

# Women in HIV cure research: multilevel interventions to improve sex equity in recruitment

Mary E Grewe<sup>1,2a</sup>, Yuntong Ma<sup>3a</sup>, Adam Gilbertson<sup>1,2,4</sup>, Stuart Rennie<sup>5</sup> and Joseph D Tucker<sup>1,6\*</sup>

<sup>1</sup> Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

<sup>2</sup> Department of Social Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

<sup>3</sup> Washington University School of Medicine, St. Louis, MO, USA

<sup>4</sup> School of Anthropology and Museum Ethnography, University of Oxford, UK

<sup>5</sup> UNC Center for Bioethics, Department of Social Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

<sup>6</sup> University of North Carolina Project-China, Guangzhou, Guangdong Province, China

<sup>a</sup> These authors contributed equally

## Abstract

Women are underrepresented in HIV cure research. In this paper we discuss the rationale for including women and propose multilevel strategies to improve sex equity in HIV cure research. The inadequate inclusion of women in HIV cure research is concerning for both scientific and ethical reasons. Biological responses to HIV and HIV treatment, as well as social contexts, differ between men and women, and this may affect the efficacy of curative interventions. Strategies for improving sex equity in HIV cure research include addressing eligibility criteria, adapting recruitment strategies, engaging community members early in the research process, and promoting funder policy changes. We conclude by describing the Gender, Race, and Clinical Experience (GRACE) study, which is one example of how women can be effectively recruited into HIV-related clinical trials. While HIV cure research is currently in the early stages, as it continues to develop it is important to mobilise for adequate inclusion of women.

Keywords: HIV cure research, women, equity

Globally, women account for more than half of the HIV burden [1], yet they are underrepresented within HIV cure research [2,3]. As the field of HIV cure research continues to expand [2,4], it is important to consider adequate inclusion of female participants. This article reviews the rationale for sex equity in HIV cure trial recruitment and describes strategies for improving sex equity.

The underrepresentation of women in HIV cure research is concerning for several reasons. First, there may be biological differences in HIV reactivation of reservoirs between women and men. For instance, the sex hormone oestradiol inhibits reactivation of HIV replication among latent reservoirs [5]. Second, sex-specific differences in HIV viral load and CD4 cell count [2] point towards a need to account for sex when measuring the HIV reservoir. Third, ARV pharmacokinetics are different in women [6]. Women have more frequent adverse reactions to drugs in general [7], and antiretroviral therapies specifically [6], compared to men, indicating potential greater need for alternative treatments. Fourth, women's experiences in society tend to be very different from those of men, and this may influence both participation in research and the subsequent implementation of interventions. Ensuring adequate representation of women in HIV cure research may help to facilitate the eventual uptake of curative interventions among women during later implementation. Finally, the adequate inclusion of women in research is an issue of equity and a fundamental aspect of sound research ethics. Adequate representation increases the likelihood that the risks and benefits of HIV cure research are equitably shared among the larger HIV-infected population. While most HIV cure research studies are currently taking place in high-income countries [2] where there are fewer women living with HIV [8], the results of these studies will affect women globally, and it is important that participation reflects global HIV burden among women.

Underrepresentation of women within HIV cure trials may be related to several factors, some of which can be inferred from the broader HIV research literature. General barriers to participating

in HIV clinical research include patient concerns about safety (such as fear of side effects), lack of trust in researchers or research, concerns related to the research methods or requirements, logistical issues (such as travel barriers or family responsibilities), concerns about confidentiality and stigma, lack of information and ineligibility [9]. While research on understanding sex equity in recruitment of trials has so far been limited [10], broader exclusion criteria related to pregnancy or requiring multiple forms of birth control may also help to explain part of these differences [11,12].

