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Barriers to Adolescents' Participation in HIV Biomedical Prevention Research

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Abstract

The inclusion of adolescents in HIV prevention clinical research has the potential to improve the current understanding of the safety and efficacy of biomedical prevention technologies in younger populations that are at increasing risk of HIV infection. However, there are significant individual, operational, and community-level barriers to engaging adolescents in clinical prevention trials. This paper identifies and addresses individual, operational, and community-level barriers to adolescents' participation in HIV biomedical prevention research. Barriers identified and addressed in the paper include: (1) insufficient understanding of clinic prevention research, (2) self-presentation bias, (3) issues surrounding parental consent, (4) access to clinical trials, (5) mistrust of research, and (6) stigma associated with participation in clinical trials. Examples of programs where adolescents have been successfully engaged in prevention research are highlighted and the lessons learned from these programs indicate that establishing collaborations with key stakeholders in the community are essential for conducting biomedical research with vulnerable populations, including adolescents. Given the importance of understanding young peoples' reactions to, acceptability, and utilization of new biomedical prevention technologies it is imperative that researchers acknowledge and address these barriers to enhance adolescents' participation and retention in HIV biomedical prevention research.

Keywords

adolescents; HIV prevention; clinical research

Introduction

The broader inclusion of adolescents in HIV prevention clinical research has the potential to improve the current understanding of the safety and efficacy of new biomedical prevention technologies such as microbicides, pre-exposure prophylaxis, and vaccines in younger populations that are at increasing risk of HIV infection. Moreover, including adolescents in clinical trials provides an opportunity to learn more about young people's understandings and reactions to these prevention products (e.g., vaginal microbicides), including the product's acceptability, utilization, and the degree of adherence to differential dosing regimens. Obtaining these data are critical given that adolescents seeking protection from HIV infection will invariably use products as soon as they are licensed for adult indication.

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There are significant regulatory and ethical challenges to enrolling youth into clinical prevention trials; these issues will be addressed in a separate paper in this supplement. However, there are other significant individual, operational, and community-level barriers to engaging adolescents in prevention trials. This paper will attempt to address some of these issues and highlight some examples where at-risk youth have been successfully been engaged in prevention research. While this is not an exhaustive review, we summarize findings related to key barriers that may impede adolescents' capacity and willingness to participate in HIV biomedical prevention trials.

Individual-level and Personal Barriers

One of the most significant barriers impeding adolescents' participation in clinical HIV prevention research may be their insufficient understanding of exactly what is meant by "clinical research". This lack of comprehension may be attributable, in large part, to a simple lack of awareness of what research is and how research is conducted.¹ The fact that many adults have difficulty in understanding research indicates that the issue is more than just one of simple comprehension. Indeed, understanding the complexities of research can be truly daunting for any individual who may participate in a clinical trial.

The complexities can be further exacerbated when the research in question involves randomizing participants to various experimental conditions. Much work has already been done in the context of large biomedical HIV prevention clinical trials to develop methods to explain clinical trial procedures – such as informed consent, randomization, intervention, and the use of placebos – to adult participants who might not be familiar with such concepts. While existing research indicates that adolescents are capable of providing assent for research participation at age fourteen², adolescents vary in terms of their intellectual maturation and cognitive capability to comprehend some complex trial regimens and protocols. Problems may arise when adolescents understand research well enough to want the potential benefits of participation (e.g., access to youth-friendly health services, monetary remuneration or other incentives for participating in the trial, etc.) but don't understand important details of participation (e.g., adherence to a study regimen) or potential risks of participation (e.g., side effects from an experimental medication).³

Even if adolescents understand the concept of clinical research well enough to want to participate in a trial, some young people may avoid participation in HIV prevention clinical trials because doing so may be interpreted as an admission of sexual activity, in general, or engaging in HIV-related risk behavior, specifically.⁴ For example, lesbian, gay, bisexual, or transgender (LGBT) youth who are not comfortable with or open about their sexual orientation may refuse trial participation because they do not want to be identifiable to others (e.g., peers, parents, or other adults) as different from anyone else. Similarly, adolescents who are sexually active when the rest of their peers are not may wish to keep that information secret to avoid being teased, stigmatized, or ostracized by peers or punished by parents. Because adolescents (compared to children) are more sensitive to acceptance and rejection by their peers,^{5,6} they may be more likely to avoid any behaviors that would inadvertently disclose sensitive personal information. Inadvertent disclosure may result in a variety of troubling social and psychological consequences, including engendering negative affect (e.g., feelings of low self-esteem, anxiety, and depression) and rejection or social ostracism from peers, family, and community members.⁷ Being "outed" to others may also put sexual minority youth at increased risk of experiencing physical and emotional abuse^{8, 9} and, potentially, suicidal ideation and substance abuse.¹⁰

