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Ethical Issues to Consider in the Design of HIV Prevention Trials Involving Transgender People

Jerome Amir Singh, LLM, MHSc, PhD

Abstract: Although transgender women have been included in HIV prevention pre-exposure prophylaxis studies, no pre-exposure prophylaxis study has focused exclusively on transgender persons. Drawing on the cardinal principles of ethics espoused in the Belmont Report, this work highlights, among other issues, that (1) the principle of *Justice* requires the HIV prevention field to focus exclusively on transgender persons, (2) the disclosure of potential study-related risks to study participants demonstrates *Respect for Persons*, and (3) devising risk mitigation plans, optimizing a proposed study's standard of care, and the provision of ancillary care satisfy the principle of *Beneficence*.

Key Words: transgender, transgender women (TGW), men who have sex with men (MSM), ethics, ethical, HIV prevention, pre-exposure prophylaxis, PrEP, Belmont Report, beneficence, respect for persons, justice

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INTRODUCTION

Although transgender women (TGW) have been included in HIV prevention pre-exposure prophylaxis (PrEP) studies,[1–3] they have comprised only a small minority of participants in studies with men who have sex with men (MSM). No PrEP study has focused exclusively on transgender persons despite HIV risk being disproportionately high in the transgender community[4,5] because of a complex range of social factors, including social ejection and marginalization.[6,7] Globally, gay men and other MSM are 19 times more likely to be living with HIV than the general population.[8] In comparison, a global systematic review and meta-analysis on TGW in 15 countries found that HIV prevalence among TGW is 49 times higher than that in the general adult population.[4] It has thus been argued that studies of PrEP use in TGW populations should be designed and tailored specifically for this population, rather than adapted from, or subsumed into, studies of MSM.[9] There is a paucity of data regarding transgender men (born biologically female and expressing male gender identities) and HIV risks, suggesting a need for further research on this cohort of the transgender community.[10] Given their disproportionate burden of HIV, their historic and ongoing marginalization, and the knowledge gap related to HIV prevention specific to the transgender community, conducting focused HIV prevention research on transgender persons is an ethical imperative. However, the concomitant ethical issues implicit in such research merit exploration.

Since its publication in 1978, the *Belmont Report* has established itself as among the world's foremost research ethics guidance documents and has arguably inspired a plethora of supplemental research ethics frameworks.[11–15] The *Belmont Report* posits three cardinal ethics principles to guide research on human participants: (1) Justice, (2) Respect for persons, and (3) Beneficence. PrEP research centered exclusively on transgender persons considered in the context of these principles will help elucidate the ethical challenges and obligations implicit in such research.

Justice

One of the core values implicit in the principle of justice is that there must be an equitable distribution of both burdens and benefits related to research participation. More specifically, the principle of justice holds that particular individuals, groups, or communities should neither bear an unfair share of the direct burdens of participating in research nor should they be unfairly excluded from the potential benefits of research participation. Although transgender persons have been included in some MSM HIV prevention studies, it can be argued that the transgender community is distinct enough from the general MSM community to warrant exclusive research focus. To this end, paragraph 13 of the 2013 iteration of the Declaration of Helsinki states: "Groups that are underrepresented in medical research should be provided appropriate access to participation in research."[16] Given the distinct HIV data that characterize the transgender community globally—as compared with the general adult population or even the MSM community—and given the dearth of transgender-specific HIV prevention data, "appropriate access" for transgender persons to participate in HIV

From the Center for the AIDS Programme of Research in South Africa (CAPRISA), Nelson R. Mandela School of Medicine, Durban, South Africa.

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Correspondence to: Jerome Amir Singh, LLM, MHSc, PhD, Center for the AIDS Programme of Research in South Africa (CAPRISA), Nelson R. Mandela School of Medicine, Private Bag X7, Congella, 4013 Durban, South Africa (e-mail: singhj9@ukzn.ac.za).

prevention research will necessitate HIV prevention trials focusing exclusively on transgender persons. Such research will improve our understanding of issues specific to transgender persons in relation to PrEP access, adoption, adherence, and drug–drug interactions (in the case of transgender persons on hormonal therapy). Furthermore, focused HIV prevention research on transgender persons will evidence a better understanding of the transgender community's risk profile in relation to HIV and sexual transmitted infections, as well as their health needs.

