46] thus increasing their risk when they are sexually active. There is a tremendous unmet need for contraception worldwide[47]; the incidence of unplanned pregnancies among young women in Africa ranges from 4% to 16% in microbicide and HIV prevention trials,[48–50] and the risk of HIV acquisition and transmission has been found to be 2-fold higher during pregnancy.[51–53] A complicating factor is that some observational data indicate a 1.4-fold to 2.0-fold increased risk of HIV acquisition among women who use injectable hormonal contraceptives, particularly among depot medroxyprogesterone acetate (DMPA) users.[54,55] However, the observational data are inconsistent and must be balanced by the safety, reversibility, contraceptive effectiveness, and widespread availability and acceptance of DMPA among providers and women.[56,57]

Given the overlapping risks for HIV acquisition, pregnancy, and the need for both HIV prevention and reproductive health services, combination prevention for

young African women could be delivered through integrated reproductive health and HIV prevention services, which include behavioral, biomedical, and structural interventions (Table 2). It will be important to pilot different program models for providing youth-friendly integrated reproductive health and HIV prevention interventions to achieve high uptake of HIV testing, PrEP, and long-acting, reversible contraception options, as described below.

1. HIV testing and counseling strategies shown to be effective in reaching adolescents and young adults need to be implemented. Effective approaches include community mobilization and mobile vans, including peer-based outreach, and school-based HIV testing.[58,59]
2. Linkages to HIV care. Young women and men found to be HIV infected will be referred for HIV care to provide clinical benefits and reduce secondary transmissions, using evidence for strategies that effectively link HIV-infected persons into care.[60]
3. Reproductive health services and contraceptive planning: The same population of young women at high risk of HIV is at high risk of unwanted pregnancies and need user-friendly services with expanded contraception and counseling about the observational data on hormonal contraceptives and HIV risk.[61]
4. PrEP with adherence support is an evidence-based intervention to reduce HIV susceptibility among young HIV-uninfected women in some populations. Daily oral FTC/TDF PrEP significantly reduces the risk of sexual HIV acquisition; efficacy rates among heterosexuals range from no efficacy in studies with low adherence to 62% and 75% among young heterosexuals in Botswana in the TDF-2 trial and HIV serodiscordant couples in the Partners PrEP Study.[62–64] Gender-specific and age-specific subgroup results from Partners PrEP (>70% efficacy in women <30 years),[65] and the TDF-2 trial in Botswana, found that PrEP provides high protection from HIV infection for women.[62] FTC/TDF as PrEP works when taken; adherence is strongly related to efficacy, as demonstrated by retrospective testing of plasma tenofovir levels in the trials with efficacy[66,67] and lack of efficacy.[63,68] PrEP would be offered to young women with a partner who is HIV-infected or of unknown serostatus and could offset increased risk from DMPA, until additional data are available about HIV risk due to long-acting progestins and other contraception modalities. Thus, in a combination prevention package that includes PrEP for young women will require assessment of risk assessment and motivations, as well as adherence monitoring and support, particularly in the first few months after PrEP initiation, through SMS support, and where feasible, real-time drug levels.
5. HIV testing of male partners. Young African women often do not know the status of their partners. To reduce HIV exposure, women will be encouraged to have their male partners tested for HIV, which will be facilitated by community mobilization and mobile HIV testing. Male partner involvement may increase contraception and PrEP uptake and adherence. Higher coverage of HIV testing among young men facilitates promotion of medical MC for HIV-uninfected men and increases uptake of ART for HIV-infected male partners, which each have indirect and direct benefits to young women.

HETEROSEXUAL HIV SERODISCORDANT COUPLES IN SUB-SAHARAN AFRICA

Population data from Africa suggest that a substantial fraction of new infections may occur within stable serodiscordant marital or cohabiting heterosexual relationships, with the majority of transmissions from the HIV-infected partner in

TABLE 2. Young Women in Sub-Saharan Africa: Risk Factors, Considerations for Interventions to Include in a Combination Prevention Package, and Prioritization and Delivery Questions

Risk factors
Most women have partners of unknown HIV serostatus; their risk of HIV is high even with a single partner, given high HIV prevalence in some settings
Condom use is protective but difficult for women to condom use
Substantial proportion of infections coming from those undiagnosed, diagnosed but untreated, or not fully suppressed
Sexually transmitted infections increase the risk of HIV acquisition, with strongest evidence across studies for herpes simplex virus-2 and bacterial vaginosis
Gender-based violence is a risk factor for HIV in some settings
Young women are also at risk of unwanted pregnancies
Long-acting progestins (eg, DMPA) may increase the risk of HIV acquisition, based on inconsistent observational data
Prevention interventions considered for combination prevention package for young African women
Novel strategies for HIV testing are needed to reach young women and increase testing of their male partners (eg, coupons)
Integrated delivery of youth-friendly reproductive health services, including contraception, and HIV prevention counseling and services may increase uptake of contraception and HIV prevention services
Focus on testing and linkage to care for HIV-infected male partners
PrEP can reduce the risk for heterosexuals in Africa but requires high adherence to daily oral PrEP for efficacy; risk assessment, motivations to take PrEP, and adherence support are needed
Prioritization and combination prevention delivery questions
What service delivery model for integrated reproductive health and HIV prevention is most acceptable and scalable?
Would an interactive risk assessment tool help women select a contraceptive method in the context of expanded method mix and motivate women with greater risk to use and adhere to PrEP?
What are the effective strategies to reach their male partners for HIV testing and achieve linkages to care for their HIV-infected male partners?

the serodiscordant partnership and a substantial minority from an outside partner.[69–73] Understanding HIV prevention choices and targeting prevention strategies to this group are public health priorities. A number of countries have identified HIV serodiscordant couples as a priority population for the implementation of novel HIV prevention strategies, given their high risk, smaller number for targeting relative to the general population, ability to be targeted for prevention efforts through promotion of couples HIV counseling and testing, and clear advantage to the partnership to avert HIV transmission. Importantly, during the past 2 years, 2 pivotal novel prevention interventions—ART (through HPTN 052) and PrEP (through the Partners PrEP Study)—demonstrated high efficacy for HIV protection in clinical trials conducted among HIV serodiscordant couples and are the core of a potential integrated strategy for combination prevention in couples. World Health Organization (WHO) has released guidelines for counseling and HIV-1 prevention for HIV serodiscordant couples, which emphasize the centrality of ART and PrEP, along with the attention to other HIV prevention interventions including MC.[74,75] Determining how these efficacious interventions can effectively be delivered in real-world settings is the priority for combination prevention for this population.

HPTN 052 and Partners PrEP delivered their intervention strategies in the context of a combination package of HIV preventions, including frequent HIV counseling and testing, risk-reduction counseling (including as a couple), and access to condoms, MC, ART according to national guidelines, and other prevention strategies (eg, screening and treatment for sexually transmitted infections). The impact of these integrated services is reflected in substantially diminished HIV risk even in the delayed treatment or placebo arms of those trials. Thus, these clinical trials offer a model of combination HIV prevention for couples in the unique context of randomized clinical trials with intensive interventions and follow-up.

Recent WHO recommendations for earlier initiation of ART for HIV-infected members of HIV serodiscordant couples require translation into programmatic contexts.[75] WHO guidelines are evolving in some settings to include lifelong ART for HIV-infected mothers regardless of CD4 count for the prevention of mother-to-child transmission (PMTCT) Option B+.[76] Similarly, optimal strategies for PrEP delivery are yet to be defined and require demonstration projects and use of implementation science methods including demonstration of effectiveness among couples in which an HIV-infected partner is not yet on ART, due to refusal or other reasons (ie, PrEP as a bridge until ART is started and viral suppression achieved).[77,78] Indeed, neither ART nor PrEP use was associated with 100% protective efficacy, indicating a need for examining the effect of strategic integration of these 2 efficacious interventions, against a background of an effective prevention package. Thus, implementation science is needed to define the following:

1. Integration of testing and ongoing prevention and care for couples into routine service delivery[74–76]
2. Choices couples make for HIV prevention and the messages needed regarding different prevention strategies
3. Uptake and sustained adherence to HIV prevention interventions whether ART or PrEP[79]
4. Uptake and retention for new ways of delivering ART (eg, Option B+ for PMTCT with lifelong ART after pregnancy for HIV-positive women, early ART at high CD4 counts)[76] and

TABLE 3. Heterosexual HIV Serodiscordant Couples in Sub-Saharan Africa: Risk Factors, Considerations for Interventions to Include in a Combination Prevention Package, and Prioritization and Delivery Questions

Risk factors
Viral load in the HIV-infected partner, age, married and/or cohabiting partnerships, number of children, unprotected sex, and lack of circumcision in HIV-uninfected male partners are risk factors for HIV transmission in African HIV serodiscordant couples[78,80,81]
Condom use is protective but can be difficult for couples to use, particularly if they desire children
Pregnancy increases the risk of male-to-female and mother-to-child transmission by 2-fold[51]
Long-acting progestins (eg, Depo-Provera [DMPA]) have been associated with an increased risk of HIV acquisition and transmission in an observational study of HIV serodiscordant couples[54]
Prevention interventions considered for combination prevention package for young African women
ART significantly reduces the risk of HIV transmission, in the context of intensive adherence counseling and viral suppression[72]
PrEP significantly reduces the risk of HIV acquisition in known HIV serodiscordant couples [64]; couples are motivated to take PrEP and provide adherence support[82]
MC reduces the risk of HIV acquisition among adult HIV-uninfected men [83]; data are less consistent about relative risks and benefits of adult MC of HIV-infected men[84–86]
PrEP can reduce the risk for heterosexuals in Africa but requires high adherence to daily oral PrEP for efficacy; risk assessment, motivations to take PrEP, and adherence support are needed
Prioritization and combination prevention delivery questions
What are the most effective strategies to scale up couples HIV counseling and testing?[74]
What is the most effective strategy for couples' assessment to develop a tailored prevention plan based on partnership characteristics, fertility desires, eligibility, and readiness for ART or PrEP, MC, potentially structured around standardized risk assessment as a couple?[81]
Will HIV-infected partners in a known HIV serodiscordant couple be willing to initiate ART at an earlier stage for prevention and clinical benefits?
For couples where the HIV-infected partner is not eligible for ART by national guidelines or eligible but not willing to initiate ART, will the HIV-uninfected partner be willing to initiate PrEP?
Will HIV-infected pregnant women in a known HIV serodiscordant couple be willing to initiate ART at any CD4 count (PMTCT option B-Plus) and continue ART postpartum to reduce the risk of transmitting to her male partner and her infant?
Will HIV-uninfected uncircumcised men be willing to be circumcised to reduce their risk of HIV acquisition?

5. Uptake of MC among HIV-uninfected uncircumcised men in couples.

A potential package of combination services to evaluate using implementation science is presented in Table 3.

CONCLUSIONS

Combination HIV prevention requires rigorous review of the epidemiology of HIV infection to identify populations most impacted and at high risk, drivers of HIV infection, and efficacy of the available interventions to address these risk factors. Interventions should be considered in terms of potential synergies, feasibility of delivery at scale, and acceptability to populations. Evaluation of combination prevention packages requires a staged approach to evaluate acceptability, feasibility of delivery, and integration with other services, which should be followed by an evaluation of impact with outcome measurements, ideally based on HIV viral suppression in HIV-infected persons and HIV incidence in uninfected persons. Economic evaluation is important for costing delivery components and to estimate the cost per HIV infection averted and lives saved.

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Can Combination Prevention Strategies Reduce HIV Transmission in Generalized Epidemic Settings in Africa? The HPTN 071 (PopART) Study Plan in South Africa and Zambia

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Abstract: The HIV Prevention Trials Network (HPTN) is conducting the HPTN 071 (PopART) study in 21 communities in Zambia and South Africa with support from a consortium of funders. HPTN 071 (PopART) is a community-randomized trial of a combination prevention strategy to reduce HIV incidence in the context of the generalized epidemic of southern Africa. The full PopART intervention strategy is anchored in home-based HIV testing and facilitated linkage of HIV-infected persons to care through community health workers and universal antiretroviral therapy for seropositive persons regardless of CD4+ cell count or HIV viral load. To further reduce the risk of HIV acquisition among uninfected individuals, the study aims to expand voluntary medical male circumcision, diagnosis and treatment of sexually transmitted infections, behavioral counseling, and condom distribution. The full PopART intervention strategy also incorporates promotion of other interventions designed to reduce HIV and tuberculosis transmission, including optimization of the prevention of mother-to-child HIV transmission and enhanced individual and public health tuberculosis services. Success for the PopART strategy depends on the ability to increase coverage for the study interventions whose uptake is a necessary antecedent to a prevention effect. Processes will be measured to assess the degree of penetration of the interventions into the communities. A randomly sampled population cohort from each community will be used to measure the impact of the PopART strategy on HIV incidence over 3 years. We describe the strategy being tested and progress to date in the HPTN 071 (PopART) study.

Key Words: HIV, prevention, combination prevention, cluster randomized trial, treatment for prevention, antiretroviral therapy, HIV testing, circumcision, South Africa, Zambia

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Combining prevention interventions is a familiar approach for public health interventions in low- and middle-income countries (LMIC). Control of tuberculosis (TB), for example, is recommended through the combination of case finding, contact tracing, isoniazid preventive therapy, optimized therapy, often directly observed, and environmental risk reduction to improve fresh air exchange in airplanes, housing, prisons, or health care settings.[1–6] The public health challenge is how to implement what we know works to reduce TB transmission. Another example is malaria control that relies on the use of insecticide-treated bednets, environmental control of mosquito breeding sites, indoor residual spraying, seasonal malaria chemoprophylaxis, improved diagnosis and therapy (eg, artemisinin combination therapy) in the context of expanded primary care access, community education and engagement, and use of mosquito repellents.[7,8] A malaria vaccine may join this list of intervention tools within a decade.[9] Similar to TB and malaria, HIV now has a sound public health evidence base from both clinical trials[10] and from observational studies to suggest appropriate elements of a strong combination prevention package suitable to target the generalized epidemic of sub-Saharan Africa (Table 1).

There is mixed evidence supporting the benefits of other biomedical interventions (ie, those not listed in Table 1). A tenofovir-containing vaginal microbicide worked to reduce short-term risk in the CAPRISA 004 trial, as did

TABLE 1. Elements of Combination HIV Prevention That Have Strong Evidence Base for Decrease Risk Behavior or HIV Incidence From the Published Literature and Whether They Are Included as a Part of the HPTN 071 (PopART) Trial

Prevention Element to Reduce HIV Transmission	References
Voluntary medical male circumcision*	11–13
Treatment for prevention with integrated elements*	14–16
Expanded HIV testing as an entry point for services, both therapeutic and preventive	17–20
Linkage to care to ensure that all seropositive persons receive ongoing primary care	21
Expanded access and earlier use of combination antiretroviral therapy to benefit the HIV-infected person and reduce his/her infectiousness to others	22–32
Opt-out routine HIV testing for pregnant women and use of combination antiretroviral therapy for prevention of mother-to-child HIV transmission	33,34
Correct and consistent use of male condoms* (some evidence, too, to support use of female condoms)	35–38
Behavior change focused on reducing the number of sexual partners, avoidance of concurrent sexual partners, and selection of lower risk partners, with couples counseling when possible*	39–41
Clean needle use in the formal and informal health sectors and for persons self-medicating legal or illegal drugs	42,43
Improving decisions as to when blood and blood products should be used, and universal screening of transfused products for HIV and other key infectious agents relevant for local conditions [eg, hepatitis C virus and hepatitis B virus, human T-lymphotropic virus Type I, malaria, and others]	44
Postexposure prophylaxis for occupational exposure (eg, health care workers with a needle stick) or among recently infected infants	45–48

All the listed elements are components of our community and clinical training efforts. The * indicates those that represent a major focus of the PopART intervention package. Other elements of the PopART package are the improved control of sexually transmitted diseases and coinfections like tuberculosis (see text).

tenofovir–emtricitabine oral pre-exposure prophylaxis (PrEP) for men who have sex with men (MSM in the iPrEx trial) and discordant couples in Africa (Partners PrEP and TDF-2 trials), whereas other clinical trials have been disappointing.[49–54] Adherence levels have not yet been high enough to take full advantage of the biological potential of the topical or oral PrEP concept. Similarly, tools like the control of sexually transmitted infections (STI)[15,55–58] and diagnosis/treatment of coinfections[59–66] have demonstrated inconsistent evidence for their utility in HIV control, although they are valuable contributions to the health of individuals and the well-being of the community and may be justified as components of combination prevention in certain epidemic settings. Hence, both STI and TB programmatic improvements are being included in the PopART intervention but oral/topical PrEP are not.

