

Involving Vulnerable Populations of Youth in HIV Prevention Clinical Research

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Abstract: Adolescents continue to be at high risk for HIV infection, with young men who have sex with men and youth with drug abuse and/or mental health problems at particularly high risk. Multiple factors may interact to confer risk for these youth. Engaging vulnerable youth in HIV prevention research can present unique challenges in the areas of enrollment, retention, and trial adherence. Examples of successful engagement with vulnerable youth offer encouraging evidence for the feasibility of including these youth in clinical trials. Ethical challenges must be taken into consideration before embarking on biomedical HIV prevention studies with vulnerable youth, especially in the global context. Given the many individual and contextual factors that contribute to their high-risk status, it is essential that vulnerable youth populations be included in HIV prevention clinical research studies.

Key Words: adolescents, clinical research, HIV prevention, mental health, substance abuse

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Adolescents continue to be at high risk for HIV infection, with young men who have sex with men (YMSM) and young minority women at greatest risk within the United States.¹ Although youth as a whole represent a population at risk for HIV infection, there is a great deal of variability within this developmental period and within high-risk subgroups. In particular, the presence of mental health problems and drug abuse can increase an adolescent's risk for becoming HIV positive.^{2,3} Youth with multiple individual, community, and structural vulnerabilities (eg, sexual minority status, limited resources, homelessness, involvement with the criminal justice system) in conjunction with mental health and/or substance-use disorders can be particularly vulnerable to HIV infection.

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This article will review the factors contributing to increased risk for HIV infection among vulnerable youth, with a focus on youth in the United States with substance-use and mental health disorders and YMSM. We will discuss challenges associated with engaging vulnerable youth in trials and review HIV behavioral prevention trials that have successfully enrolled, retained, and intervened with high-risk youth. Ethical issues related to vulnerable youth and conducting research with vulnerable youth globally will be addressed. Finally, we will offer recommendations on the inclusion of vulnerable youth in future biomedical HIV prevention clinical trials.

HIGHLY VULNERABLE YOUTH

HIV Risk, Drug Abuse, and Mental Health

Adolescence is a unique period of development marked by rapid changes in brain, behavior, and social functioning. Behaviors that emerge during adolescence as part of normal development, such as an increased likelihood of risk taking and sensation seeking, and social/community factors such as an increase in the prominence of peer relationships and a reduction in parental involvement can put young people at risk for HIV/sexually transmitted infections (STIs). Structural factors (eg, laws/policies related to condom accessibility, access to sexual health services, poverty, and stigma) can also place adolescents at risk.⁴

Adolescence is also a time in which drug abuse and many psychiatric disorders first emerge.⁵ Drug and alcohol-use initiation occurs primarily during adolescence and use of alcohol and illicit drugs is not uncommon.⁶ Thirty percent of eighth graders, 53% of 10th graders, and 66% of 12th graders reported alcohol use in the past year in the Monitoring the Future study, an ongoing study of close to 50,000 students, in 400 schools in the United States. Illicit drug use during the past year was endorsed by 14.5%, 29.4%, and 36.5% of eighth, 10th, and 12th graders, respectively, although rates for illicit drugs other than marijuana were 7%, 12.2%, and 17%. Drugs associated with HIV risk were reported for all age groups, with more 12th graders reporting use of cocaine (3.4%), crack (1.3%), heroin with a needle (0.3%), and methamphetamine (1.2%) than their younger counterparts.⁶ It is important to note that these numbers reflect rates for in-school youth; rates of drug use among out of school youth are higher.⁷ Substance-use rates in homeless youth are significantly higher (up to 90%),⁸ including injection drug use (IDU; 44%).⁹ Similarly, rates of substance abuse are high for youth involved in the criminal justice system.¹⁰

Drug abuse can increase HIV transmission risk directly through IDU practices and via high-risk sexual behavior. Although the number of cases in the United States attributed to IDU has declined dramatically over the course of the epidemic, IDU is the third most frequently reported risk factor for HIV transmission after men reporting having sex with other men and high-risk heterosexual contact.¹ Almost 13% of new diagnoses from 2004 to 2007 in 34 states with HIV surveillance data were attributed to IDU. Despite massive prevention efforts, IDU practices associated with HIV transmission risk still occur.¹¹ In one study, 31.8% of IDUs reported sharing syringes and 33.4% reported sharing other injection equipment,¹ behaviors that can result in direct transmission of the virus. In addition, IDUs engage in sexual behaviors (eg, unprotected sex, exchanging sex for drugs or goods, and multiple sex partners) that increase risk for HIV. Younger IDUs can be at particular risk. HIV surveillance data from 2005 to 2006 in 23 cities found that the prevalence of unprotected vaginal sex among IDUs was highest (67%) among those aged 18–24 years.¹