Respect for Persons

The principle of respect for persons requires that research participants enter into research voluntarily and with adequate information, including awareness of potential adverse consequences of being involved in the research. The conduct of HIV prevention trials among transgender persons must include disclosure to participants of potential study-related stigma, discrimination, and where applicable adverse drug–drug interactions between PrEP and other concomitant medication the participant may be taking. Such disclosure will require the sharing of relevant findings on the link between PrEP and psychosocial health problems,[17] and disclosure of the knowledge gap regarding to drug–drug interactions between PrEP and hormone treatment.[18]

Beneficence

The principle of beneficence requires efforts to secure the well-being of study participants. Two general rules have been formulated as complementary expressions of beneficence: (1) avoiding harm and (2) maximizing possible benefits.

Avoiding Harm

Although research involves participants from vulnerable communities, added protections will be necessary to safeguard their vulnerabilities. The extent of protection afforded to study participants should depend on the risk of harm and the likelihood of benefit from such interventions. In the research ethics context, risk mitigation involves (1) identifying risks or threats that are most likely to affect study participants, study staff, and the conduct of the proposed research project, (2) developing contingency plans to address those risks should they arise, and (3) managing those risks, accordingly. In the context of research involving transgender persons, such threats/risks could include community violence against study participants (and study staff), legal persecution, or even self-inflected harm on the part of study participants. Because of the deep-rooted stigma and discrimination that many transgender persons face globally, any proposed HIV prevention study focused on transgender persons will necessitate the drafting of comprehensive site-specific risk mitigation plan(s), and standard operating procedures to manage potential risks and social harms that could arise during the course of the study. In the context of research on transgender persons, such plans will require the prospective engagement of relevant stakeholders, including health, law enforcement, and justice officials, as well as role players who could provide psychosocial support services to study participants, local community leaders, members of the study population, relevant civil society actors, human rights experts, and lawyers who could advise or represent study participants and study staff on study-related matters, if necessary. Dedicated research on transgender study participants should only proceed if the study's potential benefits outweigh its potential risks.

Maximizing Potential Benefits

Investigators and sponsors are ethically obliged to maximize potential benefits and minimize potential risks that might arise from research. In the context of PrEP and transgender participants, maximizing benefit will entail giving careful consideration to standard of care and ancillary care obligations.

Standard of Care

In September 2015, the World Health Organization (WHO) recommended that people at substantial risk of HIV infection should be offered PrEP as an additional prevention choice, as part of comprehensive HIV prevention.[19] Because of their marginalized status, transgender persons are at substantial risk of HIV infection and, accordingly, should qualify globally for PrEP access, in line with WHO recommendations. However, few groups confront as many overt barriers to health care as transgender patients[20] and it remains to be seen if country authorities will facilitate PrEP access to transgender persons. Globally, transgender persons generally face an array of social, cultural, religious, institutional, socioeconomic, and legal impediments which render them a particularly marginalized key population. In addition to experiencing stigma and discrimination because of their appearance and gender expression, many transgender persons lack access to identity documents that match their self-identified gender. Consequently, the transgender community is characterized by high unemployment and underemployment.[21] These factors precipitate homelessness and force some transgender persons to resort to sex work to survive in some settings.[22,23] Institutionalized discrimination against the transgender community results in transgender persons lacking access to gender-affirming care and health services, or being explicitly denied access to health services because of their gender identity or expression, with many reporting experiencing verbal and physical harassment in medical offices and hospitals.[24] In such settings, it may be said that transgender persons receive an unacceptable standard of care.