As evidence accumulates in the future, other prevention approaches may be considered in combination prevention. HIV vaccines are an obvious choice if products prove efficacious, safe, and are licensed and produced for use.[67,68] Future trials may prove both topical and oral PrEP to be more consistently efficacious if adherence can be improved. For example, 2 dapivirine vaginal ring microbicide efficacy trials are underway, one called The Ring Study, sponsored by the International Partnership for Microbicides,[69] and a sister trial sponsored by the Microbicides Trials Network, called ASPIRE (MTN-020).[70,71] The dapivirine microbicide ring delivers drug with only a monthly ring change needed, to potentially mitigate the adherence barrier of event-driven or daily use of oral or topical products.[72–74]

RATIONALE FOR THE HPTN 071 TRIAL

In the context of growing evidence of the efficacy of multiple modalities for HIV prevention, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) leadership determined the need to conduct research to determine the effectiveness of a combination of prevention interventions on HIV incidence at a population level. With support from PEPFAR, the National Institute of Allergy and Infectious Disease, the National Institute of Mental Health, the National Institute on Drug Abuse, and the Bill and Melinda Gates Foundation, the HPTN 071 (PopART) study [**Pop**ulation Effects of Antiretroviral Therapy (**ART**) to Reduce HIV Transmission] was designed to answer this important question. The implementation of the study interventions in South Africa and Zambia is supported through PEPFAR supplements to implementing partners through the United States Centers for Disease Control and Prevention and the U.S. Agency for International Development.

Covering greater numbers of persons with such interventions as testing and enhanced linkage to expanded care and voluntary medical male circumcision (VMMC) would both help reduce morbidity and mortality among HIV-infected persons receiving combination antiretroviral therapy (cART) and also reduce transmission risk to others. Although there are encouraging data from ecological and observational studies supporting the potential for HIV treatment to help with HIV prevention,[29–31] none to date have tested the acceptability and operational challenges of delivering a combination universal test and treat and prevention intervention package in sub-Saharan Africa (SSA).

Testing expansion as an intervention in and of itself was assessed in the National Institute of Mental Health Project ACCEPT (HPTN 043) study which found that although expanded HIV testing was well accepted,[20] it did not confer a significant reduction in population-level HIV incidence.[19] One might speculate that the lack of a substantial impact on HIV transmission from expanded testing alone was the consequence of limited posttesting behavioral change and suboptimal linkage to ART-based care for those found to be HIV infected. In addition, the balance of benefits versus risks associated with very early and longer-term therapy (currently under study in the START trial),[75] and particularly in LMIC settings, is unknown. LMIC with limited health care resources and minimal access to viral load testing might experience a high risk of the emergence of viral resistance from suboptimal adherence in asymptomatic persons, for example.[76–79] At a population level, the need for controlled clinical trials in real-world field settings is underscored by the challenges of behavioral disinhibition (also termed risk compensation) for persons on cART who may sometimes perceive themselves healthier and/or less infectious to others.[80–85] Finally, we do

not know the logistical feasibility and cost-effectiveness of implementing expanded HIV detection and cART coverage within health care systems struggling to manage high overall disease burdens.[86,87]

HPTN 071 (PopART) Study Design Synopsis

Of the 21 communities participating in the HPTN 071 (PopART) study, 14 previously participated in the Zambia-South Africa TB and AIDS Reduction (ZAMSTAR) study, conducted by some of the investigators involved in this study.[88–93] Thus, the HPTN 071 (PopART) study builds on strong relationships established between the investigators and the communities including the presence of active community advisory groups. Continuous consultative feedback from both communities and from government health officials has been essential in forging the details of the trial. The Ministries of Health of South Africa and Zambia and the relevant state, provincial, and district health authorities have been engaged fully in ethical vetting, implementation, and planning for the dissemination of study results.

The 21 communities of HPTN 071 (PopART) include 9 in the Western Cape Province of South Africa and 12 communities in Zambia and arranged in 7 matched triplets, with 4 triplets in Zambia and 3 in South Africa. Within each country, communities were matched based on the best available estimates of HIV prevalence and on geographical location and implementing partner for HIV services, with the aim of minimizing the between-community variance in baseline HIV incidence within matched triplets. Restricted randomization was used to ensure overall balance in cluster size, ART uptake and mean HIV prevalence across the study arms.[94] In a public randomization ceremony in February 2013, 1 community from each triplet was randomly assigned to each of the 3 study arms (Fig. 1).

Arm A will receive the full PopART combination prevention program consisting of the following:

- Offering voluntary HIV counseling and testing annually to every household (ie, home-based testing[18] and couples counseling) with expanded HIV testing in health facilities.
- Linking those with HIV infection to care at the local health facility.
- Offering immediate cART to all HIV-infected persons regardless of CD4+ cell count or viral load.
- Initiating cART for those HIV-infected persons already in care.
- Promoting VMMC for men who test HIV seronegative.
- Promoting prevention of mother-to-child HIV transmission services to HIV-infected pregnant women.
- Improving the diagnosis and treatment of STI.
- Providing risk reduction education and condoms in the community and in the health facilities.

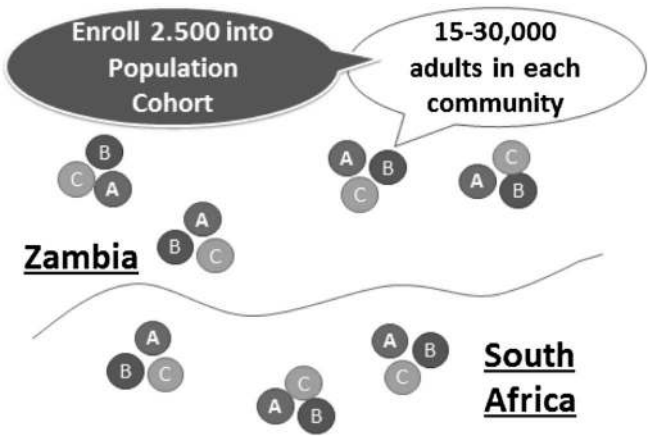

FIGURE 1. HPTN 071/PopART study schema for the 21 communities 3-arm community-randomized clinical trial in Zambia and South Africa.

Arm B will receive all the HIV prevention strategies in the PopART combination prevention program, except that cART will not be universal but will be offered to those who are eligible according to prevailing national guidelines, typically at a threshold of ≤350 CD4+ cells per microliter.[95]

Arm C will receive the current standard of care. However, special attention will be paid to ensure that there are no drug and laboratory reagent shortages or stock-outs in any of the 21 communities, ie, in all 3 study arms.

The full population in all 21 communities is estimated to be about 1.2 million persons. To measure the impact of the strategy, a population cohort will be selected from the general population consisting of a random sample of 2500 adults (one per household) aged 18–44 years from each community. Thus, the population cohort will have 52,500 persons recruited from the 21 communities (all 3 study arms; Fig. 1). A baseline survey of the cohort will be carried out at the time the intervention is initiated to assess the comparability of the 3 study arms. Follow-up surveys of the cohort will be carried out at 12, 24, and 36 months to measure HIV incidence, success in coverage of the interventions in the communities, and other outcomes.

The primary study outcome will be HIV incidence over 3 years in members of the population cohort who are HIV negative at baseline and will be compared in the intervention and control clusters to measure the population-level effectiveness of the PopART intervention. HPTN 071 (PopART) is very well powered to detect an effect of more than 35% in Arm A or Arm B compared with Arm C and is moderately well powered to detect an effect of 30%. To compare Arms A and B, the study is well powered to detect a difference between effects of 60% and 30%, 55% and 25%, and 50% and 20%. Assumptions are that there is a baseline HIV prevalence of 15% and that there will be losses to follow-up of 25% over 3 years in the population cohort.

The secondary outcomes will be measured in the population cohort to assess the effect of the intervention on a number of additional factors, including HIV incidence during each year of follow-up, reported sexual risk behavior, ART adherence and toxicity, HIV-related stigma, HIV disease progression, community viral load, ART drug resistance, herpes simplex virus-2 incidence, and TB case notification rates.

Process variables to be measured in the intervention clusters will include the following: acceptance of HIV testing and retesting; uptake of male circumcision among men testing HIV negative; proportion started on cART within 3 months of HIV diagnosis; and uptake of prevention of mother-to-child

HIV transmission services. In addition, case–control studies will be conducted to examine factors related to the following: uptake of HIV testing during the first round of home-based testing in Arms A and B; uptake of immediate treatment in Arm A; and uptake of HIV testing in the second round of home-based testing in Arms A and B.

Formative Research

To inform the intervention before it is deployed in the communities, social science research has been undertaken to better understand the communities, their previous and current HIV landscape, and attitudes toward different prevention approaches. In addition, further social science research will be carried out throughout the study period to examine the acceptability of the PopART intervention and to document the effects of the interventions on a number of factors, including risk behaviors, social networks, HIV identity, and community-level HIV associated stigma. At the end of the testing campaign in each community, random samples of individuals who accept or decline testing will be interviewed to explore the reason for their decision. In addition, interviews will be carried out with randomly selected patients with good or poor adherence to ART.

Economic Evaluations and Modeling

Economic studies are planned to measure the incremental cost of the intervention packages, to estimate their cost-effectiveness, and to measure the burden on local health facilities of implementing the intervention. Hence, we are recording costs of all implementation efforts for such activities as testing, linkage, care, VMMC, expanded laboratory and ART costs, and community-level educational efforts. Mathematical modeling will use these data to assess the magnitude of the expected impact, given the process inputs, as the trial progresses.

OTHER POPULATION-LEVEL COMBINATION PREVENTION STUDIES

A large population-based combination prevention study is also planned in Botswana with funding from PEPFAR and sponsorship of the CDC.[96–99] The study builds on work from an ongoing study of the Botswana-Harvard AIDS Institute Partnership in Mochudi, a community of 40,000 persons in Botswana.[100–105] PEPFAR and the Bill and Melinda Gates Foundation have subsequently sponsored a harmonization effort between the HPTN 071 (PopART) study and the Botswana Combination Prevention Project that shares similar goals as those of HPTN 071 (PopART) but has a different study design. Laboratory, questionnaire, cost/economic assessments, and design/analytic issues have all been addressed to facilitate future meta-analysis opportunities. Another large combination prevention study is planned by the Agence Nationale de Recherche sur le Sida et les Hépatites Virales (ANRS in France) with the Africa Centre for Health and Population Studies in KwaZulu Natal Province, South Africa.[30,106–108] Initial work of the Africa Centre is promising in suggesting the potential impact of increases in cART coverage in patients with advanced HIV disease on HIV incidence.[30,109] The findings from the latter study in rural South Africa are encouraging as it provides more rigorous ecological data than hitherto available.[31,32,110,111] Other studies addressing treatment as prevention and/or combination prevention for HIV have been reviewed elsewhere.[106]

CONCLUSIONS

The opportunity to combine known efficacious interventions for HIV prevention into combination packages allows the examination of potential synergies that may be achieved in control of HIV transmission.[10,15,16,112–115] Challenges are daunting given the need to have a high degree of coverage and efficiency in testing coverage, linkage to care, and high adherence in the context of expanded cART coverage.[86,87,116,117] The extent to which efforts are successful in deploying needed interventions to the field at the levels needed to interrupt transmission cycles is the critical unknown at present. The engagement of national health authorities and local communities is essential for conduct of the study, dissemination of results, and future scale-up of successful approaches that are discovered. Combining known efficacious prevention approaches is complex to design and test, but their use in a synergistic strategy may open the door to substantial reductions in HIV incidence in some of the world's most afflicted nations.

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A Side Door Into Care Cascade for HIV-Infected Patients?

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Abstract: HIV Prevention Trials Network studies are testing a number of new technologies for preventing HIV infections and reducing AIDS morbidity and mortality, but strengthening existing antiretroviral therapy (ART) programs may be among the most promising ways to generate greater health benefits using available resources. A cascade to care for HIV-positive patients has been described—HIV testing, retention in pre-ART care, treatment initiation, and sustained suppression on ART—and it has been noted that many patients are lost at each stage. We constructed a detailed representation by combining data from different sources about each stage. We found that, although currently available data were not sufficient to specify several key aspects, the traditional model of the cascade could not fully reconcile trends in HIV testing, linkage to care, retention in pre-ART care, and retention on ART with the large numbers of persons on ART and the large percentage of patients initiating treatment at late stages of infection. We hypothesize that supplementing the traditional linear cascade model with patient health-seeking behaviors that allow patients who are not in pre-ART care to be initiated on ART, is essential to fully characterizing the current functioning of ART programs. We have termed this additional channel to ART as the "side door." Understanding the relative roles of the different channels to care will be important to intervening effectively to improve the cascade to care, and we propose several new types of data that should be collected. With these insights, it may be possible to considerably strengthen the impact of ART programs.

Key Words: HIV care cascade, ART programs, surveillance, side door

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INTRODUCTION

Evidence has accumulated about the benefits of antiretroviral therapy (ART), both for the therapeutic impact for patients and the potential public health benefit through reducing HIV incidence,[1–4] and a substantial global mobilization has improved the availability of ART in the most severely affected settings in sub-Saharan Africa.[5] Several new HIV Prevention Trials Network studies will test the hypothesis that widespread and early initiation of ART could reduce HIV incidence very substantially.[6] However, continuing late HIV diagnosis,[7,8] low levels of linkage from HIV testing to care and treatment,[9] and high rates of dropping out from pre-ART[9] and ART[10] in settings with broad access to ART have raised concerns about the feasibility of such an intervention in practice.

Given not only the benefits but also the significant costs and challenges of providing ART[11], much attention has been devoted to examining how existing ART programs could be modified to provide even greater benefits. Investigations have included the use of different treatment regimens, dosing, and patient monitoring. However, one particularly promising direction has been optimizing treatment through addressing the "cascade of care."

As a framework for conceptualizing the challenges and barriers to successful HIV treatment, a number of steps have been identified through which patients must pass to be successfully treated[12–14]: (i) HIV testing and diagnosis; (ii) linkage to clinical care; (ii) retention in pre-ART care (ie, between HIV testing until eligibility for treatment); (iii) ART initiation; and (iv) viral suppression through retention and adherence on ART. The conceptualization of the cascade is powerful because it connects the patient's eventual outcomes and experience on ART with events that happen over time, perhaps many years before ART initiation is required, and at different locations in the community and health system. An "ideal" path for achieving the best health outcomes has been described in which HIV infection is diagnosed early and patients are continuously cared for and monitored until they become eligible for ART, at which time they are promptly initiated onto ART and become virally suppressed.[12] However, accumulating evidence from both high- and low-income settings have documented that the cascade is "leaky": many patients are lost at each stage,[9] even in settings that have achieved high levels of access to ART, many patients initiate treatment later than would be desired,[15,16] and treatment outcomes are sometimes suboptimal after patients have initiated treatment. The result is that a small proportion of people living with HIV are estimated to have achieved viral suppression in low- and high-income settings alike.[13,17] In response to these findings, there have been many calls to improve the cascade of care by making it less leaky. One underlying hypothesis is that improving the pre-ART parts would have the benefit of helping more people to start ART at a CD4 cell count closer to the thresholds for eligibility, which is expected to lead to better survival outcomes. Meanwhile, improving the on-ART parts ensures that those patients who initiate treatment receive the greatest benefit from ART. Moreover, it is tempting to think that the interventions required to make these changes to the cascade[18] would be inexpensive compared with the cost of ART provision itself, suggesting that new cheap interventions would leverage substantial existing spending.

Therefore, an important question is how to intervene on the cascade for maximal effect. Answering this question

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requires understanding the system as it functions currently. In constructing mathematical models to quantify the cascade of care, we found that surveillance data were not entirely consistent with the traditional conception of the cascade. In this article, we first describe the data must be reconciled to represent the cascade of care and present an extension to the traditional cascade concept that we hypothesize may more fully capture the pathways to ART. We discuss its implications and describe how further data collection could improve understanding of the cascade to enable interventions to be chosen strategically for maximum impact.

CAN WE DESCRIBE THE CASCADE OF CARE?

Fully characterizing the cascade of care and identifying the points of greatest weakness requires accounting for all HIV-infected persons in the population, determining the type of care each should ideally receive, and determining the care that each person is actually receiving. This requires bringing together surveillance data from the community level and from the different loci of engagements in HIV care. There are at least three major challenges in collecting and using these data to confidently establish a representation of the current operation of the cascade. First, traditionally, these streams of data have been unconnected, but it is precisely the transitions between these services that determine the cascade. Second, the data available from clinics and programs have tended to focus on aggregate indicators for populations, such as number of patients ever started on ART and the numbers of HIV tests performed in a year. These indicators obscure the trajectories of individuals that may enter and exit at particular stages. Third, we inherently do not know what happens to people who are "lost to follow-up"; if they cease to attend a clinic, their outcomes usually cannot be recorded. But, it is the persons lost from or never engaged in services who are of greatest interest for characterizing the cascade.

