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Engaging Transgender People in NIH-Funded HIV/AIDS Clinical Trials Research

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Abstract: In 2009, the National Institutes of Health recognized the need to expand knowledge of lesbian, gay, bisexual, and transgender (LGBT) health and commissioned the Institute of Medicine to report on the health of these populations in the United States. The resulting Institute of Medicine publication called for more knowledge of the health of LGBT populations, as well as improved methodologies to reach them, more LGBT-focused research, and enhanced training programs and cultural competency of physicians and researchers. Several of the National Institutes of Health–funded HIV/AIDS clinical trials networks, including the Adolescent Medicine Trials Network for HIV/AIDS Interventions, HIV Prevention Trials Network, HIV Vaccine Trials Network, and Microbicide Trials Network, have focused attention on engaging transgender (TG) individuals in research. They have identified issues that transcend the nature of research (ie, treatment or prevention, adult or adolescent) and have adopted various approaches to effectively engage the TG community. Each network has recognized the importance of developing partnerships to build trust with and seek input from TG individuals on research plans and policies. They have established standing advisory groups and convened consultations for this purpose. To ensure that trial data are reflective of the participants they are seeking to enroll, they have reviewed and revised data collection forms to incorporate the 2-step method of collecting sex at birth and gender identity as 2 independent variables, and some have also revised research protocol templates and policies for concept development to ensure that they are appropriate for the inclusion of TG participants. The networks have also initiated trainings to enhance cultural sensitivity and developed a range of materials and resources for network and clinical research site staff. They continue to identify TG-specific research needs in an effort to be more responsive to and improve the health of TG individuals, particularly related to HIV/AIDS.

Key Words: transgender, HIV, AIDS, clinical trials, research, NIH

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THE NATIONAL INSTITUTES OF HEALTH

In 2009, the National Institutes of Health (NIH) commissioned the Institute of Medicine to conduct the first-ever study on the state of the science on the health of lesbian, gay, bisexual, and transgender (LGBT) populations. The resulting landmark 2011 report, *The Health of Lesbian, Gay, Bisexual and Transgender People: Building a Foundation for Better Understanding*,[1] concluded that too little is known about the health needs of LGBT people in the United States and called for researchers and the NIH to conduct and support additional research. In response, the NIH LGBT Research Coordinating Committee was formed, later renamed the Sexual and Gender Minority (SGM) Research Coordinating Committee. Charged with developing and coordinating NIH's LGBT research and training, the committee undertook a portfolio review to identify research gaps and opportunities.[2] Based on those findings and input from researchers, advocates and the public, the *NIH FY2016-2020 Strategic Plan to Advance Research on the Health and Well-being of Sexual and Gender Minorities*[3] was developed, delineating research and research-related goals and objectives to expand knowledge of LGBT health, improve methodologies to reach these populations, and enhance training programs and cultural competency of physicians and researchers.

Although these efforts brought attention to SGM research across the NIH, the impact of HIV on transgender (TG) communities compelled HIV researchers to respond. The National Institute of Allergy and Infectious Diseases (NIAID)

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has the primary responsibility at NIH for coordinating biomedical HIV treatment and prevention research and supports 5 clinical trials networks. Three networks in particular—HIV Prevention Trials Networks (HPTN), HIV Vaccine Trials Network (HVTN), and Microbicide Trials Network (MTN)—have consulted, engaged, and developed studies including TG individuals. Additionally, NIH's National Institute of Child Health and Human Development's (NICHD) Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), which evaluates HIV treatment and prevention strategies within that age group, engages TG youth.

In April 2014, Community Partners, a group of community representatives addressing common interests and concerns across NIAID's HIV networks, advocated for increased focus on TG issues. They recommended presumptive TG inclusion in all trials; cultural responsiveness training; more accurate and uniform data collection on gender identity; and TG-specific research. In response, a Cross-Network Transgender Working Group (CNTWG) was formed to develop a coordinated approach; facilitate an exchange of information and resources for TG training and engagement; promote standardized data collection; and augment existing network activities. The CNTWG has since developed a data collection template separating gender identify from birth sex and continues to push for its widespread adoption. The group advocates for cultural responsiveness training to ensure confidentiality and respect of all participants and is compiling training materials and developing a training curriculum.