To date, there has been little research on policy- and structural-level barriers and facilitators to HIV clinical research recruitment. The few interventions aiming to increase participant diversity have largely focused on addressing individual-level barriers to research participation [13–17], and most do not evaluate the effectiveness of the intervention on improving trial participation rates [13–15,17–19]. Overall, there has been little focus on interventions addressing researcher, clinical trial, institutional or research policy factors.

Given the importance of 'macro-level' research and policy environments to trial recruitment, the broader determinants that hinder sex equity should be examined. Interventions to achieve sex equity in HIV cure research recruitment must be implemented on multiple levels. Potential interventions include study design improvements targeted at each stage of clinical trials, stakeholder engagement, strategies to overcome structural barriers, and modification of federal, state and/or institutional policy guidelines. A summary of these strategies is provided in Table 1.

First, study-design elements can be modified to improve representation of women. Many common trial exclusion criteria disproportionately affect participation of women [20,21]. Studies excluding women who are pregnant or of reproductive age often decrease recruitment of women in clinical trials [22–24]. As clinical trials move past determining the safety and efficacy of interventions into Phase IIB and Phase III, it becomes more important to ensure that females are represented in order to ensure that interventions will be effective in women. Exclusion criteria should be considered in the context of ensuring sex equity while

\*Corresponding author: Joseph D Tucker. University of North Carolina Project-China, No. 2 Lujing Road, Guangzhou, 510085, China  
Email: jdtucker@med.unc.edu

**Table 1.** Strategies to improve sex equity in recruitment

Level of intervention	Specific strategies to increase equity in recruitment
1. Improvement in study design elements	Rigorous examination and adjustment of exclusion criteria that render pregnant/reproductive age women ineligible. Expansion of inclusion criteria to include pregnant/reproductive age women in Phase IIB and III trials. Identifying and rectifying implicit bias in researcher attitudes that negatively influence recruitment of women into trials.
2. Stakeholder engagement in the community	Early dialogue with community advocates to obtain information about demographic distributions and prevailing attitudes. Establishing community advisory boards to formulate strategies to encourage participation and to prevent therapeutic misconception. Community-based participatory research to enable community members to take more active roles in clinical trial design.
3. Strategies to overcome structural barriers	Provision of adequate logistical support for study participants from a wide range of socioeconomic classes. Establishing partnerships with community organisations and selection of study sites with strong community relationships. Additional support for clinical trial study sites including training on women's health and support of flexible clinic hours.
4. Modification of policy guidelines	Rigorous review by funding bodies of project proposals' plan for inclusion of women at the scientific review stage Regular monitoring of progress in recruitment to ensure continued compliance with policy as projects get under way. Provision of additional support by the funding body to studies encountering problems with recruiting women.

maintaining scientific integrity. Furthermore, physician and study coordinator perceptions may negatively influence recruitment of women into trials [25–27]. Limited evidence exists regarding possible interventions to improve implicit bias, but greater reflection is needed to identify the ways in which inherent researcher attitudes may affect recruitment of women.

Second, stakeholder engagement is another potential strategy to increase the recruitment of women in HIV clinical research [28]. Early dialogue with community advocates and the establishment of community advisory boards may provide valuable information regarding prevailing attitudes and best methods for recruitment [29,30]. This is particularly important in HIV cure research due to the potential for therapeutic misconception [31]. Cure studies may be marked by misplaced expectations among those who are HIV-infected and give rise to confusion and distrust. Community engagement may aid in formulating strategies for explaining the complexities of HIV cure research, dispelling commonly held misconceptions, and encouraging participation of women on the basis of understandable and reliable information. Community-based participatory research has demonstrated how communities can be effective partners in HIV research [32,33], establishing the context for community members to take more active roles in clinical trial design [34,35]. An opportunity for expanded community engagement could help identify other barriers to sex equity in HIV cure trials.