To reconcile the different sources of data, we constructed a mathematical model to represent the cascade of care and applied the model to Zambia, a setting that has reached high levels of ART coverage but in which many patients initiate ART late and retention on ART is not optimal.[19] Mathematical models are useful because they impose consistency on different sources of data and produce estimates to characterize populations for which data are not available. In this case, the model brings together program and clinic indicators (numbers getting HIV tests, numbers retained in care, and numbers retained on ART and distribution of CD4 cell count among ART initiators) with separate data on the demography and epidemiology in Zambia (which determines the number of HIV positive people at a point in time and for how long they have been infected)

TABLE 1. Main Data Sources Used to Assemble a Representation of the Cascade of Care in Zambia With Summary Discussion of Challenges in Interpretation

Aspects of the System	Statistic	Source	Issues of Interpretation
Epidemiology	HIV prevalence trends over time	Sentinel surveillance data among pregnant women.	Potential for bias with respect to national prevalence level.
	HIV prevalence level	Household-based nationally representative[24]	Potential for bias because of nonparticipation.[25,26]
Disease progression	Survival times with HIV without ART	African cohort studies[27]	
	Time spent in CD4 cell count categories	International studies on disease progression[28,29]	Data available are not sufficient to robustly characterize of CD4 progression.
HIV testing	Number of HIV tests performed.	Number of test kits distributed (2012 UNGASS Report[19])	Not known if test kits were used; individuals may have been tested multiple times.
	Proportion of adult population who had HIV test last year	Self-report in household-based nationally representative surveys	Self-report information can suffer from misreporting biases
	Proportion of tests that are repeat tests.		Assumption/data not available.
Linkage and retention in pre-ART care	Proportion of persons who had positive HIV test that were linked to pre-ART care and retained until they were eligible for ART	International literature review and analysis[9]	Few studies were able to estimates the rates; studies from different countries and programs had to be combined in some cases.
	CD4 distribution at ART initiation	Retrospective assessment of medical records	Potential for a bias if records not randomly sampled (e.g. records of deceased patients undersampled).
Retention on ART	Proportion of patients initiated on ART that are alive and on ART 1 year later.	Retrospective assessment of medical records	
	Proportion of patients initiated on ART who are alive and on ART 12, 24, and 60 months later.	Longitudinal follow-up of patients in clinics, averaged to produce national estimate. (2012 UNGASS Report[19])	Potential for bias if transfers to clinics incorrectly classified as dropouts.
Reconnecting to ART following dropout.			Factors that determine reconnection to care assumed as data not available.
Numbers on ART	The number of adults receiving ART at midyear.	Aggregated clinics reports	Potential for overcounting if patients transferring to clinics are considered new or if patients are counted who are no longer receiving treatment.

with data on the natural history of disease (which determines how many people are eligible for ART). For each type of data, careful consideration is given to how the way in which they were collected affect their interpretation, and some required information is not currently available (Table 1).

In constructing this model, we find that the traditional conceptualization of the cascade of care, as described above, is insufficient to explain all the available data. In particular, the number of people estimated to make it through the apparently very leaky cascade would not predict the large growth in numbers on ART. Furthermore, although, at the beginning of an ART program, there may be large numbers of people with low CD4 cell counts to be absorbed into the program, the number of patients continuing to be initiated onto ART with very low CD4 cell counts is not consistent with the traditional cascade model, leading us to hypothesize that many people that do initiate ART had not been retained in pre-ART care since their first HIV test or were reinitiating ART following an earlier dropout.

SIDE DOORS INTO THE CASCADE OF CARE

Our proposed modification to the cascade of care concept allows for multiple paths through the stages of HIV care, which contrasts with the traditional model that describes patients passing through these states in a particular order (Figure 1). Although some individuals may initiate ART having been continuously retained in pre-ART care since their first HIV test—whom can be said to have entered ART through the "front door"—others can initiate ART following the onset of illness in advanced stages of disease without prior knowledge of their infection status: such persons may be said to have entered ART in a different way, through a "side door." Similarly, a person lost from pre-ART care on ART may reconnect with care at a later stage following an episode of illness or other event. However, while the 2 "doors" are not equal in terms of the health-benefits for patients, an entry even through the side door will generate much better outcomes than failing to initiate ART entirely.

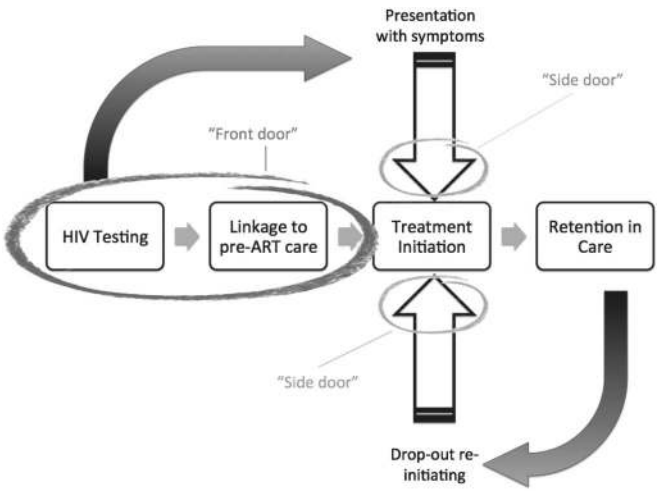

FIGURE 1. The cascade of care. The traditional version of the cascade (blue boxes: HIV testing, linkage to pre-ART care, treatment initiation, and retention in care) provides for a "front door" to ART. This can be supplemented by patients presenting for care following onset of symptoms or reinitiating ART, which provide for "side doors" to ART.

By including HIV care-seeking behavior informed by an individual's health status (e.g. experiencing clinical symptoms associated with low CD4 cell count) as an additional driver for patients initiating ART, we were better able to reconcile the representation of HIV testing and pre-ART care with the scale up of numbers on ART and the high proportions of patients initiating ART with advanced disease. Furthermore, we hypothesize that the propensity for individuals to connect or reconnect to care will be additionally informed by their knowledge of their infection and other events. For instance, a person that has previously had a positive HIV test, even if they subsequently were lost to care, may be more likely to connect to care on becoming ill than a person who was never diagnosed. By the same token, a person who has been on ART at one time may more readily return to care when experiencing certain symptoms than would a person that has never been on ART. Persons with such knowledge may also be more responsive to other events, such as a partner's negative HIV test or the introduction of a new policy (such as treating couples immediately). In this way, the value of an HIV test is not entirely lost when a patient leaves pre-ART care, because that knowledge may help that person to come back to care later on.

The inclusion of these additional channels leads to hypotheses and potential conclusions about the status of ART programs. First, ART programs may actually be more effective at averting HIV-related deaths than "leaky cascade" statistics imply because patients engage or reengage in care via the side door to start ART when they most need it, albeit later than would be considered optimal given the high risk of mortality and poorer long-term treatment outcomes associated with late ART initiation.[2] Conversely, the effect of changes in policies designed to maximize the prevention benefits of ART, such as earlier ART eligibility, may be less than would be implied by current levels of ART coverage if substantial attention is not also given to understanding the motivations for ART initiation and addressing the leaks in the cascade.

Another prediction of the care-cascade model is that there are a group of HIV-infected persons who have been diagnosed but have not been linked to or have been lost from regular pre-ART care and monitoring. We hypothesize that these previously diagnosed persons may be more likely to present for care via the side door on developing symptoms, and hence HIV testing may have an impact in helping patients initiate ART even if they are subsequently lost from care. It may also follow that interventions aiming to improve linkage between testing and the ART program, and the marginal benefit of pairing testing and linkage together over routine provider-initiated testing,[20] may not be as great as currently thought, because, even without immediate linkage and retention, persons who have had an HIV test may still stand a good chance of initiating ART.

Most importantly, it may not be possible to make an evaluation how to improve cascade unless these "side door effects" are quantified. Thus, we suggest it should be a priority to investigate those processes.

COLLECTING MORE DATA TO BETTER UNDERSTAND THE CASCADE

Our preliminary analysis points to several types of data that would be especially valuable in better understanding the cascade of care.

1. How, when, and why are people tested for HIV? To establish how effective testing programs are at finding new HIV-infected persons and the state in which they enter the cascade after testing (health and CD4 level), additional data are needed about testing. In particular, patterns of repeat testing and reasons for testing (i.e. at pregnancy or owing to illness) should be collected in a longitudinal fashion for individuals sampled randomly in communities and retrospectively for persons entering care.
2. Who is initiating ART? Data on the CD4 cell count and health states of those initiating ART, which can be linked to data on the prior experiences of those patients (their first HIV test, first CD4 cell count, and so on), would be essential to establishing the key outcome of the first part of the cascade. Information about patients' prior experience with HIV diagnosis, CD4 cell count measurement, and prior ART initiations should be recorded, particularly to detect patients who may have received care in different health facilities. Systems that can routinely identify individuals that are reinitiating ART following an earlier dropout, and even record a reason for reconnecting, would also help specify the profile of patients on ART.
3. What really happens to the "dropouts"? Studies that actively follow-up individuals who seem to have lost to care are needed. The pioneering work by Geng et al[21] has suggested that many apparent dropouts have in fact only transferred to another clinic. Dropout from ART is an especially important parameter to quantify as it influences the both the assumed scale and performance of an ART program: if apparently high dropout rates actually signify transfers, then it probably also implies an overcounting in the numbers on ART, giving the impression of a larger and more leaky program reliant on side doors than is really the case.
4. Are large numbers of AIDS deaths still occurring, and at which point in the care cascade did failure occur? Even with evidence of the epidemiological,[4] economic,[22] and social[23] benefits of earlier ART initiation, the first goal for ART programs is to prevent AIDS deaths. To ultimately identify the points of weakness, and potential points of leverage, for improving ART programs, it should be a priority to evaluate what, if any, engagement the deceased had with the HIV-care system. For example, many surveillance activities conduct "verbal autopsies" (asking family members of a deceased person about their condition). These should include specific questions about whether the deceased had ever been diagnosed, was known to have been attending a clinic, had started ART, was currently on ART, or had ceased to be on ART. This would provide some information against which models of the cascade could be compared and validated and whether side doors are effectively bringing persons into care.

CONCLUSIONS

Strengthening the cascade to care in ART programs may be among the best ways to generate further health benefits from existing resources for ART, at least in the short term. However, we have found that the data available from programs are insufficient to accurately characterize the cascade to care, although they were enough to suggest the potential importance of patients' health-seeking behavior in determining ART outcomes. We hypothesize that patients' trajectories through care can follow multiple paths and are influenced through a powerful interaction of their own health and knowledge of their condition. Indeed, many more elaborations to the care cascade would be possible than we have discussed here, such as reactions to delays in receiving test results, multiple forms of treatment outcomes (suppression, resistance, etc.), and the role of other events that drive people to health settings, such as pregnancy. Collecting the data necessary to develop a fuller understanding of the cascade, of which we have proposed several types, will be essential for a strategic approach to evaluating and improving the care HIV-infected patients receive.

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Cross-Sectional HIV Incidence Estimation in HIV Prevention Research

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Abstract: Accurate methods for estimating HIV incidence from cross-sectional samples would have great utility in prevention research. This report describes recent improvements in cross-sectional methods that significantly improve their accuracy. These improvements are based on the use of multiple biomarkers to identify recent HIV infections. These multiassay algorithms (MAAs) use assays in a hierarchical approach for testing that minimizes the effort and cost of incidence estimation. These MAAs do not require mathematical adjustments for accurate estimation of the incidence rates in study populations in the year before sample collection. MAAs provide a practical, accurate, and cost-effective approach for cross-sectional HIV incidence estimation that can be used for HIV prevention research and global epidemic monitoring.

Key Words: HIV, incidence, cross-sectional, multiassay algorithm

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Protection of Human Subjects: The procedures used in this report were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

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INTRODUCTION

Most HIV prevention research studies rely on HIV incidence as the primary endpoint because of the lack of reliable surrogate endpoints.[1,2] This presents challenges for observational studies and clinical trials. Many of these challenges arise from methodological issues with the traditional approach for determining HIV incidence: following cohorts of uninfected persons over time and documenting HIV acquisition.

Cohort studies present challenges in HIV prevention research for several reasons. First, if HIV incidence rates are low, large cohorts are required to accumulate sufficient incident infections for accurate determination of incidence rates. Second, it is often difficult to achieve adequate follow-up among high-risk uninfected persons. Third, longitudinal cohort studies are time consuming, often taking years to complete. Fourth, differential loss of follow-up between study arms can bias estimates of intervention effects. Fifth, study participation may modify HIV infection risk for reasons unrelated to the study intervention. For example, provision of risk-reduction counseling during routine follow-up of a biomedical intervention may decrease HIV incidence by decreasing risk behaviors. The Hawthorne effect may also confound prevention studies, because some behavior changes may be related to learning one's HIV status or the awareness of being observed, rather than to the intervention under study.[3]

Many challenges of cohort studies can be addressed by assessing HIV incidence using a single, cross-sectional survey. This approach does not require follow-up of cohorts. In this approach, biological samples are collected in a cross-sectional survey, and biomarkers are used to identify recent HIV infections. In early work, individuals were classified as having recent HIV infection if they were acutely infected (HIV p24 antigen positive and HIV antibody negative).[4] A limitation of that approach is that very large samples sizes are needed to identify recent infections because the duration of acute infection is very short.[5] Subsequently, the criterion for classification as recently infected was a weak anti-HIV antibody response in HIV-seropositive individuals; this was measured using "detuned" serological assays[6] or other serologic assays that measure different characteristics of the immune response to HIV infection.[7] These efforts have been largely unsuccessful because serologic assays classify some individuals with long-standing infections as recently infected.[8,9] Significant progress has been made using combinations of biomarkers eg, multiassay algorithms (MAAs)] for cross-sectional incidence estimation.[10–13] The objective of this article is to discuss this approach and the role it can play in

HIV prevention research. We discuss the conceptual and statistical framework of this approach, limitations of some existing assays, and why and how multiple assays can be effectively combined to overcome these limitations.

USE OF A BIOMARKER APPROACH FOR CROSS-SECTIONAL INCIDENCE ESTIMATION IN HIV PREVENTION RESEARCH

Here, we discuss several applications of cross-sectional HIV incidence estimation that use biomarkers.

Preparatory or feasibility studies are often performed to estimate HIV incidence rates to determine samples sizes for phase 3 HIV prevention studies. This is challenging, because even small overestimates of HIV incidence rates in sample size calculations can lead to appreciably underpowered studies. Indeed, several HIV prevention trials were stopped early because of lower than expected incidence rates, leading investigators to conclude that the trials would be unable to detect an intervention effect.[2,14–16] Furthermore, preparatory cohort studies to estimate incidence in target study populations can take years to complete; in some cases, by the time incidence estimates are obtained, the estimates may be out-of-date (eg, reflecting temporal trends in the epidemic, demographic changes, or ramp-up of HIV treatment programs). Cross-sectional HIV incidence assessments may provide an alternative, rapid approach to facilitate design of phase 3 trials.

The cross-sectional approach is especially useful in community-randomized trials of structural interventions. This approach was recently used to evaluate the primary endpoint of a large, multinational HIV prevention trial, NIMH Project Accept (HPTN 043).[17] Project Accept evaluated the impact of interventions aimed at increasing the uptake of voluntary counseling and testing, changing community norms, and increasing social support for persons with HIV infection.[18] A longitudinal cohort study was not suitable to evaluate the impact of the intervention, because HIV testing was part of the study intervention package.

The cross-sectional biomarker approach has also been applied to epidemiological studies of risk factors for HIV acquisition. An early application of this approach was a case–control study of acute HIV infection that used p24 antigen to identify incident HIV infections in HIV-seronegative patients.[19] In later work, the BED capture immunoassay (BED-CEIA) was used to evaluate risk factors for HIV acquisition in a nationally representative, population-based survey.[18] However, the inability of the BED-CEIA and other serologic incidence assays to accurately distinguish recently occurring from long-standing infections limits their utility. Development of accurate methods for identifying recent infection has important applications to epidemiologic studies of risk factors for HIV acquisition. The methods could also have important roles for identification of sexual or other networks with active disease transmission to target prevention efforts.[20]

Finally, cross-sectional incidence estimates could be used to evaluate local and national time trends in HIV incidence. Nationally representative surveys of HIV prevalence, such as the Demographic and Health Surveys, have been conducted in more than 30 countries.[21] Assessment of HIV incidence in samples collected in those surveys (eg, using a MAA) would incur marginal additional cost and could yield direct estimates of HIV incidence. Furthermore, comparisons of cross-sectional incidence in serial surveys could assess changes in HIV incidence. This approach could circumvent problems with other approaches, such as inferring incidence from changes in HIV prevalence over time, because that approach is known to be very sensitive to assumptions about mortality and migration.[22]

CONCEPTUAL AND STATISTICAL FRAMEWORK

The cross-sectional incidence approach is based on classification algorithms that use assays to classify individuals into 1 of 2 states: either MAA positive or MAA negative. An objective of these algorithms is for individuals classified as MAA positive to have shorter durations of infection than individuals classified as MAA negative. The duration of time that persons are classified as MAA positive depends on the specific algorithm that is used. Furthermore, for a given algorithm, the duration of time that individuals are classified as MAA positive varies from person to person. The mean (or average) duration of time individuals are classified as MAA positive for a given algorithm is called μ or the mean window period. From reference samples with known (interval-censored) durations of infection, one can estimate μ. One can also estimate the distribution of durations individuals are MAA positive for a given algorithm, that is, $\varphi(t)$ = the proportion of individuals infected for t days who are classified MAA positive.

