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

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Abstract

The design of studies evaluating the safety and efficacy of interventions for HIV prevention is challenging in the US context, where there is low generalized prevalence. HIV incidence is sufficiently high in the at-risk US population of men who have sex with men that prevention trials using HIV infection end points are feasible. In other US populations at higher risk of HIV exposure, clinical trials could be conducted to provide definitive evidence regarding the level of coverage that can be achieved by strategies for implementation of interventions that already have been established to be effective.

Keywords

prevention trial; trial design; HIV seroincidence; implementation

PUBLIC HEALTH IMPACT AND HIV PREVENTION

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

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

Programs to prevent mother-to-child transmission of HIV illustrate a case that has achieved considerable impact: The population of pregnant women with HIV infection is identifiable (although not large in the United States); a variety of antiretroviral regimens in the mother and newborn infant have efficacies ranging from 33% to 98%[1–6]; and high coverage has been achieved using existing antenatal care facilities in the United States. In resource-limited countries, however, achieving high coverage remains the greatest impediment to reducing perinatal HIV transmission. In the United States, other HIV prevention interventions that target small or hard-to-reach populations face a fundamental public health

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challenge, especially if efficacy is modest. As a hypothetical example, suppose a behavioral intervention for stimulant-using men who have sex with men (MSM) achieves a 30% reduction in HIV transmission. If stimulant-using MSM produce a quarter of the 50% of new HIV infections attributed to MSM in the United States each year,[7] and 50% coverage of this target population is achieved, we would expect to avert only 2% of the new infections currently occurring annually in the United States (50% new infections in MSM × 25% occurring in stimulant using MSM × 50% coverage×30% effectiveness).

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

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

The first prevention design challenge is identifying a population at substantial HIV risk. The general population in the United States is at very low risk, with estimated 56,300 new infections in 2006 and annual incidence of 22 per 100,000.[8] Low event rates necessitate very large studies: In the low incidence setting of the Thai vaccine trial,[9] even though 16,402 volunteers were followed for 3 years, only 132 HIV infections occurred. Thus, research evaluating HIV prevention in the United States needs to be conducted in targeted populations having approximately 100-fold the level of HIV risk in the overall population. As noted in the 2008 CDC Surveillance Report and Table 1,[7] the US subpopulations accounting for the highest proportion of newly detected infections are MSM (55%), especially black and Hispanic MSM (32%); black and Hispanic women, primarily at heterosexual risk (20%); and injection drug users (13%). MSM, women, and injection drug users (IDUs) have each been enrolled in HIV trials in the United States. Table 2 summarizes seroincidence rates in targeted HIV risk cohorts since 1995. In MSM cohorts at high risk of HIV exposure, incidence has consistently been above 1.5 per 100 person-years. Identifying and enrolling such MSM has been shown to be feasible in multiple HIV prevention trials,[10–14] and conducting prevention research in this population continues to be viable in the United States.

Although black and Hispanic/Latina women in the United States have heightened HIV risk, the absolute rate of newly detected infections in minority women—56 per 100,000 for blacks and 13 per 100,000 for Hispanic women and Latinas—is low.[7] Cohorts of women at heterosexual risk, selected for elevated risk of HIV exposure through personal sexual behavior and risk behavior of their sexual partners, have found low HIV incidence (Table 2). A new strategy for identifying women at risk for HIV according to sociodemographic characteristics is being tested in an ongoing study in the HIV Prevention Trials Network (HPTN), the ISIS study (HPTN 064).[15] However, until we can identify characteristics that distinguish women at high risk for HIV (ie, 20 to 40 times the background rate) and until we can demonstrate the ability to recruit and retain such women in a trial, the feasibility of conducting studies of the efficacy of new interventions for reducing HIV risk in such US populations is limited.

Injection drug users in cities with high HIV prevalence are readily identifiable and have been successfully enrolled and retained in HIV seroincidence studies (Table 2). However, the number of new HIV/AIDS cases attributed to injection drug use in the United States has fallen steadily since 1993,[16] and recent US cohorts of IDUs with high risk of HIV exposure through needle use have had low HIV incidence, even in settings of high HIV prevalence (Table 2). Ironically, the study of prevention interventions for IDUs cannot proceed unless it is possible to enroll a large IDU population that remains at risk for HIV.