Even if LGBT youth are open about their sexual identity, they may avoid HIV prevention research trials because participation might be perceived as an admission of risky sexual

behavior, which may be viewed by other LGBT peers as reckless or irresponsible given the impact that HIV/AIDS has already had on the gay community. Similarly, youth with mental health issues or those who use drugs and alcohol may also avoid trial participation because doing so may necessitate admitting that they have problems – such as mental illness or addiction -- that are also stigmatized by society. This type of self-presentation bias¹¹ may be present and entirely based on adolescents' perceptions of or assumptions about the social norms, even if the actual social norms are less stigmatizing towards these behaviors.

Familial and logistical barriers

The issue of parental consent

For research in the United States, and federally funded research conducted internationally, participation of adolescents under the age of majority in clinical trials usually requires permission from parents or guardians, as well as the informed “assent” of adolescents. While parental consent for adolescents is often necessary, obtaining parent consent represents a significant barrier to the participation of adolescents in HIV biomedical prevention research.

Parents may decline participation for their adolescent in HIV biomedical prevention research for diverse reasons. First, parents may not understand the research protocol (i.e., too complex), misconstrue the cost-benefit ratio from participating in the research (i.e., legalistic format that impedes understanding), or may question the veracity and intentions of the investigators (e.g., previous experience with the health care system or possess a negative attitude reflective of community norms towards medical research). A key concern is the potential for harm. Parents may misunderstand the potential for harm as a consequence of study participation. For example, they may overestimate the risk of adverse health events associated with participation in an HIV vaccine, preventative microbicides, or pre-exposure prophylaxis trial. Even when trial participation involves relatively innocuous treatments, such as behavioral interventions, parents may balk at granting consent. One reason, in addition to potential adverse biomedical consequences associated with trial participation, is that parents may believe that their child's participation in HIV prevention trials could inadvertently jeopardize their adolescent's confidentiality. Moreover, parents may believe that trial participation will stigmatize their adolescent as a “high risk” youth (e.g., sexually active, substance user, gay); such stigmatization could have serious and persistent repercussions for both the adolescent and the family, leading to the potential for community isolation and discrimination.

Accessing clinical trial sites

Clinical trials evaluating HIV biomedical prevention interventions impose inconvenience and uncertainty on all participants. This burden is exaggerated for adolescents. Often trial participation requires multiple research visits for social and behavioral assessments, blood and chemistry panels, and other trial procedures designed to ensure the integrity of the trial and the safety of the trial participant. This dual focus requires that adolescents maintain a strict treatment schedule, maintain research appointments, and be vigilant in reporting any perceived adverse events. In the U.S. and globally, adolescents have less access to resources that could promote their participation in HIV biomedical prevention trials.

A key limitation is logistical – lack of transportation to the research site to complete needed biomedical and psychosocial assessments. Even in the U.S., many youth will lack adequate transportation. Few will have access to automobiles. Usually investigators provide tokens for public transit (i.e., bus or train service). Though the provision of monetary resources by the trial is helpful, it does not entirely surmount the logistical barrier associated with poor access to the trial research site. Public transportation is often required, and in many cities public transportation is limited and, in some cities, non-existent. This may be especially true

in rural areas and for trials conducted in developing countries where there is a poor transportation infrastructure. Thus accessing the research site is problematic. One solution is to request parental assistance in overcoming logistical barriers. However, some adolescents may feel reticent about disclosing their trial participation; this is often the case when parental consent has not been needed/obtained. Thus, enhancing adolescents' access to the trial site is critical for encouraging their participation as well as adherence to trial research visits.