A fundamental equation in epidemiology describes the relationship between prevalence, incidence, and duration and provides the basis for how to estimate incidence from cross-sectional samples using biomarkers.[23] The estimate of the HIV incidence rate in a population from a representative cross-sectional sample of persons from that population is

$$I = \frac{w}{n\mu} \tag{1}$$

where w is the number of individuals classified MAA positive and n is the number of individuals who are HIV seronegative.[4] Confidence intervals for the incidence rate that account for uncertainty in μ are obtained using procedures described in previous reports.[11,24,25]

In general, Equation 1 is not estimating incidence at the time of sample collection but rather at a time before the collection of samples. The question of how far back in time is answered by the concept of the shadow, which is denoted by ψ.[26] Equation 1 is estimating HIV incidence ψ days before collection of the samples.[26,27] The shadow can be calculated from the curve $\varphi(t)$ using numerical integration as described in previous reports.[12,27]

Generally, it is preferable for MAAs to have large mean window periods (μ) and also small shadows (ψ). This is preferable because incidence estimates will have smaller standard errors (and variances) if μ is large and will also be more current and therefore potentially less biased if ψ is small. Although the mean window period (μ) and shadow (ψ) are

distinct numbers, they tend to be positively correlated; this presents the classic statistical tradeoff between bias and variance (Fig. 1 in Brookmeyer, Konikoff, Laeyendecker, et al.[12]). The question of how to choose optimal MAAs to address this tradeoff is discussed in the article by Brookmeyer, Konikoff, Laeyendecker, et al.,[12] which describes an approach to identify algorithms that maximize the mean window period subject to the constraint that the shadow is not too large (eg, <1 year).

HIV prevention interventions in a phase 3 trial can be compared by the ratio of their incidence rates [ie, the rate ratio (RR)], which is obtained by taking the ratio of Equation 1 for the 2 groups. In the special case where μ *is* the same for the 2 groups, the RR for group 1 relative to group 2 is

$$RR = \frac{w_1 n_2}{w_2 n_1} \quad (2)$$

We see that the mean window period, μ, cancels out in Equation 2 and, therefore, is not required in the calculation. Two points about Equation 2 should be emphasized. First, the equation is estimating the incidence RR ψ days before sample collection and not on the date of sample collection. This point is important if there is a ramp-up period for an intervention to achieve its maximal effectiveness. Second, the assumption that the mean window periods (μ) cancel out in Equation 2 may not hold for all interventions. For example, if an intervention increases uptake of antiretroviral treatment (ART) services, μ may become larger if the MAA is based solely on serologic assays, because the performance of those assays is impacted by viral suppression. MAAs that include assays for viral load or antiretroviral drug exposure can account for this effect by classifying individuals with low viral loads and those on antiretroviral drugs as MAA negative. Therefore, use of Equation 2 may be justifiable in some settings using certain testing algorithms.

An important question is how to optimize testing algorithms to maximize the statistical power for detecting an effect in comparative trials. The choice of which assay or MAA to use involves balancing the bias-variance tradeoff. The primary endpoint of NIMH Project Accept (HPTN 043), a large community-randomized trial, was based on use of a MAA that was optimized to maximize the power for detecting an intervention effect.[28]

LIMITATIONS OF CURRENT SEROLOGICAL ASSAYS

Although reliable methods exist for identifying acute HIV infections, this approach is only useful for surveying very large populations that have high incidence rates because the acute phase of infection is very short.[4,5] Serologic incidence assays that have much longer mean window periods have been developed that measure different characteristics of the anti-HIV antibody response (eg, antibody avidity or the proportion of IgG specific for HIV antigens; for review, see articles by Murphy and Parry[7] and Guy, Gold, Calleja, et al.[8]). Some serologic incidence assays are based on modifying commercial assays developed for HIV diagnosis (eg, Abbott detuned assay,[6] Vironostika less sensitive assay,[29] AxSYM HIV1/2gO avidity,[30] BioRad avidity assay[31]), whereas others have been based on noncommercial (in-house) assays (eg, V3 IDE assay[32], Luminex assay[33]). The BED-CEIA[34] and the limited antigen avidity enzyme immunoassay (Lag-Avidity EIA)[35,36] are the only assays specifically manufactured for HIV incidence testing.

Serologic incidence assays are relatively inexpensive and simple to use. However, if only serological assays are used in a MAA, some individuals remain MAA positive for long periods, whereas others who become MAA negative may subsequently revert to being MAA positive because of changes in their antibody responses to HIV infection (eg, because of viral suppression or advanced HIV disease).[29,37–40] For these reasons, the distribution of durations that individuals are classified as MAA positive using only serological assays have long right tails.[41] When serologic assays are used exclusively for incidence testing, 2 factors that commonly cause individuals with long-standing infection to be classified as MAA positive are viral suppression (natural or induced by ART) and advanced HIV disease.[29,37–40] The performance of serologic incidence assays is also impacted by HIV subtype.[29,42,43] A systematic evaluation of currently available assays used for cross-sectional HIV incidence estimation is being performed by the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA).[44]

USE OF MAAs FOR CROSS-SECTIONAL INCIDENCE ESTIMATION

The use of multiple assays in combination can increase the accuracy of cross-sectional incidence estimates. The cost of this approach can be reduced by using hierarchical, stepwise testing algorithms (MAAs). In each step, a single assay is used to refine the classification of samples that were provisionally classified as MAA positive at the prior step(s) (Fig. 1). If logistically feasible, assays can be performed in order of cost, with less-expensive, high-throughput assays in the initial steps and more-expensive or labor-intensive assays performed in the later steps.

A MAA for HIV incidence estimation in subtype B epidemics has been developed that uses 2 serologic assays [BED-CEIA (measured as a normalized optical density, OD-n) and the BioRad avidity assay [measured as a avidity index] and 2 nonserologic biomarkers (CD4 cell count and HIV viral load) as illustrated in Figure 1 (MAA #1).[10] This MAA was validated using >2200 validation samples from >1000 individuals with known duration of HIV infection (range <6 months to >8 years).[10,12] The mean window period for this MAA was initially determined to be 141 days [95% confidence interval, (CI): 94 to 150].[10] The performance of this MAA was evaluated in 3 longitudinal cohort studies.[10,11,45] The cross-sectional estimates of incidence were determined by testing samples collected at the end of the follow-up period of the cohort study. In this manner, the incidence estimates obtained using cross-sectional testing could be compared with those observed in the cohorts based on documentation of HIV acquisition. The MAA and cohort incidence estimates were very similar (Fig. 2). In a subsequent study, the same validation data were reanalyzed using

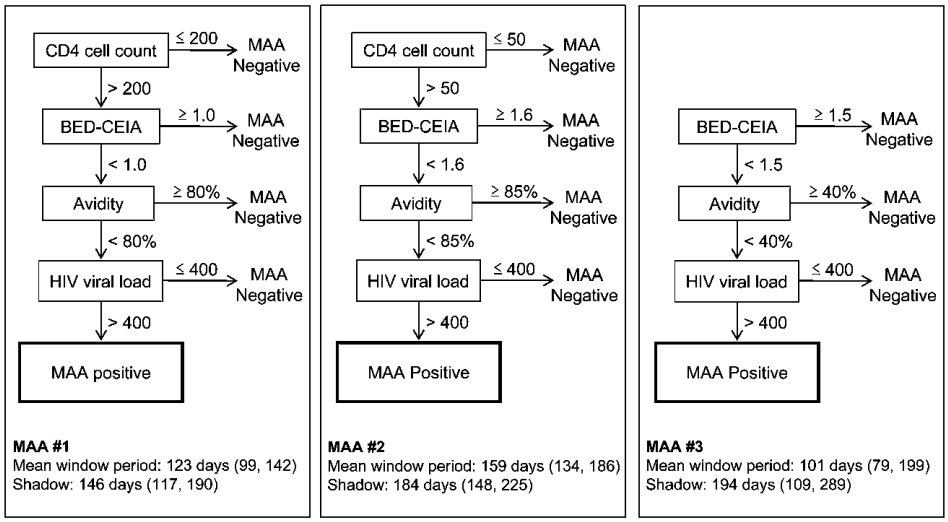

FIGURE 1. MAAs for cross-sectional HIV incidence estimation in subtype B epidemics. MAAs were developed that combine serologic markers (BED-CEIA and an avidity assay) with nonserologic biomarkers (HIV viral load, with or without CD4 cell count).[10,12] In each MAA, assays are performed using a hierarchical approach, with an optimal cutoff defined for each assay. CD4 cell count cutoffs are expressed as cells/mm^3; BED-CEIA cutoffs are expressed as normalized optical density; avidity results are expressed as avidity index values (%); HIV viral load cutoffs are expressed as HIV RNA copies/mL. For each MAA, samples that meet the criteria for all assays are classified as MAA positive. Three MAAs are shown. MAA #1 is a 4-assay MAA described in the articles by Laeyendecker, Brookmeyer, Cousins, et al.[10] and Brookmeyer, Konikoff, Laeyendecker, et al.[12] which was used to estimate incidence in 3 clinical studies (Fig. 2). MAA #2 is an alternate 4-assay MAA described in the article by Brookmeyer, Konikoff, Laeyendecker, et al.[12] which maximizes the mean window period subject to the shadow being less than 1 year. MAA #3 is the 3-assay MAA described in the article by Brookmeyer, Konikoff, Laeyendecker, et al.[12] which does not require CD4 cell count data and maximizes the mean window period subject to the shadow being <1 year. The mean window periods and shadows for all 3 of these MAAs were determined in a previous study[12]; the 95% confidence intervals for each mean window period and shadow are shown in parentheses.

multiple imputations to address uncertainty from interval-censored infection times.[12] Based on that analysis for this MAA, the mean window period was 123 days and the shadow was 146 days.[12] In the same study, the validation data were used to identify an optimal MAA by searching through 11,340 MAAs with different assay cutoffs; the goal was to find the MAA that had the longest mean window period (μ) with the constraint that the shadow (ψ) was <1 year.[12] The optimal 4-assay MAA had a mean window period of 159 days and a shadow of 184 days (Fig. 1, MAA #2). The study also evaluated MAAs that included 3 assays (the BED-CEIA, the avidity assay and viral load, but not CD4 cell count); those MAAs offer advantages in settings where CD4 cell count data cannot be obtained. The optimal 3-assay MAA had a mean window period of 101 days and a shadow of 194 days (Fig. 1, MAA #3). The 3- and 4-assay MAAs described above (MAAs #1–#3 in Fig. 2) did not classify any of 845 samples from individuals who were infected >5 years as MAA positive; the sample set included 512 samples from individuals who were infected >8 years.[8]

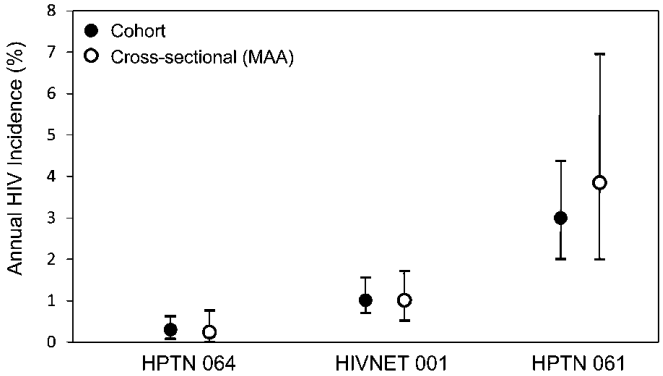

FIGURE 2. Comparison of cross-sectional incidence estimates and incidence observed from longitudinal follow-up of HIV-uninfected cohorts in 3 clinical studies performed in the United States. HIV incidence was evaluated in 3 clinical studies: the HIV Prevention Trials Network (HPTN) 064 study,[53] the HIV Network for Prevention Trials (HIVNET) 001 Vaccine Preparedness study,[54] and the HPTN 061 study.[45] Annual HIV incidence was determined in each study using 2 methods: longitudinal follow-up of HIV-uninfected individuals (filled symbols) and cross-sectional analysis using a MAA (MAA 1 shown in Fig. 1; open symbols).[10,11,45] Note that the mean window period of MAA 1 is based on the analysis reported in Laeyendecker, Brookmeyer, Cousins, et al[10] using midpoint imputation for seroconversion times; a reanalysis using multiple imputations is reported in Brookmeyer, Konikoff, Laeyendecker, et al.[12]

The MAA used to determine the primary endpoint of NIMH Project Accept (HPTN 043) was identified by analyzing the performance of MAAs for incidence estimation in a Southern African setting using a set of >5000 subtype A and C validation samples from >3400 individuals with known durations of infection (range 1 month to >10 years)[28]. The goal of that study was to select the MAA that provided the highest power for detecting a reduction in incidence in intervention communities in the Project Accept trial.[18] The performance of 403 candidate MAAs was evaluated in 3 simulated epidemic scenarios (emerging, stable, and waning epidemics). Those analyses identified the following optimal MAA for this application: BED-CEIA <1.2 OD-n and avidity index<90% and CD4 cell count >200 cells/mm^3 and viral load >400 copies/mL.[28]

In the MAAs described above, viral load testing is used to identify individuals with long-term infection who have low

BED-CEIA and avidity assay results because of viral suppression. The precision of MAAs may be further enhanced by also including a criteria of "no ART," because ART per se may serve as a supplemental, surrogate marker of nonrecent infection.[46,47] If ART is used as a component of an MAA, direct detection of antiretroviral drugs may be more reliable than self-report of antiretroviral drug use.[48] The recent development of a low-cost, high-throughput, multidrug screening assay makes this kind of screening feasible.[49] This antiretroviral drug-screening assay was used in the Project Accept trial as the final step for classifying individuals as MAA positive.[50] It is important to note that some antiretroviral drugs may not be detected in samples because of their short half-lives. Furthermore, because some antiretroviral drugs are used for HIV prevention, some individuals may be classified as MAA negative based on antiretroviral drug detection even though their duration of infection is short (eg, in recently infected women receiving nevirapine for prevention of mother-to-child HIV transmission). In addition, antiretroviral drug testing will not identify elite controllers with long-standing infection, who may be classified as MAA positive based on results from serologic assays; viral load assays are needed to identify those individuals.[38]

Viral diversity assays are also being explored for use in HIV incidence testing, either alone or in combination with other assays. The rationale is based on the premise that viral diversity increases with duration of infection and may serve as a biomarker that is independent of serologic biomarkers. A high-resolution melting (HRM) diversity assay has been developed that quantifies the genetic diversity in HIV without sequencing.[51] This assay is relatively inexpensive, easy to perform, and provides quantitative measures of diversity that are highly correlated with diversity measures obtained by deep sequencing.[52] Our recent studies suggest that the HRM diversity assay may offer an alternative to CD4 cell count in MAAs without compromising their performance.

DISCUSSION

HIV incidence is a critical outcome in HIV prevention research. Accurate methods for cross-sectional HIV incidence estimation may facilitate HIV prevention research, particularly when evaluating population-level interventions for HIV prevention. Other intermediate outcomes (eg, self-reported high-risk behaviors, frequency of HIV testing, proportion of eligible HIV-infected persons on ART) have been used as alternative endpoints for assessing the impact of prevention interventions and have provided insights into why some prevention interventions are not effective. However, changes in intermediate endpoints do not necessarily predict changes in HIV incidence. Ultimately, the question that HIV prevention research must address is whether or not an intervention decreases incidence. The cross-sectional biomarker approach for HIV incidence estimation helps address a number of challenges in incidence determination. The main advantage of this approach is that incidence can be determined from samples collected in a single cross-sectional survey, without requiring longitudinal follow-up of uninfected individuals.

Recent improvements in methods for cross-sectional incidence estimation make the approach feasible. To date, no single serologic assay has been developed that can accurately estimate incidence. To overcome these limitations, attention has now turned to using multiple biomarkers in combination. Recently, MAAs have been identified where the probability of being classified as MAA positive converges to zero within several years of infection. MAAs that use multiple biomarkers in combination are essentially binary decision trees; results from each assay are used to decide whether or not to test a sample with the next assay in the algorithm. This hierarchical approach to testing reduces costs. Recent research has demonstrated that the multiple biomarker (MAA) approach is extremely powerful and corrects the deficiencies of individual biomarkers.