Non-IDU is also associated with risk for HIV. Stimulants including methamphetamine and crack cocaine are related to high-risk sexual behavior among men who have sex with men.^{12,13} Alcohol and marijuana use are also associated with HIV risk behaviors.¹⁴ Abuse of nitrate inhalants (poppers) among YMSM has also been associated with risk for HIV.¹⁵ It is important to note that not only youth with substance-use disorders are at risk. Use of alcohol and/or illicit drugs can compromise decision-making capabilities leading to risky sexual behaviors associated with HIV for occasional or recreational users and those with substance-use disorders.

Youth with mental health disorders (depression, mania, and psychosis) have been shown to be at higher risk for HIV/STIs.^{10,16–18} Given that the prevalence of psychiatric disorders among adolescents within the United States is estimated to be between 3% and 18%,¹⁹ this represents a considerable number of youth who may be engaging in high-risk behaviors placing themselves at risk for HIV/STIs. For example, youth who have been hospitalized for psychiatric reasons are twice as likely to be sexually active, twice as likely to report unprotected sex, and twice as likely to use injection drugs when compared with school-based adolescents.¹⁶ Frequent self cutters^{20,21} and youth with externalizing disorders, such as attention deficit hyperactivity disorder and conduct disorder,^{22,23} have also been shown to be at greater risk for HIV infection. A number of mechanisms have been examined to explain this increased risk, including poor impulse control, affect dysregulation, and higher rates of unprotected sex and substance use.²⁴

Youth experiencing subclinical mental health symptoms (depressive symptoms, low self-esteem, sexual sensation seekers, and impulsive decision makers) may also exhibit higher rates of sexual risk behavior.^{25–28} For example, girls with moderate levels of depressive symptomatology reported higher rates of sexual risk behavior, whereas no relationship was found between those with high depressive symptom levels and sexual risk.²⁷ Brown and colleagues²⁵ also noted that depressive symptoms predicted later inconsistent condom use. However, it should be noted that not all affective states are

associated with risky sexual behavior. Higher levels of anxiety have been found to predict lower sexual initiation rates²⁹ among youth. Among adolescents with a psychiatric disorder, self efficacy for condom use during periods of distress was associated with safer sexual behavior.³⁰

It is important to note that the co-occurrence of substance-use disorders and mental health disorders is common.³¹ Among adolescents with substance-use disorders, between 61% and 88% are estimated to have a comorbid psychiatric disorder.³² Youth with comorbid disorders have been shown to have higher rates of treatment dropout and relapse³³ and may evidence higher rates of sexual risk behavior.¹⁰

Youth with multiple individual, social/community, and structural vulnerabilities (eg, homelessness and street involvement, poverty, sexual and/or ethnic minority status, involvement with the criminal justice system, exchanging sex for drugs or goods, social stigmatization) can be particularly vulnerable to HIV infection, especially those youth with mental health and/or substance-use disorders.^{4,34–36} For example, homeless youth have been documented to have high rates of STIs (16.7%)³⁷ and HIV (1.4%).³⁸ Juvenile detainees with substance-use disorders also report higher rates of HIV risk behaviors.¹⁰ Youth with a history of childhood physical, emotional, and sexual abuse are more likely to engage in risky sexual behavior and be at risk for STIs, substance abuse, and mental health disorders.^{39–45} It has been proposed that individuals with a history of childhood sexual abuse lack the ability to judge the level of risk in a situation, reporting higher perceived benefits and lower perceived risks when engaging in high-risk behaviors.⁴⁶

HIV Risk and YMSM

A subpopulation of youth most vulnerable to HIV is YMSM, regardless of their sexual orientation, and young transgender persons both in the United States and in low-income and middle-income countries.^{47,48} Men who have sex with men who use drugs of abuse including stimulants (methamphetamine, cocaine), poppers, and/or erectile dysfunction drugs are especially at risk.^{49–51}

