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VIEWPOINTS

US Black Women and Human Immunodeficiency Virus Prevention: Time for New Approaches to Clinical Trials

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Black women bear the highest burden of human immunodeficiency virus (HIV) infection among US women. Tenofovir/emtricitabine HIV prevention trials among women in Africa have yielded varying results. Ideally, a randomized controlled trial (RCT) among US women would provide data for guidelines for US women's HIV preexposure prophylaxis use. However, even among US black women at high risk for HIV infection, sample size requirements for an RCT with HIV incidence as its outcome are prohibitively high. We propose to circumvent this large sample size requirement by evaluating relationships between HIV incidence and drug concentrations measured among participants in traditional phase 3 trials in high-incidence settings and then applying these observations to drug concentrations measured among at-risk individuals in lower-incidence settings, such as US black women. This strategy could strengthen the evidence base to enable black women to fully benefit from prevention research advances and decrease racial disparities in HIV rates.

Keywords. HIV prevention; clinical trial designs; black women and HIV prevention; HIV epidemiology and African Americans; HIV and racial disparities.

Randomized clinical trials (RCT) are the gold standard for establishing the causal effect of treatments in preventing disease. RCTs that use human immunodeficiency virus (HIV) seroconversion as the outcome have been especially critical in determining an intervention's efficacy in preventing HIV infection; one recent trial that influenced global policy was the demonstration that administration of antiretroviral therapy to the HIV-infected member of a serodiscordant couple reduces HIV transmission to the seronegative partner [1]. Recent trials have documented the efficacy of preexposure prophylaxis (PrEP) with antiretroviral agents in preventing HIV infection in specific high-risk groups and settings, such as men who have sex with men (MSM) or women and men in sub-Saharan Africa [2–7].

However, epidemiologic features of HIV infection present challenges to exclusive reliance on traditional RCTs for developing and implementing interventions to prevent HIV infection. Moreover, whereas RCTs provide valuable information concerning *efficacy*, their sometimes limited generalizability and uncertain *effectiveness* of the intervention when delivered in a nontrial setting can leave providers and public health practitioners with substantial gaps in the information needed to inform clinical and public health.

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RCTs that rely on HIV type 1 (HIV-1) seroconversion as an endpoint also require a substantial HIV incidence in the study population and/or very large numbers of participants to demonstrate efficacy with statistical significance. However, ending the HIV epidemic will require extension of research findings to vulnerable populations, such as US black women, whose incidence, although substantially greater than that of white women, is not high enough to support a feasible RCT.

This article outlines current issues associated with testing biomedical prevention products in populations whose HIV incidence is higher than in the general population but at a level where an RCT would require thousands of participants. We outline a strategy that incorporates use of drug concentrations and recognized epidemiologic methods to estimate intervention effects.

THE PROBLEM

Women constitute more than half of people living with HIV worldwide and about one-quarter of those in the United States [8]. Whereas women throughout the world share heterosexual transmission as the most common acquisition mode for HIV, the epidemiologic context in which women acquire infection differs by geography. The HIV epidemic among young women in southern Africa is relatively generalized [9], but among US women, poverty, discrimination, and the effects of social forces on sexual networks have disproportionately concentrated HIV among blacks and Latinas [8, 10]. The Centers for Disease Control and Prevention estimates that the annual rate of new HIV infections among US black women (50.8 per 100 000) is

more than an order of magnitude greater than among white women (3.4 per 100 000) [11]. RCTs of PrEP agents among women have typically been conducted in parts of Africa where the HIV incidence among women is exceptionally high (typically >3% annually), to yield enough new HIV cases to enable determination of product efficacy [2, 4, 5, 12]. The results of these studies have varied dramatically. For example, although tenofovir/emtricitabine (TDF/FTC) has prevented HIV infection among African women who took it consistently, it has failed to prevent infection in trials where adherence was low; efficacy estimates have ranged between 66% [4] and −4.4% [12].