Statistical methods have been developed for assessing the accuracy of MAAs and for identifying optimal MAAs by calculating mean window periods, shadows, and statistical power for comparative trials. These methods require large validation sample sets from individuals with a broad range of known (interval-censored) durations of infection. The validation samples should represent the full range of durations of infection and include infected persons with the relevant HIV subtypes, with viral suppression, and with advanced HIV disease. Theoretically, the MAAs that we have identified should be capable of estimating incidence with minimal bias regardless of the stage of the epidemic (eg, mature vs. rapidly changing). The MAAs that we identified characterized individuals with either viral suppression or advanced HIV disease as MAA negative. Therefore, the mean window period and the shadow of the MAAs that we identified should not be dependent on epidemic stage. Figure 2 shows that one of these MAAs performs well in 3 very different epidemic settings. Further validation of MAAs in diverse settings is warranted. Although the MAAs should yield unbiased estimates of incidence regardless of the epidemic setting, the samples sizes needed to obtain accurate incidence estimates will vary by setting. In general, the sample sizes needed to obtain precise incidence estimates in cross-sectional surveys are greater in lower incidence settings than in higher incidence settings, which is also the case for longitudinal cohort studies.

MAAs have been successfully developed for use in settings with both subtype B and subtype A and C epidemics. These MAAs do not require any further mathematical adjustments for accurate estimation of the incidence rates. Work is now ongoing to identify optimal MAAs for other HIV subtypes and for other applications. A robust MAA has been developed that does not include the CD4 cell count. We conclude that the cross-sectional biomarker approach using MAAs is a practical, accurate, and cost-effective approach for HIV incidence estimation that can be used for HIV prevention research and global epidemic monitoring.

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Antiretroviral Pharmacology in Mucosal Tissues

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Abstract: Strategies to prevent HIV infection using preexposure prophylaxis are required to curtail the HIV pandemic. The mucosal tissues of the genital and rectal tracts play a critical role in HIV acquisition, but antiretroviral (ARV) disposition and correlates of efficacy within these tissues are not well understood. Preclinical and clinical strategies to describe ARV pharmacokinetic–pharmacodynamic relationships within mucosal tissues are currently being investigated. In this review, we summarize the physicochemical and biologic factors influencing ARV tissue exposure. Furthermore, we discuss the necessary steps to generate relevant pharmacokinetic–pharmacodynamic data and the challenges associated with this process. Finally, we suggest how preclinical and clinical data might be practically translated into optimal preexposure prophylaxis dosing strategies for clinical trials testing using mathematical modeling and simulation.

Key Words: preexposure prophylaxis, antiretrovirals, pharmacokinetics, mucosal tissues

(*J Acquir Immune Defic Syndr* 2013;63:S240–S247)

Antiretroviral therapy (ART) has saved millions of lives and greatly increased the life expectancy of individuals living with HIV.[1] The Joint United Nations Programme on HIV/AIDS set a goal of having 15 million individuals living with HIV on ART by 2015, reaffirming that widespread ART implementation is a global priority.[2] It is well recognized that these drugs penetrate into the genital tract and decrease viral shedding.[3–5] ART, therefore, was postulated to prevent transmission and acquisition of HIV. Indeed, pharmacological interventions aimed at preventing the spread of HIV using currently approved antiretroviral (ARV) medications have shown success in various settings.[6–8]

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Most recently, the successful use of ART for prevention of transmission has focused on the use of these agents to prevent HIV acquisition.[9–12] If ART stops replication in an HIV-positive individual and prevents transmission, it is reasonable to think that ART can also prevent transmission in an HIV-negative individual when confronted with a replication-competent founder virus. Accordingly, preexposure prophylaxis (PrEP) using topical or systemic (oral or injectable) ARVs to prevent HIV infection around the time of exposure makes the issue of drug penetration into genital and rectal mucosal tissues critically important. Many factors can affect drug concentrations and the concentration–response relationship in these tissues and not all are fully understood. This review will summarize these factors and propose how they may contribute to achieve protective concentrations and effective dosing strategies for PrEP. We will also address the limitations of the methods currently used to generate these data and suggest ways to improve the applicability of the results.

EVOLUTION OF DRUG CONCENTRATION DATA IN MUCOSAL TISSUES

Evaluation of drug exposure in female genital and in colorectal tissues began in the 1970s. Early publications examined the distribution kinetics of antibiotics in these tissues with the goal of identifying ideal candidates for surgical prophylaxis in gynecologic and colorectal surgery.[13] These pharmacokinetic (PK) studies of antibiotic distribution in the surgical setting continued throughout the 1980s.[14,15] Additional investigations identified antibiotics that were well suited for the outpatient treatment of gynecologic infections.[16–18] Measures of drug exposure in these early studies typically consisted of single concurrent tissue and serum samples obtained after a single dose of antibiotic and were reported as a tissue:plasma ratio. Later studies conducted more rigorous examinations using single- and multiple-dose kinetic data to report tissue:plasma ratios.[19–21] Due to different distribution characteristics in tissues compared with plasma, single time point concentration ratios could over- or underestimate true tissue exposure.[19] Therefore, a more comprehensive measure of drug exposure in these tissues, the area under the concentration time curve (AUC), was used to calculate tissue:plasma AUC ratios. These early studies made it clear that drug concentrations at sites of action cannot be assumed to be the same as plasma concentration and that the ability of drugs to penetrate into tissue can vary greatly even among members of the same drug class, which may prove quite important in clinical trials.[22]

Mucosal tissues of the vagina, cervix, and colorectum are a primary target for early HIV infection and replication.[23] Simian immunodeficiency virus pathogenesis research in macaques has demonstrated rapid viral penetration into genital and rectal tissues after local inoculation. Viral DNA has been detected in the vaginal epithelium within hours after inoculation, and founder populations of virus can be detected in cervicovaginal tissues as early as 24 hours postinoculation.[24–26] Clinical studies have confirmed cervical, vaginal, and colorectal transmissibility of HIV.[27–29]

Although initial viral populations are small, rapid local and systemic dissemination occur during the first 4 days of infection, making this time period a critical target for pharmacological interventions.[24] Therefore, an important determinant in successful PrEP must be the ability of ARVs to achieve and sustain adequate concentrations in the mucosal tissue, whether through topical or systemic administration. To prevent the index infection in the new host, sufficient concentrations of ARVs must be present at the time of exposure and for some yet-to-be-defined length of time afterward. Penetration of ARVs into the colorectum, semen, and tissues of the female genital tract (FGT) has been extensively researched.[19,20,30–33] The resulting data have revealed a high degree of variability in penetration, both between and within drug classes.

The penetration profiles for the ARVs are summarized in Figure 1.[19–21,30,31,33–42] Oral ARV formulations comprise the majority of penetration data. Generally, the nucleoside/tide reverse transcriptase inhibitors achieve high concentrations in the FGT. Zidovudine (ZDV), emtricitabine (FTC), and lamivudine (3TC) all have single- and multiple-dose tissue:plasma AUC ratios greater than 1.00. Ratios of protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) are more variable, with most protease inhibitors having poor penetration (<0.20) into the FGT and NNRTIs having highly drug-specific penetration. The CCR5 antagonist maraviroc penetrates well into the FGT (AUC ratio 1.9–2.7), whereas the integrase strand transfer inhibitor raltegravir shows moderate penetrative ability (AUC ratio 1.00 in HIV-negative women and 4.00 in HIV-positive women, driven primarily by differential blood plasma exposure).[35]

There are some inconsistent trends in penetration between single and multiple doses. In the case of efavirenz, stavudine, and atazanavir, the extent of penetration is constant regardless of the number of doses given, reflecting a constant relationship between systemic and local exposure. However, for tenofovir (TFV), abacavir, and lopinavir (LPV), drug exposure declines in the genital tract with repeated dosing. The tissue:plasma AUC ratio declines from 1.1 after a single

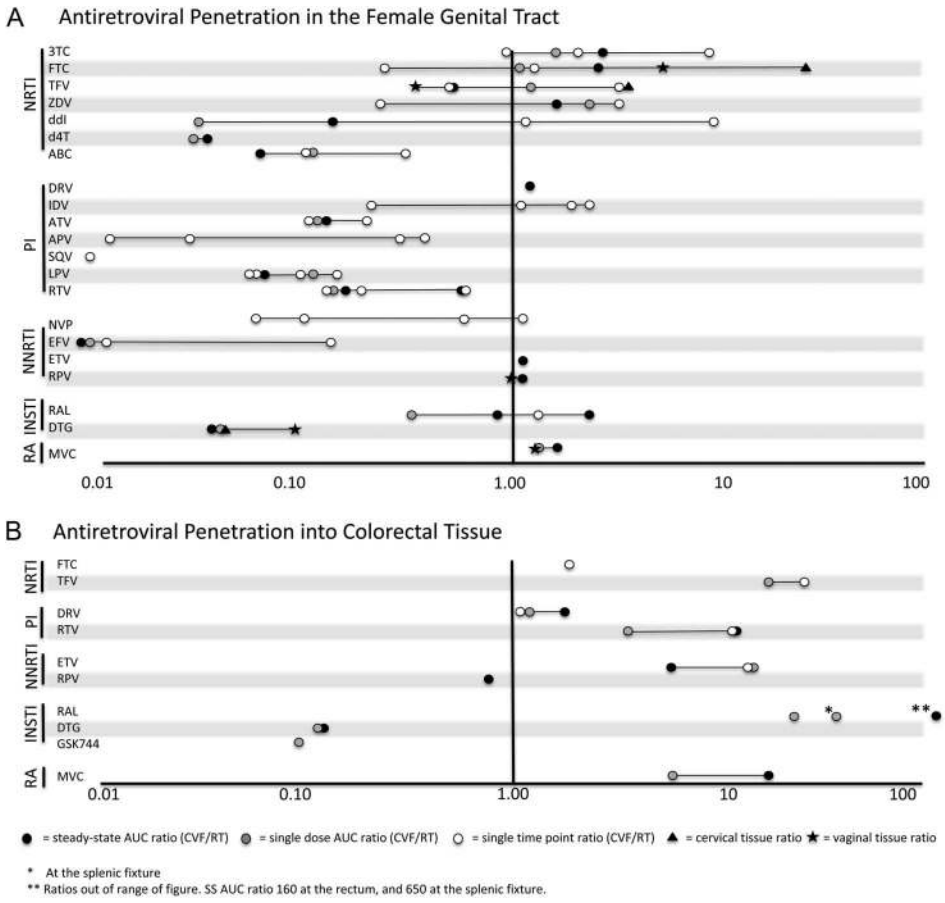

FIGURE 1. A and B, ARV penetration into mucosal tissues. Data are from references Dumond et al[19,20], Min et al[21], Patterson et al[30], Kwara et al[31], Brown et al[33], Patterson et al[34],Jones et al[35], Yeh et al[36], Launay et al[37], Clavel et al[38], Greener et al[39], Brown et al[40], Else et al[41], and Andrews et al.[42] ABC, abacavir; APV, amprenavir; ATV, atazanavir; ddI, didanosine; d4T, stavudine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETV, etravirine; IDV, indinavir; INSTI, integrase strand transfer inhibitor; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RA, receptor anatagonist; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SQV, saquinavir.

dose to 0.75 after multiple dosing for TFV, from 0.21 to 0.08 for abacavir and from 0.17 to 0.08 for LPV. This suggests that, with repeated dosing, entry mechanisms for some ARVs either become saturated, upregulated (eg, efflux transporters) or downregulated (eg, uptake transporters), decreasing the ability of these drugs to reach the FGT.

The PK profiles of alternative ARV formulations have also been studied. Topical TFV gel has been successful in preventing HIV infections in clinical trials and achieves favorable tissue concentrations when applied vaginally or rectally as either a gel or a ring.[43,44] This formulation has also been shown to rapidly distribute between vaginal and rectal tissue after application to either site, although the exposure in the nondosed site reaches only approximately 5% of the exposure seen at the site of dosing.[43] A study in 24 HIV-negative women showed that a vaginal ring formulation of dapivirine achieved cervicovaginal fluid concentrations that were 3 log units higher than plasma concentrations and 4 log units higher than the reported in vitro EC_{50} of HIV-1_{LAI}.[45] Furthermore, a novel NNRTI rilpivirine has shown penetration of AUC ratios of 1.2–1.95 in cervicovaginal fluid and 0.48–1.0 in vaginal tissue when administered as a long-acting injectable formulation.[41]

FACTORS INFLUENCING DRUG ENTRY INTO TISSUES

The data described above highlight the need to identify the variables affecting mucosal penetration of small molecules. Once these variables are understood, they can be considered in the ARV development process and help identify ideal drug candidates for PrEP.

There are several physicochemical factors that influence tissue penetration: blood perfusion, protein binding, molecular size, lipophilicity, ionization state, and membrane transporter affinity. Adequate tissue blood flow is a necessary requirement for drug efficacy, particularly for drugs that are efficiently metabolized by target organs, also called "high extraction compounds." For highly extracted drugs, there is a direct relationship between tissue perfusion and drug entry into tissues, and lack of perfusion is a likely contributor to the difficulty of treating infections at certain anatomic sites (eg, central nervous system, bone). One of the primary determinants of pharmacodynamic (PD) efficacy is the fraction of unbound drug available to cross the cellular membranes and enter tissues and cells.[46,47] Differential protein binding between 2 similar drugs can have large PD implications. For example, it has been shown that ARVs which are highly protein bound (eg, efavirenz, LPV), have much lower exposure in tissues than those which have less protein binding (eg, FTC, TFV).[19] Chemical characteristics can also affect drug entry into tissues and cells, mostly by affecting the ability of a compound to diffuse across cellular membranes. Perhaps the most well-established characteristic is the inverse relationship between the molecular size of a drug and its penetrative capability.[46] An additional factor is the lipophilicity of a drug. Highly lipophilic compounds (eg, propranolol) are able to cross the cellular membranes much more easily (and have better intestinal absorption) compared with hydrophilic drugs (eg, hydrochlorothiazide). This is an important consideration in drug development, where formulation changes can occur as a result of poor intestinal absorption. Finally, the ionization state of a compound, which is determined by its pKa, is another element that can aid or hinder diffusion across membranes. Drugs that are mostly ionized at physiological pH (eg, ZDV) are much less likely to enter tissues and cells compared with drugs that are neutral at an identical pH (eg, FTC). It should be noted that although a drug's pKa is unchanging; its ionization state can differ among tissues due to local pH changes. For example, an acidic environment (eg, prostatic fluid; pH 6.6) can cause a drug with a pKa $>$ 6.6 (eg, ZDV; pKa 9.68) to be ionized and trapped.[48,49]

In addition to physicochemical properties, the effect of transporter expression and differences in transporter affinity among ARVs may play a critical role in determining mucosal penetration. The effect of transporters on ARV uptake and elimination from tissues has been thoroughly evaluated. A review by Kis et al[50] summarizes the inhibitory and induction effects of ARVs on the ATP-binding cassette and solute carrier transporter families, which are known to contribute ARV penetration into various tissues and compartments. Briefly, the efflux transporters of the solute carrier family, especially p-glycoprotein (P-gp), are the primary method of cellular efflux for almost all ARVs with the exception of the NNRTIs. Transporters responsible for ARV uptake are more varied but are generally comprised the organic anion transporters. Importantly, all ARVs with the exception of raltegravir inhibit and/or induce one or more of these transporters to some degree, irrespective of whether they are substrates for the transporters. This has implications not just for drug disposition in tissues but also for drug–drug interactions. Notably, the authors mention a lack of data on the expression of these transporter groups in the FGT, despite adequate expression data in other compartments. One study examined P-gp localization by immunohistochemistry staining in the upper genital tract of 14 women and found P-gp expression in the ovaries, fallopian tubes, corpus luteum, ectocervix and endocervix, though the degree of expression was highly variable between patients and tissues.[51] Additional publications on transporter expression in the FGT are severely lacking. A recent study examined the expression of uptake (OAT1, OAT3, OATP1B1) and efflux (MDR1, MRP2, and MRP4) transporters in vaginal, cervical, and rectal tissue.[52] Gene expression of the efflux transporters was variable between subjects but consistently expressed, whereas uptake transporters were rarely expressed in these tissues. Similar trends were observed in protein levels and are supported by drug disposition data.