Although the recognition of nonheterosexual sexual orientations as an element of normal human variation among adults is slowly finding acceptance among health professionals and the general public, among young people's sexual behavior—and in particular, same-sex sexual behavior—is still a stigmatized topic. Same-sex experiences are often tolerated as part of a process of experimentation toward the development of presumably “normal” heterosexual behavior.⁵² The perception of such double stigma (ie, the one associated with any sexual activity and especially with nonheterosexual sexual activity) can motivate feelings of guilt and low self esteem among young YMSM, some of whom are in the process of developing a gay identity. Guilt can lead to closeted sexual experimentation and heightened sexual risk. In other cases, families learn about their gay children and react with violence, forcing them to change or to get psychiatric care. The verbal and physical abuse by peers and family members can lead to high levels of chronic stress among this population.⁵³ As a result, some adolescents are forced out of their homes or run away and become involved in drug use, sex exchange, or sex

work.^{54,55} Engagement in survival sex (exchanging sex for food, shelter, drugs, etc.) has been found to be fairly common among homeless or street youth globally^{56–58}, is not always voluntary,⁵⁹ and has been identified as the primary risk factor for HCV acquisition among homeless youth.⁵⁷

Young transgender persons represent an especially vulnerable group for a number of poor health outcomes, including HIV infection. HIV prevalence rates have been documented to be extremely high among male-to-female transgender youth in the United States (19%–22%).^{60,61} Youth report discrimination at school that leads to high dropout rates and difficulties finding work.^{60,62} These circumstances are thought to contribute to the high rates of engagement in sex work that have been found in this population (59%),⁶⁰ which has been associated with homelessness and use of street drugs.⁶¹ Transgender youth in low-income and middle-income countries also find themselves in difficult situations. For example, in the slums of Iquitos, in the Peruvian Amazonia, transgender adolescents as young as 12 years old feel rejected by their families and leave their homes to start a life in street youth communities as sex workers.⁶³

Contextual Factors

Youth vulnerable to HIV infection are a heterogeneous group who may manifest different risk behavior profiles depending on contextual factors. Contextual factors refer to characteristics in an individual's environment that may influence their behavior and outcomes (eg, HIV prevalence rates, economic opportunities, homophobia within the community). HIV risk profiles may vary based on environmental context (eg, residing in rural, urban, or suburban locations; living with family, on the streets, in prison; living in Northern or Southern countries; living in countries with a generalized or concentrated HIV epidemic) and structural factors (eg, access to sexual health care, laws, stigmatization). These contextual factors interact with individual factors (eg, ethnicity, gender, age, sexual minority status, history of abuse or trauma, neurobiology, substance use, mental health).⁶⁴ Contextual factors play a role in the risk behavior profiles of youth with psychiatric and substance-use disorders. Factors such as hostile parental control and negative peer influence⁶⁵ have been associated with sexual risk behavior, whereas the presence of parental monitoring⁶⁶ and discussions between parents and adolescents regarding condom use are protective.⁶⁷ Contextual factors (eg, community resources for YMSM, social stigma) may also be related to risk for YMSM.⁴ Because vulnerable youth experience multiple contextual factors, interventions that address multiple levels of risk may be most beneficial.⁶⁸

ENGAGING VULNERABLE YOUTH IN HIV PREVENTION CLINICAL TRIALS: RESEARCH CHALLENGES

Including vulnerable youth in research presents a number of challenges. In particular, mental health symptoms and substance use can affect enrollment, retention, and adherence among youth in clinical trials. For these reasons, some studies include exclusionary criteria whereby adolescents with

a history of a major psychiatric disorder or substance-abuse disorder are ineligible to participate.

Vulnerable youth, especially minority youth, have expressed distrust in researchers and research institutions,^{69,70} resulting in lower rates of recruitment. Depression,⁷¹ marijuana use,⁷² and methamphetamine use⁷³ have all been shown to result in lower rates of adherence to HIV medications. Depression, intimate partner violence, and low self esteem are associated with dropping out of an HIV prevention intervention among Latinas from a low-income community.⁷⁴ Obtaining consent from parents or guardians can be another barrier to enrolling vulnerable youth in clinical trials. Youth may be reluctant to ask for parent's permission due to concerns that parents or caregivers will learn about their same sex sexual behavior or their substance use or mental health disorders. Homeless or street involved youth may be estranged from their families and wary of research that asks for parental permission.

