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Preparing for the unexpected: The pivotal role of social and behavioral sciences in trials of biomedical HIV prevention interventions

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Abstract

A range of efficacies have been reported for biomedical HIV prevention interventions, including antiretroviral treatment, male circumcision, pre-exposure prophylaxis, microbicides and preventive vaccines. This range of efficacies likely 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 science, 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 science provides 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 socio-cultural context. Integration of social and behavioral science 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.

Keywords

biomedical interventions; HIV; populations; adherence; social science; behavioral science

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 pre-exposure 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

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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, two using an rgp120 subunit vaccine alone^{9,10}, one using a recombinant adenovirus type 5 (Ad5) vector vaccine (Step Study)¹¹, and one 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 three 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 likely 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 science 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 science in the context of HIV prevention trials

In the conduct of HIV prevention trials, social and behavioral science provides the framework and tools¹⁹ for investigating factors which 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 questions²⁰ 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, as well as likely dissemination and uptake of efficacious interventions. Utilizing a conceptual framework for social and behavior science in HIV prevention trial research¹⁹ can assist in the integration and concurrent conduct of biomedical and social and behavioral science research in the context of trials. Below we discuss three factors: potential study populations to include and retain in trials, quantifying HIV exposure and documenting intervention dose (Figure 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 participation³² 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 six US cities indicated that while >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 has been 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 employed 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 HIV³⁸. 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 pregnancy³⁹ 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 (e.g., testing for Prostate Specific Antigen) or biomarkers of spermatozoa confirm recent sexual activity (e.g., 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 utilized 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 was 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, i.e., 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% non-adherence estimates derived from blood tenofovir levels⁴⁵. 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 (e.g., electronic devices (Wisepill, MEMS), unannounced product counts, returned applicator testing) with biological markers (e.g. 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 measures⁴⁶ permitting targeted interventions for participants experiencing adherence lapses. At the same time, movement towards 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 as well as 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 (e.g., PrEP, self HIV testing) among enrolled study participants must be designed.

While 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 (e.g. 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 utilizing 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 three 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 science will be essential to meet forthcoming challenges.

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