HIV VACCINE TRIALS NETWORK

While the CNTWG is relatively new, the networks have been working with TG communities for many years. Among the earliest were HVTN initiatives to engage TG individuals in vaccine trials beginning in 2007. These efforts expanded when HVTN's Global Community Advisory Board submitted a call to action, advocating for changes across protocols to eliminate barriers to TG enrollment; the HVTN Transgender Working Group (TWG) was established to identify and inform those efforts. The TWG (including 2 TG members) revised the Demographics Case Report Form (CRF) in 2009 to adopt the US Centers for Disease Control and Prevention recommendation of separating birth sex and gender identity into 2 variables (the 2-step method),[4] allowing participants to self-identify with preferred terminology. An explanation of "birth sex" for those unfamiliar with the distinction was added and among the gender terms, "other" was replaced with "additional category," as individuals do not think of themselves as "other." The TWG also contributed to revised protocol template language to make pregnancy testing language more gender-sensitive and improve language regarding birth control requirements. Recent TWG discussions have considered how best to assess and define TG individuals' HIV risk and risk-related eligibility for trial participation.

HVTN 505, HVTN's first trial naming TG women as an eligible population distinct from men who have sex with men (MSM), opened in 2009. In 2011, focus groups with TG women were held in 4 US cities to assess barriers and facilitators to trial participation, and an environmental survey was conducted among 11 US TG study participants to assess their experiences. Factors affecting participation were identified[5] and recommendations to improve TG participants' experiences were incorporated into subsequent trials. To further inform engagement, enrollment, and retention, an analysis was conducted among 14 TG participants in phase 1 and 2a protocols with low behavioral risk for HIV, and 44 TG women participating in HVTN 505 with high behavioral risk for HIV, comparing both groups to cisgender participants.

Phase 1 and 2a TG participants' primary reasons for participating were altruistic. Mental health disorder prevalence was similar to that of other surveyed TG individuals in the general population. Rates of social impacts (social harms and social benefits), adverse events, missed visits, and retention were similar among TG and cisgender participants. The 44 phase 2b TG participants were more likely than cisgender participants to have demographic characteristics associated with HIV risk, including non-white race and young age. Although missed visits were more frequent among phase 2b TG participants, there were no statistically significant differences in other retention parameters (eg, discontinuation of vaccination, dropout). Overall HIV incidence was higher among TG vs. cisgender participants, but the difference was not statistically significant, possibly because of limited power resulting from the small number of TG individuals in the studies. These findings indicate that TG individuals can be successfully recruited and retained and can contribute meaningfully to HIV vaccine trials.[6,7]

To support TG inclusion, the HVTN has created a glossary and resource references and increased staff training to improve cultural awareness, knowledge, and trans-sensitive care; facilitated collaboration between trial sites and local TG-service organizations; improved workplace environments, including availability of gender-neutral bathrooms; and developed recruitment advertisements featuring TG men and women. Future efforts will seek authentic and successful TG inclusion; explore options to address limitations of laboratory reference ranges and immunogenicity analyses, typically based on birth sex; expand TG community consultations and implementation of Good Participatory Practice guidelines[8] to enhance cultural responsiveness; publish data regarding TG participation to inform engagement activities; and appropriately engage TG populations outside the United States.

MICROBICIDE TRIALS NETWORK

Given the high rate of HIV infection in TG communities attributable to unprotected anal intercourse,[9] MTN efforts have focused on TG inclusion in discourse and research related to rectal microbicides, currently being tested to protect against HIV transmitted through anal intercourse. These efforts come as the MTN reports data from the first phase 2 rectal microbicide trial (MTN-017), testing the safety and acceptability of a reduced glycerin formulation of tenofovir gel, and pave the way for TG inclusion in future studies.

Before starting MTN-017, the MTN convened a consultation with TG women and men, and advocates. The

meeting, held jointly with Be the Generation Bridge, a former NIAID program to increase awareness of and support for HIV prevention research, provided a forum to discuss advances in prevention research, as well as opportunities and challenges posed by conducting rectal microbicide research with TG individuals.