Retaining highly vulnerable youth in trials can also be challenging. Logistical impediments (eg, work schedules, lack of transportation, language barriers, and access to medical treatment) can impede continued engagement with individuals who remain at high risk.^{75–77} In a study on differential attrition in under-represented minorities participating in drug-abuse treatment, youth were particularly vulnerable to study drop out.⁷⁸ Mobile populations, for example, homeless and street-involved youth, can be highly transient and require a number of strategies to track successfully.

Research with YMSM may require special consideration especially for youth from families or communities that stigmatize same-sex sexual behavior. Special strategies may need to be implemented to recruit YMSM. Although schools often serve as an appropriate location for recruiting youth, other venues may need to be included when targeting YMSM, such as community events or local lesbian, gay, bisexual and transgender youth centers.⁷⁹ Recruitment of youth who identify as heterosexual but engage in same-sex sexual behavior can also present challenges. Different fliers and other promotional materials for a study may need to be developed for youth who identify as gay and bisexual and those who identify as questioning or heterosexual. For youth requiring parental consent, consent forms need to present accurate information about the study although ensuring privacy for YMSM who do not identify as gay or who have not disclosed their same-sex behavior to their families. Young gay men may also require informed consent procedures that increase their knowledge about clinical trial concepts such as partial efficacy and placebos.⁷⁹

In regard to biomedical prevention trials for HIV, vulnerable youth with cognitive limitations associated with substance abuse and mental health disorders may have difficulty understanding the nuances of a clinical trial, such as the concept of partial efficacy, or adhering to a complicated treatment protocol. Recent biomedical HIV prevention trials among adults have highlighted the importance of adherence to the study product and protocol.⁸⁰ Given that adherence to HIV medications has been shown to be worse among adolescents than adults⁸¹ and among substance abusers,⁸² adherence may present a particular challenge in biomedical HIV prevention trials

among vulnerable youth. Efforts therefore need to be made from the very beginning of a trial to appropriately measure and support adherence in biomedical clinical trials for youth. Youth may also have fears associated with being tested for HIV that may have to be addressed to encourage participation.

Last, for youth enrolled in HIV biomedical prevention trials and who are prescribed study drug, issues regarding drug–drug interactions need to be taken into consideration for those youth taking psychotropic medication or medication to treat their substance abuse disorder (eg, bupropion or methadone) or who use substances of abuse. For example, serotonin syndrome has been reported in HIV-infected individuals taking antiretroviral and antidepressant therapies.⁸³ For persons on methadone maintenance therapy, antiretroviral therapy may lessen the effects of methadone, whereas opioids may compromise the metabolism of HAART.⁸⁴ Careful monitoring of all medications and drugs of abuse is recommended.

ENGAGING VULNERABLE YOUTH IN HIV PREVENTION INTERVENTION TRIALS: RESEARCH SUCCESSES

A number of HIV behavioral prevention trials have successfully recruited, enrolled, retained, and intervened with vulnerable youth.^{67,85–87} For example, within the Reaching for Excellence in Adolescent Care and Health (REACH) study, an observational study of both HIV-positive and HIV-negative youth, including young men who had sex with men, 87% of youth were retained over the course of 4 years.⁸⁷ The EXPLORE study (<http://www.explorestudy.org>), an HIV prevention intervention for men who had sex with men included young men aged 16–25. Results indicate YMSM had greater mental health difficulties, substance abuse, and sexual risk behaviors than their older counterparts.⁸⁸ Other trials—such as Familias Unidas⁸⁶ and Project Strengthening Today's Youth Life Experience (STYLE) (http://www.lifespan.org/services/child_health/style/)⁶⁷—have successfully enrolled youth with psychiatric disorders into HIV prevention trials. Project STYLE effectively recruited adolescents in mental health treatment from outpatient mental health settings and at the time of discharge from inpatient psychiatric units. Of all the adolescents who were screened for participation, 94% were enrolled.⁶⁷ As part of drug abuse and delinquency treatment with substance abusing juvenile offenders, a family-based HIV/STD risk reduction module was implemented as part of the National Institute on Drug Abuse Criminal Justice Drug Abuse Treatment Studies. Preliminary findings of reductions in sexual risk and drug-use behaviors are promising.⁸⁰ Recently, the internet has emerged as a useful tool to recruiting men who have sex with men,⁸⁹ given the high rates of internet use among this population for information on sexual health and to find sexual partners.⁹⁰ Last, a number of investigators have developed effective strategies for retaining homeless youth in HIV-related clinical trials.^{54,91–93} Working with homeless individuals requires the implementation of a number of strategies to effectively follow these highly mobile youth. These efforts show that recruitment and retention of vulnerable youth into clinical trials is complex, yet feasible.