The inability to visualize the distribution of ARVs within mucosal tissues hinders the progress of PrEP research. Even for ARVs that are known to permeate well into FGT and colorectal tissue, there are few data evaluating drug exposure in specific areas or cellular subsets vulnerable to HIV infection (ie, mucosa vs. submucosa vs. lymphoid aggregates; mononuclear vs. epithelial cells). Techniques that would allow visualization and quantification of ARVs in tissues would be invaluable not only for prevention but also for treatment and eradication strategies. One such approach is matrix-assisted laser desorption/ionization (MALDI): a mass

spectrometry technique that has been used since the 1980s for peptide identification.[53] Through the use of multiple laser ionizations, MALDI is able to generate information about relative concentrations of tissue constituents which, when coupled with imaging software, allow for the visualization of target analytes within a tissue. Recently, this technique has been modified to identify small molecules within specific tissue areas and even within individual cells.[54,55] MALDI has been used previously to quantify ARVs in plasma and represents a promising approach to understanding drug disposition in tissues.[56]

Another possible avenue for future research could include the use of a quantitative structure activity relationship (QSAR) model to isolate the chemical moieties and PK parameters (eg, protein binding) that improve or hinder penetration. These models have been successfully used to identify structural characteristics that enhance HIV inhibition, but to date, no validated QSAR model has been developed for ARV penetration into the mucosal compartment.[57] This model was used to determine penetration of drugs across the blood–brain barrier and achieved a positive predictive value of 100% and negative predictive value of 83%.[58] The authors were also able to identify factors, such as binding affinity to efflux transporters, which affect blood–brain barrier penetration. We recently used a similar approach to develop a QSAR model for drug entry into female genital tissues using a newly validated QSAR model for transporter affinity.[59] Our model was modestly predictive and identified MRP4 as a novel contributor to FGT penetration.[60] Validation of this model and/or the addition of other models of drug penetration into vaginal/cervical and rectal tissues would greatly inform the drug development process and identify PrEP candidates from an early stage.

Finally, biologic factors can affect both ARV penetration into tissues and infection susceptibility. For example, the nucleotide reverse transcriptase inhibitors require intracellular phosphorylation to their active forms through cellular kinase activity. It has been determined that kinase activity in quiescent or activated cells changes the rate and extent of phosphorylation of ARVs. Specifically, zalcitabine, 3TC, stavudine, and didanosine are preferentially phosphorylated in activated cells.[61,62] No noted differences in phosphorylation have been found between activated and quiescent cells for TFV.[63] Importantly, these differences in active metabolite concentrations may not correlate with antiviral activity because zalcitabine, 3TC, and didanosine are more active against HIV in quiescent cells, despite lower metabolite concentrations than in active cells.[62] It may be that increased concentrations of endogenous nucleotides in activated cells decrease their effectiveness.

Altered mucosal integrity may also result in large interindividual variability in ARV penetration, particularly for topical dosage forms. Compromised mucosal integrity has been associated with increased viral penetration.[64] It is not known whether this relationship holds true for topical ARV penetration, but inflammation and physical breaks in skin are known to increase plasma exposure to topical products. Furthermore, although the integrity of the upper genital tract tissues (eg, endometrium) is heavily influenced by the menstrual cycle, hormonal influence on the vaginal and rectal mucosa is less understood. There are numerous studies examining the role of estrogen on HIV susceptibility; however, studies exploring the hormonal influence on drug exposure are lacking.[65,66]

DRUG PERSISTENCE AND FUNCTIONAL HALF-LIFE

Given that the index infection likely takes place within the mucosa or submucosa of mucosal tissues, the presence of adequate concentrations of ARVs at the time of exposure is critical in PrEP. Also critical is the length of time compounds reside in the tissue. Compounds with long tissue half-lives (or delivery systems with continuous drug exposure) would be favored for both virological and adherence factors.[4,9,11] For any ARV used in PrEP, the time spent above target concentration must at least be as long as the length of time that viable virus remains in the mucosal cavity after coital exposure. The life span of the HIV virion in plasma has been reported as 6 hours, whereas HIV-infected $CD4^+$ T cells have a life span of approximately 2 days in plasma.[67] The life span of both infected cells and virion in the mucosal cavity remains unknown and demands exploration. One study examined virion persistence after vaginal inoculation of simian immunodeficiency virus in macaques and found that low levels (hundreds to 10,000 copies per microgram tissue) were present 1 day after inoculation.[25] If we assume that the life span in the mucosal cavities are identical to those in plasma, then protective ARV concentrations would need to be continually present for up to 3 days after each exposure. Recently, the iPrEX, FemPreP, and VOICE studies have demonstrated that study volunteers have difficulty adhering to a once-daily dosing regimen, which compromises PrEP efficacy.[9,11,12] These studies demonstrated that daily prophylaxis against HIV infection (whether oral or topical) will be minimally effective if the functional half-life is too short, or the mucosal tissue penetration too low, to permit any reasonable degree of tissue protection.

TFV and FTC have reported plasma half-lives of 17 and 10 hours, respectively. However, the half-lives of their active intracellular metabolites (TFV-dp and FTC-tp) in peripheral blood mononuclear cells are much longer at approximately 144 and 38 hours, respectively.[68,69] In mucosal tissues, we have documented that TFV-dp and FTC-tp have half-lives of 2–6 days.[30] We have also noted that the high TFV and TFV-dp exposures achieved in colorectal tissue (×100 higher than vaginal or cervical tissue) after a single dose were advantageous to the iPrEX cohort of men who have sex with men who did not take daily TFV/FTC (Truvada) as instructed but rather intermittently and yet were still protected from HIV infection.[9,70]

Despite potential advantages in PrEP, a number of concerns are inherent with a long half-life compound: in particular, the development of resistance. Due to an increase in elimination time, there may be extended periods where drug concentrations are subtherapeutic in mucosal tissues. If HIV transmission occurs during this time, prolonged exposure to subtherapeutic drug concentrations has the potential to

select for viral resistance.[71] This is especially true for long-acting injectables, where subtherapeutic concentrations may persist for weeks rather than hours.[41] Obviously, allergic reactions might also be exacerbated with unremitting exposure to an allergen as was observed with penicillin and serum sickness.[72]

GENERATING EFFECTIVE DRUG TARGET CONCENTRATIONS AND DOSING STRATEGIES

To ensure adequate ARV drug concentrations within mucosal tissue, therapeutic tissue concentration targets must be defined. To date, target ARV tissue concentrations for HIV prevention have not been established, but if determined would represent an important advance in PrEP research. Once the appropriate models for defining these are identified, dosing strategies can be designed to achieve concentrations above this target while preventing long periods of subtherapeutic drug exposure and minimizing the risk of drug resistance.

The variable efficacy of topical and systemic PrEP observed in clinical trials is highly dependent on adherence but is also due to limited mucosal tissue penetration for the ARVs studied thus far. Numerous methods are currently under investigation to identify those drugs and concentrations that successfully prevent HIV infection on exposure to the virus. These include cellular studies, humanized mice and nonhuman primate models, the human mucosal tissue explant model, and retrospective analysis of clinical trial data.[73–75] The generation of "threshold" ARV concentrations above which HIV transmission is unlikely would provide a target around which dosing strategies could be generated for clinical studies.

PD measures of efficacy, such as time above minimum inhibitory concentration, have been successfully implemented as targets to guide antibiotic dosing. Similar measures of efficacy need to be developed for HIV chemoprophylaxis. The process is complex, requiring dose fractionation to determine the best efficacy target.[76] Unfortunately, establishing target concentrations in mucosal tissues is a complex process. For example, although bacterial infections are extracellular, and the concentration of antimicrobials in the interstitial fluid is pharmacodynamically active (and can be measured with dialysis techniques or in blister fluid), the intracellular nature of HIV requires an understanding of active intracellular concentrations.[76,77] Based on the physicochemical and biologic factors listed above, it is therefore more important to understand protein-unbound drug concentrations in tissues or cells rather than plasma. Furthermore, due to differences in rates of tissue distribution, single time point estimates of drug concentration may be inadequate to fully describe these PK–PD relationships, and multiple sampling to quantify area under the concentration-time curve is necessary. With newer technologies such as MALDI imaging, simultaneously exploring the PD of drug distribution with the PD of anti-HIV effect may be possible.

PK modeling and simulation approaches can identify optimal (preferably coitally independent) dosing strategies for clinical trial investigation, which surpass the target mucosal tissue concentrations for a predefined critical length of time.[78–80] Indeed, it would be unreasonable to identify a target concentration that was only achievable by dosing multiple times per day because even once daily dosing has been challenging for some clinical study subjects to adhere to. Adherence has been shown to correlate with efficacy in multiple studies and has been thoroughly reviewed by Koenig et al[10,81,82] The factors affecting drug adherence are complex, but the frequency and complexity of the dosing regimen in a healthy population is certainly a contributing factor.[83] Several novel formulations are currently in development and may be useful to overcome the adherence barrier.[84] For example, a long-acting parenteral ARV formulation or a slow-release vaginal ring formulation should increase the probability of achieving consistent target concentrations. It has yet to be determined if these drug delivery modalities will be acceptable to study volunteers and used more consistently than daily dosed products.

FUTURE DIRECTIONS IN PREVENTION PHARMACOLOGY

The necessity of an effective prophylactic regimen is highlighted by the inability of treatment regimens to completely prevent viral shedding in genital and rectal tissues. HIV RNA is easily detectable in the genital tissues and fluids of HIV-infected women and in the seminal fluid and rectal tissue of HIV-infected men and is highly correlated with plasma RNA levels.[85–87] Importantly, viral shedding is reduced by ART as much as 2 log units, demonstrating that therapy likely reduces the infectivity of HIV-infected individuals.[5,88] Reduced viral shedding can have profound clinical implications. The HPTN 052 study demonstrated that among serodiscordant couples, early initiation of ART in the infected partner was associated with a 96% reduction in HIV transmission compared with deferred initiation.[6] The large decrease in transmission observed in this study would not have been possible without decreased viral shedding. Unfortunately, both genital and rectal shedding have been shown to persist even in the setting of undetectable plasma viral RNA.[89–91] Although it is unknown whether the viral RNA found in these tissues represents viable and infectious HIV, it is a concerning finding nonetheless. The apparent inability of treatment regimens to eradicate HIV in the genital tract suggests that effective PrEP will require novel dosing strategies or dosage forms to prevent infection at these sites. What remains unclear is whether a disparity exists between effective ARV concentrations for prevention of acquisition versus prevention of transmission. Concentration–response relationships are well characterized for ARVs in plasma but have not been studied at the tissue level. It is possible that differences in immune cell populations between plasma and tissue have an effect on drug efficacy. For instance, higher levels of HIV targets in rectal tissue compared with blood may require higher concentrations of drug at this site to prevent infection.[28]

The in vitro and preclinical methods developed to understand ARV PKs and efficacy in mucosal tissue compartments have greatly improved our understanding of ARV pharmacology. However, these are not without limitations.

Nonhuman primate models of prevention are limited by the numbers available for study and have some clinically relevant pharmacological and virological distinctions. The humanized mouse model can use clinically relevant viruses, but challenges remain in characterizing pharmacological differences with smaller sampling capacity.[73] The human tissue explant model can use relevant tissue and viruses, but data on ARV disposition and PK-PD relationships are lacking because nonstandardized methods and approaches are used.[74] Target effective ARV concentrations can be generated from all these models, but a lack of robust and consistent data across all models currently limit our ability to determine how they should be used for informing drug development go/no go decisions and clinical trial design. As previously indicated, PK modeling is critical for generating dose–concentration relationships even in early drug development and should be used for PrEP.[92–94] Simulations run on a successful PK model will identify which dosing regimen best achieves target concentrations, once identified. This information will streamline trial development and increase the likelihood of success. The use of modeling and simulation for dosing regimen selection and clinical trial design is an important cost-effective technique, particularly in chemoprophylaxis studies whereby clinical dose-finding studies are unattainable due to patient risk and sample size requirements. Models can be generated which take into account what is already known about a drug and factor in various assumptions, such as intra- and interpatient variability, adherence, and dropout rates.[95,96] These strategies have been used in the past for faster market approval.[97] An additional benefit of modeling is that once generated, a model can be used not only to evaluate the drug for which it was developed but also for other drugs within that class as well.[95] This will be extremely beneficial for PrEP, with multiple candidates being available in similar therapeutic drug classes.

CONCLUSIONS

Successful HIV prevention strategies have been demonstrated in clinical trials, but implementation in the real world is a challenge. Use of ARV treatment as prevention has already become policy in the setting of discordant couples and may be expected to inform when ART is started and continued and which drugs are selected.[98,99] Curing HIV infection will require that ART stop replication in every compartment, a feat that has already proven a challenge. The mixed results of both topical and systemic PrEP trials demand preclinical and early phase strategies to improve the knowledge of efficacy targets and develop maximally effective dosing strategies that will be accepted by study participants and eventually the target market. The mucosal compartment plays an important role in transmission as the site of first exposure to HIV. Therefore, research aimed at understanding drug targets to prevent infection at this location or even distal to this location (eg, regional lymph nodes) is essential for developing successful next generation PrEP strategies. Determining the optimal time that drug should reside in mucosal tissues will also help define dosing strategies. Factors influencing tissue disposition are poorly understood but should be identified so that chemicals and formulations can be optimally designed for this purpose. Validating animal and ex vivo models against clinical outcomes in humans will determine their utility in making go/no go decisions and informing clinical trial design. Finally, PK/PD and clinical trial modeling and simulation have an important role to play in potentially informing the drug development process and increasing the probability of PrEP success in large clinical trials.

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Future of Phylogeny in HIV Prevention

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Abstract: The success of the HIV Prevention Trials Network 052 trial has led to revisions in HIV-1 treatment guidelines. Antiretroviral therapy may reduce the risk of HIV-1 transmissions at the population level. The design of successful treatment as prevention interventions will be predicated on a comprehensive understanding of the spatial, temporal, and biological dynamics of heterosexual men who have sex with men and intravenous drug user epidemics. Viral phylogenetics can capture the underlying structure of transmission networks based on the genetic interrelatedness of viral sequences and cluster networks that could not be otherwise identified. This article describes the phylogenetic expansion of the Montreal men who have sex with men epidemic over the last decade. High rates of coclustering of primary infections are associated with 1 infection leading to 13 onward transmissions. Phylogeny substantiates the role of primary and recent stage infection in transmission dynamics, underlying the importance of timely diagnosis and immediate antiretroviral therapy initiation to avert transmission cascades.

Key Words: HIV transmission, phylogenetics, treatment as prevention, primary infection

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INTRODUCTION

Over the past 30 years, HIV-1/AIDS has evolved into an increasingly heterogenous disease composed of multiple epidemics each influenced by a complex array of biological, behavioral, and cultural factors.[1–3] Highly active antiretroviral therapy (HAART), introduced in Western World settings in 1995, has reduced morbility and mortality, stabilizing subtype B men who have sex with men (MSM) and intravenous drug user (IDU) epidemics.[1–4] Heterosexual (HET) epidemics in Africa have diversified to several major subtypes (A, C, D, F, and G) and circulating recombinant (eg, CRF01_AE and CRF02_AG) forms.

Global initiatives to scale-up antiretroviral therapy (ART) over the last decade have led to 25%–50% reductions in infections in Africa and Asia despite weak health care systems.[5–9] The landmark HIV Prevention Trials Network (HPTN) 052 trial showed that earlier ART initiation (550–350 vs. <250 cells/μL) could result in a 96% reduction in the risk of transmission in HIV serodiscordant couples.[7] The success of HPTN 052, preexposure prophylaxis, and microbicide trials, and observational cohorts, has advanced the concept of "Treatment as Prevention" (TasP) to avert new infections at a population level.[7–18] Guidelines have been revised to reflect these goals, recommending universal annual testing and immediate ART initiation for all persons.[10,19,20]

There remains a debate on the generalizability, feasibility, and sustainability of TasP initiatives.[19–21] The resurgence of MSM epidemics and the rise in complex HET/IDU/MSM epidemics in Brazil, East Europe, China, and Southeast Asia emphasize the need for tailoring ART with other prevention interventions.

One of the central disputes surrounds the issue as to whether transmissions in early-stage infection, frequently undiagnosed, will compromise TasP strategies.[22–26] Acute/early-stage infection has been postulated to account for 5%–70% transmissions depending on epidemiologic and mathematical modeling assumptions.[27–30] Epidemiological analysis of MSM transmission dynamics is complicated by patterns of risk behavior, frequent anonymity of sexual partnerships, low risk of infection per coital act, and long infectivity periods.[27–33]

Phylogeny provides a unique framework to capture underlying structures of transmission networks that could not be otherwise identified.[23,24,34–40] Phylogenetics can identify the genetic interrelatedness of viruses in HIV-infected persons.[23,24,34–40] The "clustering" of sequences can infer transmission networks whereby dynamic HIV spread can be assessed on chronological and stage of infection time scales. Phylogenetic cluster analysis can be combined with epidemiological, demographic, and behavioral data to describe the underlying factors contributing to the growth of individual epidemics.[23,24,35,36,41,42]

This article will use phylogenetic findings based on the Montreal MSM cohort to illustrate the role of phylogeny in the design of prevention strategies. Transmission clustering is the driving force of 75% of the MSM epidemic wherein 1 infection can lead to 10 onward transmissions. These findings substantiate the necessity for targeted testing and immediate ART initiation to curb resurgent MSM epidemics.[23,24,34,36,37,43–45]

PHYLOGENETIC ANALYSIS OF MSM TRANSMISSION DYNAMICS

The Montreal MSM epidemic began in the early 1980s. By 2008, prevalence rates in sexually active MSM had risen to 15% despite low HIV incidence (0.62 per 100 person-years) with 75% of diagnosed persons receiving HAART.[46] The provincial genotyping began in 2001 and has sequence data sets on half of the diagnosed HIV population. Transmission dynamics have been assessed based on phylogenetic analysis of coclustering patterns of newly diagnosed primary infections (subtype B, male only) over the last decade.