It was suggested that the paucity of TG participation in HIV prevention research be "…an alert for public health and a call to action."[10] Highlighting barriers to inclusion, participants advocated for acknowledgment of unmet basic needs and daily hardships that prevent TG people from trial participation. The use of certain language and labeling based on sexual behavior and misperceptions of what that may include were also discussed as factors that keep TG people from seeking care and support.[10] Participants suggested that appropriate language be used consistently across all sites and that people "…be allowed to identify as they want and not have to fit into a box because of what researchers assume."[10] The need for culturally competent, nondiscriminatory, and respectful health care providers was noted, as was a desire for researchers to establish relationships with TG communities and hire TG people as clinical staff and investigators. It was requested that TG women be recognized as distinct from gay men and other MSM and that prevention interventions and studies be tailored to them. Finally, concerns were raised about potential interactions between rectal microbicides and hormones, and monitoring for possible drug interactions was recommended. Although myriad challenges were discussed, participants appreciated the information about prevention research and rectal microbicides and were eager to inform their communities."[10]

Launched in September 2013, MTN-017 reported results in February 2016. Among 195 participants, 12% identified as TG, many from the Chiang Mai, Thailand site, which had TG-specific recruitment activities. According to site staff, most TG women felt that joining the study was beneficial because they gained knowledge about HIV prevention and access to clinicians to discuss health concerns, and got tested regularly for HIV.

Three subsequent consultations to address next steps included trial design and ethics experts, scientists, advocates, and representatives from MSM and TG-service organizations. They resulted in a recommendation to move forward with MTN's rectal microbicide research agenda. This includes a phase 1 study (MTN-033/IPM 044) of dapivirine gel comparing administration with an applicator vs. a coital simulation device. This study will provide safety and pharmacokinetic data to help inform whether rectal microbicides could be delivered as lubricants. The MTN remains committed to involving TG people in this and future studies, and to addressing their unique HIV prevention needs related to anal intercourse.

HIV PREVENTION TRIALS NETWORK

The HPTN implemented internal sensitization and study-specific cultural responsiveness trainings to mitigate enrollment disparities: less than 1% of participants in 5 trials identified as TG, and less than 2% as "other gender preference." HPTN also convened a meeting to raise awareness of TG-specific HIV prevention needs and develop TG-focused research proposals.

Two 4-hour sensitization workshops were held with the HPTN's Community Advisory Group, comprising approximately 60 individuals—2 community representatives from each HPTN clinical research site. These workshops, designed and conducted by a PhD-level, TG HIV researcher, provided information on TG populations world-wide and a forum to discuss sites' deficits and/or accomplishments in engaging, enrolling, and retaining TG people in research.

To enhance staff TG cultural sensitivity, the HPTN and HVTN collaborated to adapt the HPTN Black Caucus' "Presence at the Table" curriculum, initially developed as a Black MSM cultural responsiveness training. It emphasizes the commonality of certain human and life experiences, addressing the complexity of workplace relationships, understanding and valuing differences, and nurturing positive relationships with research participants. The adapted curriculum was part of study-specific training for site staff working on HVTN 704/HPTN 085, the first HIV prevention study to name both TG men and women as eligible populations for enrollment. It aims to improve the sites' capacity to value diversity and engage marginalized communities in research implementation and information dissemination.

In the training, approximately 150 staff from 19 US sites explored the values, attitudes, and perspectives related to engaging MSM and TG populations, with a specific focus on people of color, as well as approaches to identify and constructively address cultural inappropriateness in clinic and field settings. The training will be adapted for other HPTN and HVTN studies targeting marginalized populations, and training data will be published to further inform the field.

The HPTN also facilitated a 2-day science-generating meeting in June 2015 to develop HIV prevention interventions for TG men and women and other gender nonconforming individuals. Attended by approximately 70 global community advocates, researchers, and ethicists, it included updates on the global HIV epidemic among TG populations and a review of published TG-specific behavioral and biomedical research. Meeting outcomes included a recommendation for inclusion of TG populations in phase 2 and 3 studies with target enrollments that would ensure study end points; formation of writing teams to conceptualize and publish manuscripts on TG-focused research; and establishment of a team to develop an HIV prevention research concept for TG people, and lay the foundation for future HPTN TG engagement and research.

ADOLESCENT MEDICINE TRIALS NETWORK FOR HIV/AIDS INTERVENTIONS

The ATN formed the Transgender Advisory Group (TAG) in October 2012 in response to concerns regarding exclusion of TG adolescents from some protocols and use of surveys that did not represent the experiences of TG and gender nonconforming (TGNC) youth. TAG provides monitoring and advisory functions to the ATN and serves as a resource for those interested in research and clinical practice inclusive of and sensitive to TGNC youth.

TABLE 1.