Heterosexual HIV risk can be identified through cohorts of HIV discordant couples. The National Institute of Mental Health's EBAN study enrolled 535 US African American discordant couples in stable relationships. But HIV incidence was low (Table 2), and the study took 4 years to accrue, making this population, too, challenging to utilize for studying HIV prevention interventions in the United States.

ELEMENT 2: EFFICACY TRIAL DESIGN IN A US TARGET POPULATION

The design of randomized clinical trials (RCT) to test prevention efficacy is intimately linked to the specifics of an intervention, its intended mechanism, and its target population. An intervention that targets HIV-uninfected individuals is most efficiently studied with an individually randomized design. These have been used in most HIV prevention trials, with intervention efficacies ranging from modest decreases (25% to 35%)[12,13,17,18] to substantial reductions (50% to 60%).[19–23] The resources required to evaluate HIV prevention interventions increase exponentially with decreased effectiveness and linearly with decreased incidence of HIV infection: In an individually randomized trial, to achieve 90% power with one-sided 2.5% false positive error rates for detecting anticipated effectiveness of 50%, 40%, and 30%, requires 88, 161, and 330 events, respectively. For a trial with (control arm) incidence of 2.0 per 100 person-years, achieving these targeted numbers of events requires planning for 5,866, 10,062, and 19,412 person-years of follow-up, respectively; a rate of 1.0 per 100 person years requires double the required person-years. Given these constraints, it would be feasible to conduct individually randomized trials in the United States with HIV incidence end points in MSM populations. But trials in other risk populations in the United States are not feasible until we are able to identify substantial subpopulations with HIV risk levels similar to the risk found in MSM cohorts.

Interventions that target HIV-infected persons to prevent sexual transmission to their HIV-uninfected partners require an HIV discordant couple or community randomized design. The resources required to enroll and follow a discordant couple cohort are close to double that of an individually randomized design, which largely offsets the potential design efficiency achieved from relatively high incidence. It should also be noted that a substantial fraction of the transmissions in the HIV-uninfected partner may occur outside the couple,[24] resulting in a dilution of effectiveness and consequently necessitating an increase in sample size. Finally, discordant-couple studies require stable, long-term partnerships—short-term partnerships compromise the study design, since HIV-uninfected partners who leave the partnership are no longer exposed to the intervention (effect dilution), and new partners identified post-randomization may be subject to referral bias. In sub-Saharan Africa, HIV-discordant couples have been rapidly accrued, and HIV seroincidence has remained sufficiently high to allow successful completion of prevention trials with HIV end points,[24,25] a situation that has not yet been replicated in stable discordant couples in the United States.[26] Discordant partner studies appear better suited to generalized epidemic settings, such as sub-Saharan Africa, where the high prevalence of stable discordant couples facilitates rapid accrual, rather than the United States, where the epidemic is concentrated in specific risk populations.

Structural interventions or community-wide delivery of prevention services mandate a community randomized trial (CRT) design to evaluate effectiveness.[27–29] However, CRTs are inevitably more costly than individually randomized trials. Several factors lead to increased study size for CRTs: partial coverage and/or adherence lead to effect dilution; correlation of outcomes within a community increases the variance of the estimated intervention effect; and the intervention mechanisms of action are often indirect. For example, in Project ACCEPT (HPTN 043), a CRT of mobile voluntary counseling and testing,[29] only a subset of the community (ie, those who receive voluntary counseling and

testing) experience the intervention, diluting the anticipated effectiveness. Also, the expected mechanism of action—decreasing risky behavior in HIV-infected individuals through awareness of their infection—results in indirect protection of HIV-uninfected individuals. Finally, underlying variation in the HIV epidemics across communities leads to a need for a large number of participating communities to detect an intervention effect.

Conducting HIV prevention CRTs in the United States presents unique difficulties. First, defining communities in the United States is challenging. The ideal community is closed: Ideally, to prevent contamination and/or dilution of the intervention effect, neither people nor the intervention would travel among communities during the trial. High mobility and efficient communication in the US adult population makes defining a community problematic and may result in rapid diffusion of the intervention between control and intervention communities. Second, low incidence in the general US population means that HIV incidence must be measured in a sentinel population, raising concerns about bias, retention, and generalizability. These factors are particularly relevant for a CRT HIV prevention trial, since the intervention effect may take several years to be fully realized,[30] thereby requiring the communities to remain largely intact (ie, stable, with constant background prevention efforts) for an extended period.