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Genotyping requisitions completed by prescribing physicians distinguish primary HIV infection (PHI) (PHI < 6 months post seroconversion) populations from chronic drug-naive (PHI > 6 months) and treatment-experienced populations.[23,36] Viral transmission clustering has been based on robust criteria of high bootstrap values (>98%), short genetic distance (<1.5%), and similarity in signature mutational motifs.

In 2007, half of primary/early-stage infections (PHI < 6 months) were observed to cocluster with other primary infections although PHIs rarely coclustered with drug-naive and treated chronic populations (1% and 2.7%, respectively).[36] High rates of coclustering of primary stage cohorts are consistent with frequent retransmissions among individuals who are recently infected and often unaware of their status.[23,34,36–38,47–51]

Three phylogenetic patterns of PHI clustering have been observed: unique "dead-end" primary infections, small cluster (2–4 PHI), and large cluster (5–60 PHI) networks (Fig. 1). The growth of the MSM epidemic can be attributed to the stepwise increase in large clustered transmissions, rising from 16 clusters in 2005 (n = 140, 9 PHI/cluster) to 60 clusters in 2012 (n = 750, 13 PHI/cluster). The cumulative contribution of large clusters to the epidemic has risen from 30% of the epidemic in 2005 to 54% of the epidemic in 2012 (Fig. 1). Unique transmissions have declined from 42% of infections in 2005 to 26% of infections in 2012. Small clusters (2–4 PHI) accounted for the remaining 28% and 20% infections in 2005 and 2012, respectively.

The temporal growth of individual small and large clusters highlights the role of primary (<6 months) and early-stage infection in onward transmission dynamics. Individual small clusters expanded over median 4.75-month periods with a 1- to 11-month interquartile range (Fig. 2). The temporal expansion of large clusters occurred over a median 11-month period with an 8- to 21-month interquartile range (Fig. 2). These results are similar to findings in the United Kingdom, the Netherlands, and France.[23–25,34,36,37,52] Taken together, 25%–30% of transmissions in large clusters occur over a 6-month period and half of transmissions occur over a 14- to 17-month period (Fig. 2).

RELATIONSHIP TO OTHER STUDIES

Comparisons of MSM transmission dynamics have been confounded by the use of different inclusion criteria and methodologies. Molecular phylogeny studies have been assessed using acute/PHI (<6 months) and recent infection (<12–18 months) MSM cohorts and national genotyping programs that include chronic populations and different risk groups (MSM), hetersexual (HET), and intravenous drug users (IDU).[23,34,36–38] The criteria for designation of transmission "clustering" have varied in bootstrap values (>95%–98%) and genetic distance (<0.015–0.045).[34–36,51] The rates of coclustering of MSM early-stage infections have varied

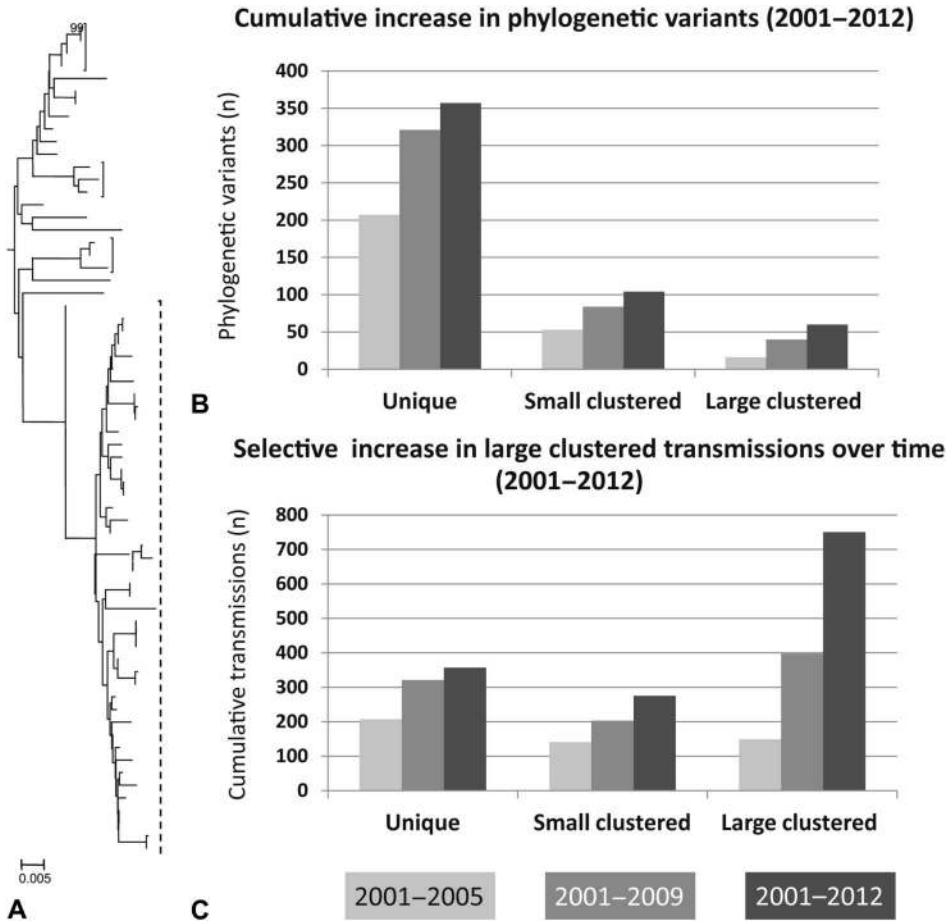

FIGURE 1. Phylogenetic inferences on the expansion of the MSM epidemic in Montreal (2002–2012). Phylogeny shows 3 patterns of clustering of primary infections. A, A short region in the maximum-likelihood tree shows 3 small clusters, 1 large cluster, and 13 unique transmissions. B, The cumulative increase of unique transmissions, small clusters, and large clusters over the 2001–2005, 2001–2009, and 2001–2012 periods. C, The cumulative number of infections in the 3 cluster groups depicts the rising role of large clustered transmissions representing 30%, 43%, and 54% of transmissions in 2005, 2009, and 2012, respectively.

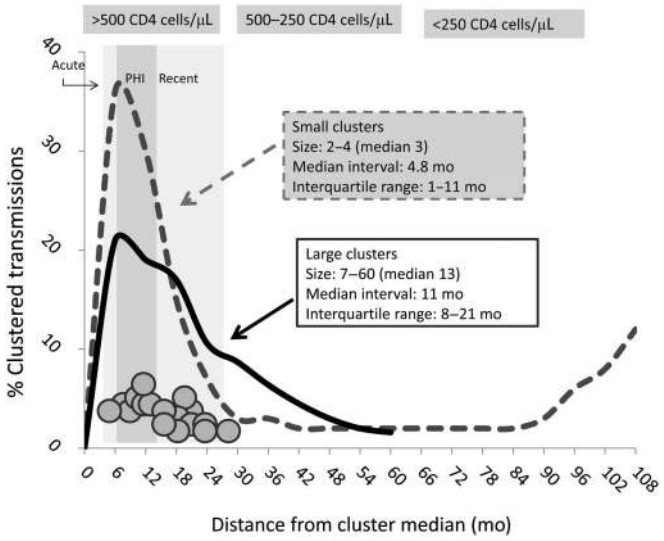

FIGURE 2. The temporal expansion of small and large clusters. A frequency histogram plot shows the temporal spread of primary infections associated with small and large clusters, estimated by calculating the branch length (distance in mo) of individual primary infections from the median dates of their respective clusters. The overall temporal interval was 4.75 months (1- to 11.5-month interquartile range) for small clusters and 11.0 months (3.5- to 25.5-month interquartile range) for large transmission chains.

from 17% to 70% in different regional settings, based on differences in prevalence rates, demographics, and depth of sampling.[23,34,36–38,47–51]

Clustering in most MSM cohorts was related to early-stage infection and high CD4 cell count.[36,44,51,53] The nationwide United Kingdom survey showed that 15%, 21%, and 15% of infections were interlinked to 1, 2–10, and >10 infections with high bootstrap values (>95%) and genetic distance below 4.5%.[24] The transmission interval occurred over median 17-month intervals with 20% of infections occurring over 6-month intervals, confirming the role of early infection in onward transmission.[24,34] The Brighton study showed 24% clustering of MSM infections with onward transmission related to recent infection, concomitant sexually transmitted disease, higher viral load, and unawareness of status; clustering was reduced by effective HAART.[54] The Swiss HIV cohort, a mixture of HET, MSM, and IDU epidemics, showed 42% overall clustering (bootstrap values > 98%).[55] Inclusion in clusters was associated with MSM transmission (52% clustering) and recent infection (<1 year post seroconversion, <0.5% ambiguity).[55]

PHYLOGENETIC INFERENCES AND PREVENTION STRATEGIES

Transmission clustering is clearly the driving force of MSM epidemics. The patterns of phylogenetic coclustering implicate a complex interplay of biological, behavioral, and interventional factors in the rise of large cluster transmission cascades. Although 75% of persons may ultimately receive HAART, there remains the precarious ART-free period of early-stage infection. The expansion of 60 clusters over 8- to 21-month intervals is inconsistent with a role of primary stage (<6 months), recent (1 year), and early stage (<24 months) in 25%, 50%, and 75% of onward transmissions. The duration of clusters indicate that onward transmission is not instantaneous but occurs over an extended period, involving the overlap of persons engaging in low- and high-risk behavior. Unawareness of status and poor testing habits are fueling onward transmission among treatment-naive individuals.

Although it has been postulated that early-stage infection will compromise TasP strategies, our findings argue that it is the delay in ART initiation that has contributed to the episodic development of new phylogenetic variants capable of overriding severe transmission bottlenecks. The failure to test, link to care, and initiation of early treatment is fueling the epidemic. This has had dangerous implications in the spread of drug resistance and the introduction of non–B subtypes.[56–60] Six large clusters in our cohorts (n = 60, n = 29, n = 21, n = 9, n = 6, n = 6) harbor G190A or K103N, conferring resistance to first-generation nonnucleoside reverse transcriptase inhibitors.[56] The crossover of non–B subtype HET and MSM epidemics has been rare, although 3 non–B subtype MSM clusters have arisen in Montreal, including CRF01_AE (n = 6) and CRF02_AG and 1 CRF_AB (n = 25) variants.[44,59]

Clearly, TasP interventions are needed to curb the development of drug-resistant subepidemics. High rates of transmitted drug resistance among drug-naive MSM and IDU populations have been related to clustering.[56,58,59,61,62] This is of concern in resource-poor settings, where stavudine, didanosine, and nevirapine-based regimens may facilitate development of K65R or nonnucleoside reverse transcriptase inhibitor resistance.[63,64] Pooled drug resistance testing may be needed to identify emergent resistance in resource-poor settings.[65]

The extended infectiousness of phylogenetic variants in large clusters may be related to multiple factors, including viral homogeneity, extended viremia, immature immune response, and risk behavior among those unaware of status.[66] Fundamental research is needed to characterize the genotypic and phenotypic signatures of unique vs. cluster viral variants.[67–72]

These findings argue that the success of TasP will be predicated on timely diagnosis.[73–75] SPOT, a Montreal community-based initiative, was begun in 2008, both as an intervention and a research study, to understand structural and attitudinal barriers to frequent testing and linkage to care. The site provides anonymous rapid testing and individualized motivational counseling. The SPOT findings point to the need to diversify services to reach priority populations who are less likely to use existing services. Half of the individuals seeking testing had not had an HIV test in the previous year. The overall rate of seropositivity was 2.1% (n = 36 of 1718) compared with the 0.14% seropositivity among MSM in the Montreal area (260,000 annual tests).

No persons at SPOT were identified with acute infections (n = 1682) using nucleic acid antigen testing, suggestive of a limited role of acute infection in transmission dynamics. Eight persons (25%) had primary infection (1–6 months since last test). Sequence-based assays, including nucleotide diversity, X4 *env* coreceptor usage, and next-generation sequencing and cluster association, were used to estimate recency of infection because half of newly diagnosed persons had not had a test in the previous year.[76–80] Overall,

80% of seropositive persons had early-stage infection (<1 year) and were potentially infectious. Linkage to care and immediate ART is a viable option to curb the MSM epidemic.

PHYLODYNAMICS OF HET EPIDEMICS

The global expansion of relatively few viral subtypes is indicative of clustering at a global level. Subtype C accounts for half of worldwide infections, distributed mostly in Ethiopia, central and southern Africa, Brazil, India, and China.[1,2,4] Subtypes A and CRF01_AE epidemics (17% of global infections) have spread from East Africa into Southeast Asia, China, and former Soviet Union nations through intravenous drug use (IDU), commercial sex work, and HET networks. Subtypes CRF02_AG and G (13% of global infections) have spread from West and North Africa into Europe.[1,2,4] Subtype D remains mainly localized to Uganda. Subtype F, endemic in Angola, has spread to South America and Romania through MSM, IDU, and/or blood product infections. Newly emerging mosaic recombinant forms are emerging through the crossover of the HET, MSM, and IDU epidemics in different regional settings.[81]

The fastest growing epidemics worldwide are the IDU epidemics in Eastern Europe where subtypes A1 and CRF03_AB are most prevalent.[82] In heavily populated regions, including India, China, and Southeast Asia, epidemics have rapidly shifted from predominant IDU epidemics to HET and MSM epidemics with selective expansion of subtype C, CRF07_BC, CRF08_BC, and CRF01_AE subtypes.[81,83,84]

There remains a paucity of phylogenetic studies on transmission dynamics of HET epidemics at the population level, although temporal cluster dynamics of the domestic subtype C epidemics in the United Kingdom seem to parallel those observed for the Montreal large cluster subset (Fig. 2).[38] Phylogenetic clusters are relatively small (2–4 infections) and represent approximately 20% of transmission events. It will become increasingly important to monitor increased clustering with the extended use of ART in resource-poor settings.

Phylogenetics remain an endpoint metric in prevention trials of serodiscordant couples. The HPTN 052, Partners in Prevention, Zambia, and Uganda prevention trials showed that 21%, 26.5%, 13%, and 8%, respectively, of identified transmissions among enrolled couples were phylogenetically unlinked.[16,17,28] Relationships outside partnerships may account for 10%–65% of HIV transmissions in sub-Saharan Africa.[85]

The HPTN 052 trial showed that the majority (83%) of linked transmission events involved the subtype C population in Africa, although this group represented only half of the recruited participants.[7,86] The differential transmissibility of variants may affect the success of different clinical trials. A Botswana study showed that 34% of participants had extended viremia (>100,000 copies/mL) for median periods of 318 days (282–459 days), although no subtype differences were observed in The Partners to Prevention trial.[87,88]

FUTURE DIRECTIONS FOR PHYLOGENY IN PREVENTION

Testing, treatment, and other prevention interventions require major public health commitments. Phylogenetics can delineate underlying trends in regional settings to establish evidence-informed decisions.[40] The integration of phylogenetic, epidemiological, clinical, and demographic data will be important in delineating the role of linkage to care, behavior, socioeconomic factors, and migration on transmission dynamics.[40] Although early-stage infection may dominate in regional settings with universal access to health care and ART coverage, significant contributions of chronic stage infections may be related to socioeconomic factors, including lower awareness of status and poor linkage to care and treatment.[89–94] Phylogenetic inferences of local epidemics may assist in the design of targeted prevention policies for distinct demographic groups, such as young adults and racial/ethnic minorities.[92,95,96]

The ultimate success of TasP will require improved strategies to target "Seek, Test, Link, Treat, and Retain" most-at-risk populations.[97,98] Control interventions to limit HIV transmission are predicated on early diagnosis.[27,29,30,33,54,99–101] Rapid testing programs are needed to target most-at-risk populations in a timely fashion. In Montreal, the SPOT site represents an MSM community-based initiative offering anonymous testing with peer group motivational counseling. The newly instituted clinic-based initiative, Actuel-sur-la-Rue, now provides rapid testing for HIV-1 and sexually transmitted diseases testing with linkage to care. The success of both testing initiatives in recruitment will be assessed in real time by phylogenetic analysis of cluster association and growth over time. Phylogeny will be used to assess the success of early treatment initiatives in reducing rates of clustering at a population level.