Cross-Cutting Themes	Actions Taken by NIH-Funded Research Networks			
	ATN	HPTN	HVTN	MTN
Data collection forms using 2-step method, to ensure data accuracy and sensitivity to participants	Case report forms revised; use of 2-step method incorporated; new measures of gender affirmation developed	Case report forms revised to include 2-step method	Case report forms revised to include 2-step method and terminology for gender identity improved in 2009	Case report forms revised to include 2-step are used for relevant protocols
Revised protocol design and language appropriate to transgender inclusion	Rationale for inclusion/exclusion criteria required in concept development; recommended single-items method of assessing transgender status, and 2-item method of assessing socially assigned gender expression; modified a sexual activity and sexual risk measure used across protocols to be inclusive of TG youth sexual experiences	Transgender people on Site Community Advisory Boards (CABs) provide input for transgender-specific language in protocols In HPTN 083 study product is injected into the buttock. Study includes transgender women, but protocol exclusion criterion for surgically-placed buttock implants was amended to include injected silicon/industrial product implants. Study is being conducted in regions where this type of implant is common among transgender women so those with this type of implant are ineligible.	Revised protocol template regarding pregnancy testing language and birth control requirements in 2008; behavioral risk assessment revised in 2015 for phase I trials, and a phase II template is in development; risk-related eligibility criteria revised in 2009 to address use of hormone therapy and pre-/post-operative considerations	Protocol language has been updated related to inclusion/exclusion criteria, birth control and pregnancy testing
Training of all staff to increase cultural sensitivity	Webinars and trainings held	Trainings at annual Network meetings; extensive protocol-specific training; development of resources and materials Several members of the Bangkok 067 CAB who are transgender women including the CAB leader were employed by the site	Trainings at annual Network meetings began in 2009; extensive protocol-specific training is ongoing; continuing education training of protocol medical monitors re: relevant clinical considerations is ongoing; development of resources and materials is ongoing	Webinars and presentation related to findings from consultations with transgender individuals
Solicitation of guidance on engagement and research plans	Creation of a Transgender Advisory Group	Consultation on HIV prevention research for transgender men and women and other gender nonconforming individuals	Transgender Working Group created in 2007	Consultations held with transgender men, women, and advocates
Research inclusive of or specific to transgender individuals	Study of transgender and nonconforming youth experiences across continuum of HIV care; others in development	HPTN 069 (phase 2), HPTN 071 (phase 3), and HVTN 704/HPTN 085 (phase 2b) inclusive of transgender men and women. Feasibility studies HPTN 061, HPTN 064, and HPTN 75; and HPTN 067 (phase 2) and HPTN 083 (phase 2b/3) inclusive of transgender women	HVTN 505 (phase 2b) included transgender women; HVTN 704/HPTN 085 (phase 2b) inclusive of transgender men and women; transgender people have always been eligible for phase 1 studies based on study eligibility criteria	Inclusion of transgender women in MTN-017 and other rectal microbicide studies

TAG consists of ATN members and external members, including TGNC community members and allies. It has implemented several structural-level changes, such as modifying the policy for study concept development to require that investigators provide explicit rationale for the inclusion/exclusion of TG youth in proposed studies. Research teams are also encouraged to consult with TAG during early protocol development to assure appropriate sensitivity to TGNC youth issues. Additionally, to more uniformly assess gender identity and expression, and pool data across studies, CRFs were modified to include a 2-step method of assessing sex assigned at birth and current gender identity. TAG also recommended use of a single-item method of assessing TG status, and a 2-item method of assessing socially assigned gender expression. A TAG subcommittee revised a sexual activity and risk measure to first assess sex assigned at birth and history of genital reassignment surgery so participants then receive questions appropriate to their own and their partners' anatomy. Recently, TAG worked in collaboration with TGNC youth to develop 3 new measures of gender affirmation and gender minority stress related to health and HIV care.

TAG facilitated 2 trainings delivered by experts in the field: "Cultural Competency for Medical Providers and Research Staff Working with Transgender Youth"[11] and "Sex, Gender, and Why the Distinction Matters: Reaching Transgender Adolescents in Research."[12] These, and a new training on "Basics of Feminizing and Masculinizing Hormone Management,"[13] are available as free online webinars on the ATN website, along with other training tools, recommendations, guidance documents and publications.[14]

A major achievement of TAG was executing the first ATN study of TGNC youth's experiences across the HIV care continuum (ATN 130), which completed data collection with 184 TGNC youth. This was a multiphasic mixed-methods study that collected data on barriers and facilitators affecting TGNC youth's engagement. The study team includes TGNC community members and has an active Youth Advisory Board representing TGNC youth from 3 geographically diverse areas of the United States. The study aims to create theoretical and empirical models for intervention development, as well as best practice recommendations and multimedia resources for providers and clinics.