Even in settings that are considering PrEP rollout, transgender persons may be overtly denied PrEP access or face substantial indirect barriers accessing PrEP. Seen in this light, a key ethics issue is whether settings that outlaw and actively prosecute homosexuality/transgender activities, and/or deny transgender persons access to HIV prevention services, should be considered as candidate host countries for HIV prevention trials focused exclusively on transgender persons. Furthermore, if that country's prevailing standard of care for transgender persons is "no provision of HIV prevention services," should the sponsor and study investigators still conduct HIV prevention research on transgender persons in that country? From an ethics perspective, if

a country criminalizes homosexuality and transgender activities and actively persecutes alleged "offenders," and/or if a trial sponsor and study investigators are unable to convince a country's health authority to commit to facilitating HIV prevention services to its transgender community, that country should not be considered as a candidate host country for a HIV prevention study focused exclusively on transgender persons. Conducting a transgender-focused HIV prevention study in such a setting could expose study participants and staff to unacceptable legal and social risks. Furthermore, conducting a HIV prevention trial in a setting where country authorities are unwilling to facilitate health access to transgender persons will inadvertently create an "island" of care and services for the study duration. Such factors could constitute an undue inducement for transgender persons desperate to access such services, thus vitiating the element of voluntariness in the informed consent process and compromising the principle of respect for persons.

However, should a country not have an oppressive regulatory framework in regard to homosexuality and transgender expression, and should the country commit to facilitating PrEP access to transgender persons, even if such services do not currently exist in that setting, investigators and study sponsors should use the opportunity of working in that setting to pioneer and establish gender-affirming care and optimal HIV prevention health services for transgender persons. The establishment of such services will require the development of core competencies among study staff and collaborating partners, specific to transgender persons.[25,26] In such instances, investigators and study sponsors will need to engage with health authorities and other partners to ensure the posttrial sustention of such services. Such actions will realize the principle of beneficence.

Ancillary Care

Ancillary care has been defined as care "which goes beyond the requirements of scientific validity, safety, keeping promises, or rectifying injuries."[27] Alternatively, health care that research participants need "but that is required neither to successfully answer the researchers' scientific question nor to avoid or mitigate harm resulting from participation in the research."[28] Ancillary care considerations will be crucial in any HIV prevention research endeavor focused exclusively on transgender persons. Studies of individuals presenting at gender clinics have observed levels of anxiety and depressive disorders that are much higher than the general population.[29] Similarly, community surveys suggest rates of violence, substance abuse, depression, and suicidality among transgender persons that are likewise much higher than the corresponding rates in the general population[7,30,31] Accordingly, it has been suggested that in addition to the provision of HIV prevention modalities such as PrEP, comprehensive HIV prevention efforts will require a consideration of a number of health-related issues specific to transgender persons.[32] These include the following:

- Health care in locations that are welcoming and safe for transgender individuals and that offer information that is pertinent to transgender issues, as well as the provision of care without the stigma attached to gender identity disorder.
- Treatment of mental health issues, including all psychosocial concerns such as gender identity disorder and violence and abuse.
- Substance abuse treatment, including treatment for both drugs and alcohol abuse.
- Culturally specific health care with recognition that transgender individuals come from a variety of ethnic and cultural backgrounds.

Researchers and research sponsors should develop research plans in dialog and partnership with potential study participants, the proposed host community, local medical and psychosocial support communities, and health authorities to meet the ancillary care needs of study participants that are likely to arise during the course of any proposed HIV prevention trial focused on transgender persons. Where foreseeable ancillary care obligations exist, researchers and research sponsors should take steps toward meeting these obligations, including hiring specialized staff who could help address the identified obligations, setting aside a budget to meet such obligations, and forming partnerships with those who can assist in addressing identified ancillary care needs.[28] As is the case with pioneering a novel standard of care, investigators and sponsors will need to engage with authorities and partners to ensure the posttrial sustention of such services. Such actions will realize the principle of beneficence.

CONCLUSIONS

HIV prevention research focused on transgender persons is an ethical imperative but fraught with ethical challenges. Considering such challenges in the context of the principles of justice, respect for persons, and beneficence offers the scientific community an invaluable opportunity to ensure that any PrEP study on the transgender persons leaves study participants and that setting's transgender community better off than would be the case in the absence of such research.

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