ETHICAL ISSUES

Given the unique social, behavioral, and clinical specificities of vulnerable youth populations, findings from trials on other groups of young people may not necessarily generalize to vulnerable youth. Because biomedical prevention strategies, if effective and feasible, will be particularly valuable to those youth most at risk for HIV, the involvement of vulnerable youth in biomedical prevention trials is urgently needed.

Research on vulnerable populations has always generated concern, mainly because vulnerable individuals are assumed to have restricted autonomy, that is, they might not be able to assess the risks of participating in research or provide informed consent under the same considerations as persons not regarded as vulnerable. Typical examples include the added benefit of participant reimbursements among poor people or the limited perceived ability to decline participation among patients or incarcerated people. The principle of autonomy and respect for people is, together with beneficence and justice, one of the key criteria under which the ethical soundness of research endeavors is judged.^{94,95}

The main argument for involving vulnerable youth is that findings from biomedical prevention trials in other youth populations may not generalize and, thus, specific trials tailored to the unique needs of vulnerable youth are warranted. Recommendations for the protection of human subjects when vulnerable populations are involved in research have already been developed,^{96–99} and those should be applied when appropriate. Institutional Review Boards responsible for evaluating research with vulnerable youth can incorporate members of vulnerable populations to guarantee a better-informed perspective. Community advisory boards involving these populations are also recognized as a good practice that should be reinforced and further improved.^{100,101}

Finally, although international research issues are not the main focus of this article, the future implementation of multicountry studies involving vulnerable youth from low-income and middle-income countries would require preliminary research on the ethical and regulatory challenges posed by such endeavors. These issues need to be addressed with local authorities and community representatives.

VULNERABLE YOUTH: GLOBAL PERSPECTIVES

Although many issues concerning vulnerable youth in the United States raised here are arguably valid globally, a comprehensive approach to vulnerable youth around the world, including low-income and middle-income countries, is beyond the scope of this article. Reasons for this are numerous as follows: social contexts generating youth vulnerability are not the same internationally or even within single nations (including conflict and religion); sexual risks resulting from social vulnerability are also diverse and the legal status of young people and the degree of autonomy and social protection they receive.¹⁰² Evidence of the link between social vulnerability and sexual risk is rather limited in most low-income and middle-income countries, although several documents commissioned by the United Nations organizations have begun to provide evidence of these links.^{103,104} There is also lack of clarity regarding the extent to which theoretical

frameworks conceptualizing risk reduction in higher income contexts are valid when significant economic, cultural, and legal differences come into play in low-income and middle-income countries.

For some populations of vulnerable youth, more in-depth studies in low-income and middle-income countries are warranted before international participation of vulnerable youth in biomedical HIV prevention trials is considered. Special consideration will be needed to address the ethical issues raised by such potential participation, particularly in light of diverse legal frameworks regarding youth and autonomy.

CONCLUSIONS

Given the increased vulnerability to HIV conferred by substance use and mental health problems, and the increased risk that YMSM face, it is important to consider including these youth when conducting biomedical HIV prevention trials. Although there are challenges to enrolling, retaining, and intervening with vulnerable youth, several successful behavioral HIV prevention trials have been conducted that provide guidance for the successful inclusion of vulnerable youth in future trials. Vulnerable youth can be included as part of a large trial or intervened with separately. Because even subclinical symptomatology can affect behavior, biomedical HIV prevention trials should include measures of mental health and substance use to better understand the role these may be playing on recruitment, retention, risk behavior during the course of the trial, adherence to the study protocol, and study outcomes. Additionally, data from youth that are recruited but do not end up enrolling in a trial should be gathered to determine if there are certain groups of vulnerable youth who are not being engaged in the research process and why they are not being engaged.

Given the multiple individual, social/community, and structural risk factors in the lives of vulnerable youth, interventions that combine prevention approaches (eg, biomedical and behavioral and/or structural interventions) are warranted. Although this article focuses predominately on domestic trials, trials conducted in locations outside of the United States need to take into consideration ethical and contextual factors related to enrolling vulnerable youth in biomedical HIV prevention clinical trials.

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