Ideally, an RCT conducted among high-risk US women would provide the evidence base to support guidelines for US women's use of PrEP. But such a study likely is not feasible: Despite the nation's marked racial disparities in HIV rates, the absolute incidence of infection among US black women is substantially lower than among women in southern Africa. Although HIV rates are higher among the poor and in areas of the northeastern and southern United States, predicting which US black women will acquire infection remains difficult. A recent study enrolled US women at exceptionally high risk for HIV acquisition; their annual HIV incidence at 320 per 100 000 person-years (95% confidence interval, 140–740 per 100 000 person-years) was 5 times that of black women in the general US population [13]. However, even at that higher HIV incidence, a 5-year RCT (with 10% loss to follow-up) would require a total of 10 000 participants to demonstrate the 44% efficacy of TDF/FTC (compared to placebo) seen, for example, in the preexposure prophylaxis initiative (iPrEX) trial among MSM [3]. Studies comparing a new PrEP intervention with TDF/FTC as a control would need to be substantially larger, as the incidence in the TDF/FTC arm would be lower, even if TDF/FTC demonstrates only modest efficacy.

PREVIOUSLY PROPOSED STRATEGIES

Solutions for this fundamental problem of fielding trials in lower-incidence settings have been proposed, but none successfully ameliorates the need for exceedingly large sample sizes. One suggested approach, for example, is to use alternative outcomes as surrogates for HIV acquisition, such as transmission rates of other sexually transmitted infections (STIs). However, although other STIs could potentially substitute for HIV as an evaluation outcome when condoms or behavioral interventions for HIV prevention are tested, other STIs are not in the pathway between HIV infection and antiretroviral agents that only prevent HIV infection and are an inadequate HIV surrogate in this setting. In 2 large studies of PrEP efficacy, substantial reductions in HIV incidence were accompanied by no change in STI incidence [6, 14].

Mathematical models are valuable for estimating the population impact and effectiveness or cost of implementing interventions to prevent HIV infection (see, eg, [15–17]) but are unable to determine product efficacy in individual patients and depend on reliable estimates of efficacy. Another potential approach is to generalize results of studies conducted in other parts of the world, such as sub-Saharan Africa, to women in lower-incidence regions. However, currently available interventions for women, such as oral and topical PrEP, depend on high adherence, and dramatic variations in adherence among different African study populations have contributed to markedly different trial results and therefore substantially limit generalizability [4, 5, 12, 18]. Moreover, social and contextual factors may further impact adherence, making it even more difficult to generalize results across cultures. It may be possible to estimate efficacy by accounting for adherence in a per-protocol analysis [19]. Once the per-protocol effect is estimated, it can be mapped to the clinically relevant population of interest [20, 21]. However, this strategy requires that important differences between the trial and target populations that affect generalizability are measured and correctly modeled [20].

Unfortunately, all of these approaches require information that is typically unavailable, such as the causes of nonadherence that also affect the outcome, and the presence and extent of relationships between covariates and nonadherence.

OUR PROPOSAL

We propose to circumvent the low-incidence-setting requirement for large sample sizes by evaluating the relationship between HIV incidence and drug concentrations measured among participants in traditional phase 3 trials conducted in high-incidence settings, and then applying these observations to drug concentrations measured among individuals in lower-incidence settings. The steps would be as follows: First, conduct a phase 3 trial in a setting where the results are needed for the benefit of the population in which the study will be conducted and, as in similar past trials, HIV incidence is the outcome and incidence among women exceeds 3000 per 100 000 per year [2, 4, 5, 7, 12, 18]. Measure drug concentrations at multiple time points among all participants as well as effect modifiers of the relationship between drug concentration and incidence (such as anal sex, STI coinfection, types of sexual partnerships, known polymorphisms that affect drug metabolism). In addition to estimating the intent-to-treat effect, use the various levels of observed drug concentration to estimate the per-protocol treatment effects [19]. We assume that we have measured the set of variables that jointly determine drug concentrations and HIV risk. Second, in the lower-incidence setting, enroll participants from the at-risk population into an open-label trial with measurement of drug concentrations and the same effect modifiers as previously outlined in the phase 3 trial in the high-incidence setting. Standardize the per-protocol treatment effects from the phase 3 higher-incidence trial to this