Lack of adherence to treatment protocols may be a barrier to recruiting adolescents into HIV biomedical prevention trials

While many of the aforementioned barriers focus on the adolescent, their parent, or community norms that work against participation in HIV biomedical prevention research, investigators can also pose a barrier to adolescent research participation. Often HIV biomedical prevention trials are not “adolescent-friendly”, meaning that they are primarily designed for adults and adolescents are recruited as an afterthought (often in numbers far too small to yield precise or valid statistical associations). In addition, trial investigators may perceive that adolescents' participation may be more problematic than beneficial, in fact, potentially jeopardizing the integrity of the trial and the validity of the resultant data. Of particular concern is adolescents' perceived lack of adherence to trial protocols.

Clinical trials are rigorously designed and include precisely calibrated treatment dosing and assessment protocols to maximize the data, thus yielding valid statistical associations between study conditions and trial outcomes. One threat to the internal validity of a trial is participant non-adherence. Unfortunately, adolescents are perceived as more likely to be non-adherent to trial protocols than adults, especially to complex trial regimens (both medication and treatment dosing schedules and assessment schedules). Understanding adolescents' non-adherence to trial protocols can be perplexing, illogical and frustrating to trial investigators with limited experience in adolescent medical care or research.

While there are diverse conceptualizations of non-adherence, we have elected to adapt and modify the taxonomy described by Greenstein and Siegal¹² and subsequently applied by Rianthavorn and Ettenger¹³ in their studies of non-adherence with immunosuppressive medications among young kidney transplant patients. In this taxonomy¹² there are at least three broad distinct patterns of non-adherence that can be observed in adolescent trial participants: accidental, invulnerable, and intentional (referred to by Greenstein and Siegal as “decisive non-adherence”). Accidental non-adherence represents simply forgetting to take medications as per trial dosing protocols. Adolescents may have a number of competing issues and lack organizational skills needed to follow a rigid medication or treatment routine. Thus, they often require assistance with organization and formation of habits that will improve adherence, particularly to medication or treatment that requires daily administration. Useful aids are available to reduce “forgetting” as a threat to adherence. These include dosette boxes (i.e., pill organizers) and cueing; helping adolescents to link treatment (e.g., use of Truvada for pre-exposure prophylaxis) to their daily routines may reduce accidental non-adherence. This would also apply to missed trial assessment visits.

A second category is comprised of adolescents who are termed “invulnerable non-compliers”. These adolescents may believe that not adhering to the trial medication or treatment schedule (i.e., missing doses of medication or taking medication off-schedule) will not result in adverse physiological effects. These adolescents may not notice an adverse effect after missing medication, and they therefore reason that omitting doses of the trial medication or treatment will not negatively impact their health. For example, in a trial of pre-exposure prophylaxis, while adolescents may not know to which trial arm they have been assigned (the intervention arm in which participants receive the active treatment or the

control arm in which participants receive a placebo), if they miss a dose and engage in risky sexual behavior without any ostensible negative sequelae (i.e., HIV infection), they may, for all intents and purposes discount their risk by adopting an optimistic bias¹⁴, assuming that they do not need to adhere to trial protocols since they feel themselves invulnerable to the effects of missed treatment or medication doses. Observing the lack of apparent, immediate impact of the missed doses, adolescents may assume that the investigators needlessly emphasized the importance of adherence to the trial's medication or treatment dosing schedule. This may have negative ramifications for the validity of the trial results and, moreover, could inadvertently enhance adolescents' behavioral disinhibition and, consequently, increase their HIV-associated risk behavior and exposure to HIV infection. This may be a particularly problematic issue in HIV biomedical prevention trials, as there is often not an immediate and ostensibly negative consequence associated with missing treatment or medication doses.

Intentional non-adherence reflects adolescents' active and independent decision to ignore trial guidelines for medication and treatment dosing. Similarly, they may choose to ignore the research visit schedule. While it may be perceived that adolescents are willfully ignoring trial protocols, there may be mitigating circumstances that affect adolescents' adherence. For example, many of the adolescents that would be recruited to HIV biomedical prevention trials may also experience depression, PTSD, substance use, or other trauma and adverse life experiences (i.e., abuse from parents or other adults) that could negatively affect their adherence to trial procedures (i.e., missing regularly scheduled research assessments and not adhering to medication and treatment dosing schedules).