Given the low incidence in most US populations, surrogate end points such as self-reported behaviors, viral load, or acquisition of other sexually transmitted infections are often proposed as more feasible outcomes. Ideally, a surrogate end point lies in the causal pathway between the intervention and the end point (HIV incidence) and captures the entire intervention effect.[31] Unfortunately, none of these surrogates has proved reliable as a proxy for HIV incidence, and the use of imperfect surrogates can be misleading. A potentially useful role for surrogate end points in HIV research in the United States might be in the evaluation of strategies for implementation of known effective interventions.

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

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

To illustrate the opportunity for rigorous study of implementation strategies for prevention in the United States, we describe the Test, Link-to-Care Plus Treatment study (HPTN065: TLC-Plus[15]), which includes a component designed to assess the impact of financial incentives to achieve high linkage to care and high adherence to antiretroviral therapy for HIV-infected individuals in the United States. Definitive trials are underway to evaluate the efficacy of HIV testing and linkage to care for HIV prevention[29] and the efficacy of antiretroviral treatment for prevention of HIV transmission.[32] However, there is clear therapeutic benefit for the HIV-infected person in improved linkage to care and treatment.

TLC-Plus will compare the use of financial incentives to standard of care for linking newly diagnosed and out-of-care HIV-infected patients to a medical provider, using a cluster randomized trial design, with 40 HIV test facilities assigned at random to either strategy. For

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

CONCLUSIONS

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

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

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Table 1

Estimated New HIV Diagnoses in 2008, Proportion of Total New Diagnoses by Gender, Transmission Category, and Race in the 37 States with Confidential Name-Based Reporting (N = 41,087)[7]

	Transmission Category	All	Black	Hispanic	White
Male	MSM*	55%	22%	10%	21%
	IDU	6%	3%	1%	1%
	MSM+IDU	3%	1%	1%	1%
	Heterosexual	11%	8%	2%	1%
	Other	0%	0%	0%	0%
Total Male (N=30,754)		75%	35%	14%	24%
Female	IDU	4%	2%	1%	1%
	Heterosexual	21%	15%	3%	3%
	Other	0%	0%	0%	0%
Total Female (N=10,333)		25%	17%	3%	4%

*MSM denotes men who have sex with men; IDU, injection drug users.

Table 2

Cohorts Followed for HIV Seroincidence in the United States since 1995

	N	No. of HIV Seroconversion	Person Years	Seroincidence Rate	95% CI
Men Who Had Sex with Men					
VPS[14] (1995–1997)	3,257	72	4,645	1.55	1.23–1.95
EXPLORE[13](1999–2003)	4,295	259	12,240	2.12	1.9–2.4
VAX004[12](1998–2002)	5,095	362	13,407	2.70	2.43–2.99
STEP[33](2004–2007) *	1,058	44	1,225	3.59	2.61–4.82
Women at Heterosexual Risk					
Project ACHIEVE[10](1995–1997)	89	0	122	0	0.00–3.13
VPS[14](1995–1997)	511	8	705	1.13	0.57–2.27
VPS 2[34](1998–1999)	1,647	13	1,411	0.92	0.51–1.52
VAX004[12](1998–2002)	308	6	750	0.8	0.29–1.74
STEP[12](2004–2007) *	445	1	433	0.23	0.00–1.26
Discordant Couples					
EBAN[26](2003–2008)	535	5	535†	0.94	0.30–2.18
Intravenous Drug Users					
Baltimore IDU[35](1995–1998)					
Women	399	16	845	1.89	1.08–3.08
Men	1,447	42	2,308	1.82	1.31–2.46
VPS[14](1995–1997)					
Women	354	6	482	1.24	0.56–2.77
Men	770	4	1,053	0.38	0.14–1.01
New IDU (1997–1999)					
Women	109	2	46	4.32	0.72–13.3
HPTN037[36](2003–2006)					
Men	385	4	608	0.66	0.18–1.68

	N	No. of HIV Seroconversion	Person Years	Seroincidence Rate	95% CI
Women	181	4	276	1.45	0.39–3.71

*73% of the STEP cohort was enrolled in the United States; the balance comprises participants from the Caribbean, South America, and Australia.

†Person-years of follow-up not explicitly stated

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