lower-incidence setting, using established methods for generalizability [20, 22]. As before, we assume that we have measured and controlled for the relevant effect measure modifiers whose distribution differs in the 2 studies. Under these additional assumptions, one can compute the causal effect of the treatment on HIV infection in the lower incidence setting. While the trial in the lower-incidence setting would require considerably fewer participants than an RCT, it would need many more participants than the usual early-phase pharmacokinetic studies: sufficient participants would be required to yield a representative range of samples to estimate concentrations in the target population with adequate precision and to accurately measure variables that modify the effect. It is also critical that the enrollees be highly representative of the population at risk, in contrast to typical pharmacokinetic studies that may be conducted in low-risk populations.

DISCUSSION

We propose a strategy for estimating the efficacy of HIV prevention interventions in lower-incidence populations without conducting large RCTs in these populations. The method requires collection of drug concentration data, analyzing its relationship to efficacy, and then standardizing these results to drug concentrations observed in lower-incidence settings. These results will enable estimation of the efficacy of prevention in these settings and provide considerably more data to enable treatment and policy recommendations than is currently available.

This strategy relies on several assumptions. First, we assume there is a relationship between observed drug concentrations and efficacy. Second, we assume the relationship between drug concentration and efficacy is similar in the higher- and lower-incidence populations. Thus, potential effect modifiers, such as frequency and distribution of anal sex, must be considered and assessed. Initial determinations of the relationship between concentration and efficacy must be performed in a *population where HIV incidence is high enough to make such measurement feasible*; otherwise, the relationship cannot be determined.

In addition, we assume the observed drug concentrations accurately reflect typical concentrations that are consistently achieved. This assumption would be violated if, for example, a participant on daily oral medication only takes the drug before levels are measured but otherwise does not. Incident infection in this participant would be inaccurately associated with a high drug level. Additional use of electronic monitoring of access to medication bottles (eg, MEMSCap) could improve the performance of drug concentration data. Of note, directly observed therapy, such as long-acting injections, substantially reduces this problem. Long-acting agents may enable more accurate estimation of the relationship between drug concentration and HIV acquisition. Because clinicians will directly administer these drugs, pharmacokinetic assessments will allow more accurate estimation of drug concentrations at the time of HIV infection, which may be separated from the drug sampling time by weeks. Analyses of the relationship would not require the assumption that the patient has continued adherence at the same level as when the drug concentration was sampled, a likely assumption for evaluating adherence/acquisition relationships with short-acting oral therapy.

Limitations of the proposed strategy include the assumptions outlined above, as well as the logistical concerns and increased expense associated with measurement of drug concentrations. But these costs would be modest compared to those of a huge traditional RCT in a lower-incidence setting. Although use of existing specimens from completed or ongoing prevention trials could theoretically obviate the need for conducting a de novo phase 3 trial in a high-incidence setting, even when such specimens exist, they are generally not collected frequently enough and not accompanied by enough information (eg, timing of specimen relative to drug administration) to allow the proposed analysis. But addition of the appropriate samples and measurements to a planned efficacy study in a high-incidence setting would be an efficient way to reduce costs and gather the most relevant data.

Another limitation of our suggested approach is that the phase 3 trial still requires enrollment of a study population with a substantial HIV incidence. In addition, ethical considerations now require use of an effective drug in the control arm instead of a placebo. Use of an effective drug in the control arm would decrease the HIV incidence in this arm, which would reduce the likelihood of observing an effect of the experimental drug—and mandate a larger total sample size (or a noninferiority trial design) for determination of efficacy.

In summary, we propose a strategy that leverages the relationship between drug concentrations and efficacy obtained from phase 3 HIV incidence studies to derive estimates of efficacy and effectiveness in lower-incidence populations, such as US black women, among whom randomized phase 3 trials are likely to be prohibitively large. A next step to assess the performance of the method we propose includes Monte Carlo simulation using currently available pharmacokinetic, incidence, and other clinical data. Pursuit of this strategy will be important to further develop the evidence base to enable disenfranchised populations to benefit from the advances in prevention research and eliminate racial disparities in HIV infection rates.

Notes

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