While there is no panacea for identifying adolescents who are likely to be non-adherent, a run-in research design (i.e., a design that places all trial participants in single-blind placebo treatment for a short period of time prior to randomization to monitor trial-associated behaviors, placebo responses, etc.) may be useful in identifying those adolescents who are not adherent with assessment procedures or medication/treatment dosing schedules prior to randomization and initiation of the actual trial. These adolescents would, just like any adult participant, be excluded from participation based on the run-in results. While a run-in design limits generalizability of the trial findings, it may optimize internal validity of the results.

Community-level barriers

Barriers at the community-level also influence adolescents' decision to participate in HIV-related research. Although community-level barriers are not as thoroughly examined in adolescent populations, the few studies that assess or report community-level barriers for research participation among adolescents have observed similar types of barriers cited by adults.¹⁵⁻¹⁷ Specifically, community-level barriers include mistrust of research, lack of perceived advantage to participation in a clinical trial, and perceived stigma associated with trial participation.

Mistrust of research

Historically, among minority communities, particularly African American communities, nonparticipation in biomedical or clinical research has been associated with mistrust of medical research.^{18, 19} This mistrust stems from the medical research abuses documented in the Tuskegee syphilis study^{19, 20} among other examples. Moreover, with the emergence of HIV and HIV-related trials, suspicions among African American communities toward AIDS-related public health policy have also been cited as barriers to research participation by adults and adolescents.^{16, 21-23} Although few studies have been conducted exclusively among adolescents to examine how mistrust of research may influence their participation in HIV biomedical prevention research, the findings from the adult literature regarding mistrust

are particularly important given that parental consent is often needed for adolescents to participate in these research programs. Thus, even if adolescents do not have mistrust in HIV biomedical prevention research, their parents/guardians may.

Lack of perceived advantages to participation

Concerns regarding lack of benefits from participating in research were raised in studies conducted with adults, particularly in minority communities.^{18-19, 23} Specifically, African Americans believed that medical research was mostly beneficial to the investigators, and they felt that the African American community would be least likely to benefit from findings obtained through research because of racism or socioeconomic barriers (i.e., inability to pay for services).¹⁹ However, participants did express that, if there were clearly articulated benefits of participation for themselves or their families, they would be more willing to participate in research trials. Although this sentiment was not expressed in the limited adolescent literature, Zimet and colleagues found that when adolescents had higher perceived benefits to HIV vaccination they were more willing to accept a hypothetical HIV immunization.¹⁵ Again, as noted above, because adolescent participation in HIV biomedical prevention research often requires parental consent, understanding parental attitudes and the perceived barriers may be equally as important for adolescent participation.

Stigma associated with participation

Research has shown that both adults and adolescents have concerns regarding perceived stigma or perceived negative social consequences stemming from participation in HIV-related research.^{17, 23-25} Concerns regarding what family and friends would think if they knew about their participation in HIV-related research were expressed, as well as concerns regarding the social consequences of vaccine-induced seropositivity (i.e., the false positive HIV test that can occur as a result of participating in HIV vaccine trials).^{23, 26} Indeed, the stigma associated with testing positive for STDs, in general, has been identified in both adults and adolescents as a significant barrier to individuals seeking prompt and appropriate diagnosis and treatment for STDs.²⁷⁻²⁹ Specific to adolescents, those with higher levels of STD-related stigma were more likely to delay seeking STD services.²⁷ In two studies on adolescents' willingness to receive a hypothetical HIV vaccine, those perceiving oneself to not belong to a traditionally identified risk group, when simply being associated with such groups can be stigmatizing, were less willing to accept HIV vaccination.^{24, 25} Thus, perceived stigma or negative social consequences associated with being a participant in HIV-related research may be a significant barrier to adolescent participation in such research.

Lessons learned regarding the recruitment and retention of youth in HIV prevention trials

In light of the various challenges presented above, HIV prevention research efforts with youth require targeted efforts to ensure adequate participation of high-risk youth. Multiple trials have successfully engaged vulnerable youth. In this section we will review specific strategies and lessons learned from these trials.

Table 1 lists strategies by which clinical trials have attempted to improve recruitment and enrollment, retention, and treatment delivery. It must be noted that many of the strategies can be applied across all of these areas, and that some strategies work better with specific subpopulations. For example, in a study comparing recruitment approaches for gay and bisexual men³⁰, recruiters were more effective in reaching younger MSM (those under 30), whereas they were less effective in recruiting men with a history of injection drug use.