Sequence-based assays may be used to better monitor transmission dynamics and evaluate the impact of HIV prevention/intervention trials. The frequency of ambiguous calls in bulk sequencing can serve as a surrogate marker to distinguish recent infection (<0.44% ambiguity in the first year) from chronic infection (predictive value 98.7%).[77,79] Single-genome amplification–direct sequencing, next-generation sequencing, and high-resolution melting assays may be applied in dating the recency of infection and viral evolution in a highly accurate manner.[76,102–104]

The upcoming HPTN 071 (PopART) and Mochudi HIV-1 prevention project in Botswana will examine the benefit of early ART on population level HIV-1 incidence in Africa. Phylogenetic analyses may be of assistance in monitoring the success of intervention trials, vis-à-vis, (1) assessment of viral linkage in partnerships, (2) clustering of transmission events, and (3) determination of the proportion of new infections attributable to acute and chronic stage infection.

Future research will broaden our knowledge of underlying mechanisms, leading to the preferential selection and expansion of transmitted ancestral strains. Phylodynamic inferences will be important in the design, implementation, and assessment of candidate public health and therapeutic and behavioral interventions for the ultimate prevention of new HIV infections.

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Perspectives on HIV Prevention: Priorities for a New Era

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Abstract: The field of biomedical HIV prevention has undergone remarkable changes over the past 5 years. These advances have expanded conceptions of what should belong in the prevention "toolbox," particularly for infection via sexual exposure. New findings have also added complexity to previous theoretical discussions about plans for introduction and access to these interventions. Finally, scientific developments in biomedical prevention have activated a prevention-focused advocacy movement working at the grassroots, national, and global levels. This advocacy seeks to use existing tools to begin to end the AIDS epidemic while maintaining a prevention research agenda to develop additional tools to eventually end the epidemic.

Key Words: HIV prevention, AIDS vaccine, PrEP, voluntary medical male circumcision, ARV-based prevention, advocacy, microbicide

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OVERVIEW

The field of biomedical HIV prevention has undergone remarkable changes over the past 5 years. Clinical trials have demonstrated efficacy with interventions such as voluntary medical male circumcision (VMMC),[1–3] a topical vaginal microbicide,[4] daily oral preexposure prophylaxis (PrEP),[5–7] and the use of antiretroviral treatment (ART) to reduce the risk of HIV transmission in HIV-serodiscordant heterosexual exposure.[8] AIDS vaccine research has been complex and challenging, but it is at its most promising point in decades.[9]

These advances have expanded conceptions of what belongs in the prevention "toolbox," particularly for infection via sexual transmission. They have also added complexity to previous theoretical conversations about plans for introduction and access to these interventions. Finally, scientific developments in biomedical prevention have activated a prevention-focused advocacy movement working at the grassroots, national, and global levels. This advocacy, backed by epidemiological models,[10,11] seeks to use existing tools to begin to end the AIDS epidemic while maintaining a prevention research agenda focused on developing additional tools to eventually end the epidemic.

Together, all these advances have helped create a new environment. But these new prevention approaches are not created equal. They may be preferentially suited to certain populations or for certain periods of an individual's life. Furthermore, there are fundamental differences in outcomes. For example, ARV-based prevention using ART for HIV-positive people to reduce risk of transmission may also deliver a clinical benefit for those taking the medications,[12] whereas VMMC has primary population-level and individual-level benefits for HIV-negative men and secondary benefits for women by decreasing the number of HIV-positive men.[13] Daily oral tenofovir-based PrEP may be most appropriate in HIV-negative individuals during periods of high risk of HIV exposure. Epidemiological models predict different levels of impact of various strategies when used alone or in combination.[11] There are also major differences in the next steps warranted for each strategy: from follow-on trials to build on the modest positive results from the Thai RV144 AIDS vaccine trial[9] and CAPRISA 004 microbicide trial[4]; to demonstration projects for use of oral PrEP[14]; to ambitious "catch-up" campaigns targeting millions of adult men for VMMC[15]; and to trials that demonstrate the effectiveness of ART for prevention at community level.[16]

The challenge for prevention advocacy today is to fashion a coherent and focused agenda that sets and tracks priorities for strategies that can be implemented and scaled-up now; those that need further study and implementation in the near- and mid-term; and those that need to be developed through iterative investigations including basic science and clinical trials. Addressing this challenge is of the utmost importance; key priorities and specific barriers are addressed below.

DEFINING COMBINATION PREVENTION

Terms such as "high-impact prevention" and "combination prevention" are widely used by researchers, public health professionals, and by funding entities such as the US President's Emergency Response for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and normative agencies like UNAIDS.[17–19] Yet, there is a pervasive lack of clarity and specificity about definitions. Combination prevention must be tailored to specific contexts—but this reality should not justify maintaining nebulous definitions and avoiding difficult conversations about what strategies should be included or excluded from high-impact packages. Available modeling suggests that in epidemics driven by heterosexual transmission, core components of high-impact prevention would include expanded testing, VMMC, ART to maximize the benefits of treatment as prevention, and PMTCT programs.[11,20] The use of such interventions will need to be complemented by ongoing male and female condom promotion and safe syringe access, and prevention focused on key populations including gay men and other men who have sex with men, transgender women, sex workers, adolescents, people who inject drugs, and others. At a minimum, this language—and the development of implementation strategies—should be clear and

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consistent across PEPFAR, GFATM, and UNAIDS documentation and activities. There should, in addition, be the development of models that provide country programs with information regarding the relative impact of each strategy and match investments to the scale-up needs required to achieve coverage for maximum impact.

TREATMENT AS PREVENTION: NARROW GAPS IN THE TREATMENT CASCADE

The most widely embraced element of high-impact prevention is the expanded use of ART to reduce the risk of HIV transmission. This "treatment as prevention" strategy was confirmed in serodiscordant heterosexual couples in the HPTN 052 trial and is now subject to much debate, normative policy guidance, and further investigation to understand the potential population-level benefit on prevention. The potential multiple benefits of expanding access to ART for prevention will only be realized if there is a concerted effort to define and address gaps at every stage of what is now popularly known as the treatment cascade: the flow from testing HIV positive, to linkage to care, to initiation of ART to ongoing follow-up that results in effective viral suppression.[21] Research is needed on optimal solutions to address gaps in this cascade. In addition, these steps (and gaps) often exist in areas where drugs and services are available to those who wish to access it, but there are even larger gaps in the cascade where there is no or quite limited access to health care and where availability of drugs is inconsistent.[22] Clinical trials evaluating the effectiveness of ART for prevention at the population (or community) level are being developed, with some already in the field. In many other instances, implementation of key interventions, such as community-based service provision, can be effective if scaled up.[23]

COORDINATION ON VMMC

In the 5 years since the World Health Organization (WHO) and UNAIDS issued a recommendation for VMMC as a prevention tool in specific African countries,[24] there has been some progress in implementation, including development and rollout of high-efficiency service delivery models, increasing country-level ownership and effective campaigns that have met or exceeded targets in short time frames in some countries.[25] However, there is limited coordination and clarity about what is needed in terms of demand creation, advocacy, and communication coordination. Despite notable past and ongoing efforts to define effective strategies for demand creation, there are still major gaps in the understanding of how to efficiently promote VMMC for maximum uptake by the target population.[26] These demand creation efforts are distinct from advocacy, which is urgently needed to ensure that VMMC is recognized as a core component of combination prevention both by the civil society groups that are effectively organizing around scale-up of treatment as prevention and by public health leadership at national and global levels. As one example, the 2012 Declaration of Commitment issued by the International AIDS Society at the International AIDS Conference in Washington, DC, did not specifically mention VMMC as being integral to an effective global response.[27]

From a civil society perspective, it seems that increased coordination is needed on the part of normative agencies, major funders, and implementers of VMMC to segment and define issues related to demand creation, advocacy, and communication and prepare for decision making regarding newer circumcision methods such as nonsurgical devices.[28] Prevention advocates have a critical role to play in making the case for VMMC as part of a comprehensive global response. Advocacy groups emphasizing that treatment is prevention, but not yet incorporating VMMC as core to long-term success in reducing incidence, need to become allies in promoting a broader message that prevention is prevention—with ART and VMMC as 2 fundamental pillars.

GATHERING DATA TO SETTLE UNCERTAINTY ON PrEP

VMMC and treatment as prevention are interventions that have been validated in clinical trials and embraced as appropriate for implementation and scale-up. An equally important but far murkier area for civil society advocacy relates to strategies that have shown some proof of concept but that are yet to be confirmed in other studies or those for which demonstration projects are needed. The main example in the latter category is the area of PrEP and specifically the use of daily oral tenofovir-based PrEP. It has been nearly 2 years since data from 2 PrEP trials of the daily oral combination pill tenofovir/emtricitabine (TDF/FTC) in heterosexual men and women[6,7] were released to complement data from the iPrEx trial in gay men and transgender women[5]—all of which demonstrated efficacy of daily oral TDF/FTC. In that time period, the US Food and Drug Administration (FDA) approved daily oral TDF/FTC for HIV prevention in HIV-negative adults,[29] and the WHO issued guidance on PrEP demonstration projects targeting low-income and lower- to middle-income countries.[30] A range of other guidance documents and position statements have also been issued by various professional associations.[31–34] The situation is complicated by the results of 2 recent studies in young heterosexual women (FEM-PrEP and VOICE) that did not demonstrate efficacy of daily oral TDF/FTC for PrEP because of participant's lack of adherence to the study drug.[35,36] This has led to a lack of clarity about whether such an intervention is efficacious in such women and whether it can be effective in real-world settings, where young women may not take the drugs regularly as prescribed. A core set of pilot or demonstration projects needs to be implemented to evaluate the feasibility, acceptability, and potential effectiveness of this new strategy. It is acknowledged that the use of daily oral TDF/FTC for PrEP will have implementation challenges[37] because it requires regular HIV testing to ensure that those receiving PrEP are HIV negative and receive adherence support and monitoring for potential seroconversion, long-term side effects, and toxicities. But, it remains unclear how to weigh these challenges against the demonstrated efficacy of this intervention in specific populations that could benefit most from this new option, such as in serodiscordant couples, where the negative partner with pregnancy intentions may benefit from PrEP during those periods or where the

HIV-infected partner may not be able or willing to take ART. In the absence of a strategic suite of projects designed to answer this and other questions, there will remain unfortunate gaps in understanding of how to translate clinical trial efficacy into public health effectiveness.

To confront this dilemma, one line of argument emphasizes the potentially greater acceptability and potential efficacy of next-generation strategies such as a long-acting injectable antiretrovirals or an antiretroviral-containing vaginal ring used for PrEP. Another emphasizes the risk of setting aside a strategy that has been shown to work—particularly one that does not need to be used at the time of sex or with explicit partner consent. The reality is that both arguments have merit and that the debate cannot be settled without a suite of well-designed and well-coordinated demonstration projects answering critical questions. Public health agencies, and funders, should work with implementation partners to swiftly fill this gap—before the 1-year anniversary of FDA approval and WHO's publication of the rapid guidance on PrEP demonstration projects.

SUSTAINING SUPPORT FOR RESEARCH OVER THE LONG TERM

Perhaps, the greatest challenge facing biomedical prevention research advocacy is balancing activism around delivery of existing tools and developing new ones. It is important to capitalize on the momentum of the movement to begin to end AIDS and to use existing tools more efficiently and for maximum impact—while also sustaining support for operations research to understand how to integrate and deliver interventions effectively and efficiently and for ongoing trials of emerging strategies including PrEP, microbicides, and vaccines (see Fig. 1).

Why is there the need to develop new tools if the available tools today can begin to end the epidemic? How to sustain support for research when there are long timelines for follow-on trials: the next AIDS vaccine trial of a strategy related to the one evaluated in RV144 may not begin until 2016.[38] Other strategies, such as passive immunization using potent broadly neutralizing antibodies or a vaccine that induces similar immune defenses, could be even further off.[39] Cure research is also in relatively early conceptual stages, with long timelines for clinical evaluation of specific interventions.[40]

In the context of constrained resources for all aspects of the global AIDS response, it is a particular challenge to advocate for sustained investment that will not show dividends —in terms of new efficacious interventions—for many years. Yet, this sustained financial and community-level support for further biomedical prevention research is essential. Successful implementation of currently available strategies in high-impact combination packages could dramatically reduce rates of new HIV infections, morbidity and mortality.[41] Such action will also reduce the cost of the global AIDS response over the long term. But it will not eliminate new HIV infections or reduce the need for simpler highly effective prevention tools such as a vaccine that can sustain the gains made with more resource-intensive prevention packages.[11]

Prevention advocates are working to convey the message that implementing today's available prevention interventions provides a bridge to long-term additional solutions. In addition, advocates are working to define expectations about when various strategies—including improved ART, for example, a new drug or formulation that might only require quarterly or

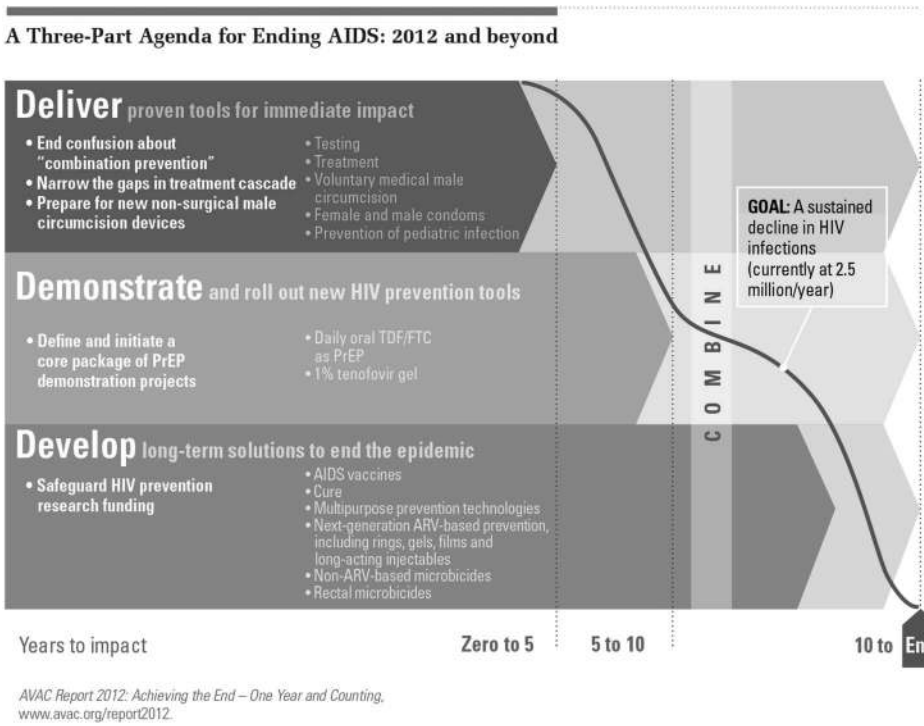

FIGURE 1. A three-part agenda for ending AIDS: A framework that incorporates short-, medium-, and long-term goals for ending the epidemic.

monthly dosing for effective viral control—might be available. This effort should be matched by trial sponsors and scientists developing interventions providing transparent communication of timelines and proactive engagement on trial design issues and by sustained research funding from governments and other donors.

In resource-limited countries, some of the most passionate advocacy regarding the "why invest in research" question has come from individuals and communities who have historically been underserved by existing prevention strategies. Paradoxically, or perhaps inevitably, communities that have received limited attention from HIV prevention programming and/or have been unable to use the strategies that have been offered to them have become passionate advocates for emerging technologies. For example, gay men and other men who have sex with men, along with transgender women, have become outspoken PrEP and rectal microbicide advocates—even as they affirm and eloquently describe the structural barriers of criminalizing legislation and rampant homophobia, along with the lack of basic prevention: lubricant, condoms, stigma-free clinics and service providers.[42]

Women, including women living with HIV, also remain mobilized around the need for sustained research. There is a vibrant history of grassroots awareness raising and advocacy for women-controlled HIV prevention focused primarily on female condoms and microbicides.[43] More recently, both PrEP and treatment as prevention have been configured as potentially female-controlled prevention strategies, with HIV-positive women stating the need for PrEP for both men and women.[44] As one participant at a community consultation said, "I want PrEP because I am HIV-positive, and I don't want the burden of prevention to be on me as an HIV-positive woman."[45]

The audacious vision of an end to the HIV epidemic is years from coming to fruition. But the creative tensions and frictions at play in the world of biomedical prevention research today are the growing pains of a movement seeking to ensure that this goal is reached.

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