TAG has published on HIV care for TG adolescents[15] and will document site experiences with TGNC youth. It continues to provide advice and support to ATN and other researchers and practitioners, expand its website, which is vital to educating about TGNC youth, and will explore cross-sectional and longitudinal analyses of TGNC-specific data across multiple ATN studies.

SUMMARY

The NIH and several of its HIV/AIDS clinical research networks have identified common themes and developed a number of strategies to effectively engage TG individuals in research, and they remain committed to continuing to do so (Table 1). They have identified the need for more inclusive terminology on data collection forms and in protocol templates, and have recognized that cultural sensitivity among staff members throughout the research enterprise is critical. As such, training materials and resources continue to be refined and sessions to increase sensitivity and awareness among staff members continue to be implemented. Partnerships between both the TG and research communities foster increased understanding of, and comfort with, the research within the TG community, and helps researchers gain insight, solicit input, and develop studies that better address TG-specific needs. A variety of approaches are also being used to seek advice and guidance from the TG community regarding TG engagement and research plans, including advisory and working groups inclusive of TG individuals, focus groups, and consultations. It is through a combination of these and other strategies that the NIH and its research networks will continue to develop a comprehensive approach to addressing the needs of transgender individuals as they relate to HIV research.

REFERENCES

1. *The Health of Lesbian, Gay, Bisexual and Transgender People: Building a Foundation for Better Understanding*. Institute of Medicine of the National Academies; 2011. Available at: https://www.nap.edu/read/13128/chapter/1. Accessed March 1, 2011.
2. *National Institutes of Health FY2012 Sexual and Gender Minority Health Research Portfolio Analysis Report*. 2015. Available at: https://dpcpsi.nih.gov/sgmro/reports. Accessed October 1, 2015.
3. *NIH FY2016-2020 Strategic Plan to Advance Research on the Health and Well-being of Sexual and Gender Minorities*. Available at: https://dpcpsi.nih.gov/sgmro/reports. Accessed November 1, 2015.
4. Sausa LA, Sevelius J, Keatley J, et al. *Policy Recommendations for Inclusive Data Collection of Trans People in HIV Prevention, Care & Services. Center of Excellence for Transgender HIV Prevention*. San Francisco, CA: University of California; 2009. Available at: http://transhealth.ucsf.edu/pdf/data-recommendation.pdf.
5. Andrasik MP, Yoon R, Mooney J, et al. Exploring barriers and facilitators to participation of male-to-female transgender persons in preventive HIV vaccine clinical trials. *Prev Sci.* 2014;15:268–276.
6. Karuna S, Andrasik M. Transgender participants in phase 1-2a trials of the HIV vaccine trials network (HVTN): a descriptive analysis. *AIDS Res Hum Retrov.* 2013;29:A67–A68.
7. Karuna ST, Grove D, Broder G, et al. Transgender participants in the HIV Vaccine Trial Network's HVTN 505 trial: a descriptive and comparative analysis. *AIDS Res Hum Retrov.* 2014;30(suppl 1):A189.
8. UNAIDS/AVAC. *Good Participatory Practice: Guidelines for Biomedical HIV Prevention Trials*. 2011. Available at: http://www.avac.org/sites/default/files/resource-files/Good%20Participatory%20Practice%20guidelines_June_2011.pdf. Accessed June 1, 2011.
9. Herbst JH, Jacobs ED, Finlayson TJ, et al. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav.* 2008;12:1–17.
10. *Rectal Microbicides for HIV Prevention: A Transgender Update and Consultation*. Microbicide Trials Network; 2013. Available at: http://www.mtnstopshiv.org/node/5124. Accessed 2013.
11. Olson J. *Cultural Competency for Medical Providers and Research Staff Working with Transgender Youth*. 2014. Available at: https://www.atnonline.org/public/TransYouthRes.asp. Accessed 2014.
12. Resiner S. *Sex, Gender and Why the Distinction Matters: Reaching Transgender Adolescents in Research*. 2014. Available at: https://www.atnonline.org/public/TransYouthRes.asp. Accessed 2014.
13. Wesp L. *Basics of Feminizing and Masculinizing Hormone Management*. 2015. Available at: https://www.atnonline.org/public/TransYouthRes.asp.
14. *Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions Website*. Available at: https://www.atnonline.org/public/default.asp. Accessed 2015.
15. Jadwin-Cakmak L, Radix A, Popoff E, et al. Transgender adolescents: care and support. American Academy of HIV Medicine. *HIV Specialist Magazine*. 2015;7:12–17.