Collaborations with members of the community are essential for conducting research with vulnerable populations. There is a strong history in HIV-related research of working with Community Advisory Boards (CAB) and Youth Advisory Boards (YAB).³¹ CABs and YABs ensure that research design decisions are culturally relevant and address logistical and perceived psychosocial barriers to trial involvement.³⁰ Additionally, CABs and YABs can facilitate the integration of adolescent input into multiple aspects of a research trial, including providing suggestions for trial design, suggesting appropriate recruitment and retention strategies, and proposing strategies to aid adherence to trial procedures. In addition to advisory boards, community-academic partnerships are crucial when designing recruitment and retention strategies³²⁻³⁴, and they have been instrumental in recruiting and engaging high-risk youth into research protocols. These collaborations have the added benefit of being able to increase their respective research capacity by strengthening group infrastructures and operating procedures.³⁵

Conclusion

Despite the many challenges that investigators countenance when trying to engage young people in HIV research trials, prior efforts have demonstrated that it is possible to engage, enroll, and retain young people in clinical research trials. Prior examples of “lessons learned” from other research studies that have successfully engaged adolescent and young adult populations could be extremely beneficial to future HIV biomedical prevention research trials that aim to recruit young people as study participants. Engagement efforts such as the development and involvement of CABs and YABs for research trials could strengthen efforts to enroll young people, as well as strengthen community awareness and support of research.

There is little research examining how young people themselves manage and/or overcome the personal, familial, and logistical barriers they face when trying to participate in clinical research studies. More research is needed in this area. Results from such studies could be useful in informing researchers about how they might be better able to support youth who wish to participate in research, as well as how community education efforts might be able to reach out to families and social networks to demystify the research process, debunk negative myths and misconceptions held about research, and establish trust in communities that are most in need of HIV prevention strategies.

Given the magnitude of the epidemic and the tremendous burden of new infections among young people worldwide, the engagement of young people in HIV biomedical prevention research is essential. The personal, operational, and community-level barriers are challenging, but not impossible to overcome. In addition to the obvious benefit of more fully engaging young people in the broader HIV prevention effort, enrolling young people in biomedical prevention trials will accelerate the accumulation of youth-specific data that can be taken into consideration when successful products are put forward for regulatory approval and licensure. Optimally, the result will be the licensure of a product that young people will be able to safely use to protect themselves from HIV.

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Table 1

Strategies for Ensuring Adequate Representation of Youth in HIV Prevention Trials

Title	Strategies	Study Example
Recruitment and Enrollment	Time-space sampling	This technique was used to recruit 500 LGBT and non-LGBT youth at various venues to answer questions about their tobacco use and sexual identity. ³³
	Using recruiters that youth feel comfortable with	Fortune and colleagues ²⁹ elicited feedback from young African American adolescent males prior to initiating recruitment efforts in order to determine the best type of recruiter for the study.
	Relying on youth's social networks	HIV+ adolescents were willing to recruit members of their social network for a vaccine preparedness study. ³⁴ Other examples include respondent driven sampling (currently being tested in ATN trials).
	Internet-based recruitment strategies	This article presents an excellent overview of the advantages and limitations of using the internet in HIV prevention research. ³⁵
Retention	Maintaining contact with study participants in between appointments	Study coordinators in the REACH study spent a significant amount of time making phone calls, sending out mailings and acknowledging holidays with study participants, which helped yield a 94% retention rate over 4 years. ³⁶ Text messaging, emailing and contacts through social networking sites may be additional strategies to explore with youth as ways to stay in touch during the trial.
	Maintaining continuity in research staff	Efforts to keep study staff and have continuity for the participants so that they interact with the same person over the course of the trial was found to be beneficial in a study of African American male adolescents. ²⁹
	Youth friendly study personnel	Staff members that are reported as being caring, funny and easy to talk to have been documented as important for high risk youth. ^{36, 37}
Treatment Delivery	Developing engaging and developmentally appropriate interventions for youth	Adolescent Impact, a secondary prevention and adherence intervention for youth living with HIV developed the intervention in collaboration with youth to ensure that it was interactive and developmentally appropriate, which resulted in high retention rates. ³⁸