Third, strategies to overcome structural barriers faced to a greater extent by women may improve sex equity. Institutional review board limits on incentives and logistical support for participation must balance the potential for undue inducement with compensation that is adequate for participants from a wide range of socioeconomic classes. In actual trial implementation, partnership with women-focused community organisations and selection of study sites with strong community relationships may lead to higher recruitment and retention rates [29,36,37]. National Institutes of Health (NIH)-funded HIV clinical trials are often conducted at study sites within the AIDS Clinical Trials Group network that have experience in conducting trials and the personnel necessary to support a clinical trial unit. These study sites may benefit from additional interventions to increase female participation, such as training on women's health, encouraging community-provider interactions, and supporting flexible clinic hours [36].

Policy interventions that promote sex equity at the level of research funder requirements may be useful in changing norms about recruitment. Beginning with the NIH Revitalization Act of 1993, which was further amended in 2001, the NIH required that all funded clinical research include participants of both sexes and

diverse racial and ethnic groups [38]. Since its institution, the NIH policy has increased attention on the inclusion of women and minority participants in clinical research. One survey of NIH Scientific Review Group members showed that they believed the current NIH guidelines are adequate for encouraging inclusion [39]. However, preliminary studies have shown that even in NIH-funded HIV clinical trials, female participants continue to be underrepresented [39,40]. Further policy changes that provide support to studies encountering problems with adequate recruitment and that ensure continued compliance with NIH policies as studies progress may increase participation of women.

Finally, the Gender, Race, and Clinical Experience (GRACE) study is one example of how women can be more effectively recruited in HIV clinical trials [36]. The GRACE study evaluated sex-based differences in darunavir/ritonavir-based therapy by enrolling a high proportion of women living with HIV in the United States [41]. During trial design, exclusion criteria were decreased and mandated enrolment quotas for women were instituted. Early engagement with physicians and community advisors fostered participants' connectedness to the study, and investigators hypothesised the enrolment success of the study may have hinged on such relationships [36]. To address structural barriers, investigators sought study sites with strong patient-physician relationships, and the trial provided study sites with the resources to adapt practices as necessary to support patients [36]. More extensive clinical trial planning such as that developed in the GRACE study may also be effective in recruiting women in HIV cure clinical research.

In this paper, we have identified individual, community, structural and policy level barriers that are likely to challenge the recruitment of women into ongoing and future HIV cure research, and put forward ideas for strategies targeting change at each of these levels. Currently, striking disparities in HIV cure research participation exist. While HIV cure research is still in an early proof-of-concept phase, it will be important to determine the differential effects of curative interventions. Recognising this need, as well as the ethical imperative to recruit both men and women, we must mobilise for greater inclusion of women in HIV cure research.

## Acknowledgements

We acknowledge Liza Dawson and Ada Adimora for providing helpful feedback on an earlier version of this manuscript, and Elizabeth Kelly for providing editorial support.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

## Funding

Support for this work was provided by the Social and Ethical Aspects of Research on Curing HIV Working Group (NIAID R01A108366-01). The Working Group's composition and rationale is explained at <http://searchiv.web.unc.edu/>. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Thanks to the UNC Center for AIDS Research (NIAID P30 AI050410).

## References

- amfAR. *Statistics: Women and HIV/AIDS*. 2014. Available at: [www.amfar.org/about-hiv-and-aids/facts-and-stats/statistics-women-and-hiv-aids/](http://www.amfar.org/about-hiv-and-aids/facts-and-stats/statistics-women-and-hiv-aids/) (accessed December 2015).
- Johnston RE, Heitzeg MM. Sex, age, race and intervention type in clinical studies of HIV cure: a systematic review. *AIDS Res Hum Retroviruses* 2015; **31**: 85–97.
- Curro MJ, Rossi S, Hodges-Mameletzis I *et al*. A systematic review of the inclusion (or exclusion) of women in HIV research: from clinical studies of antiretrovirals and vaccines to cure strategies. *J Acquir Immune Defic Syndr* 2015.
- Blankson JN, Siliciano JD, Siliciano RF. Finding a cure for human immunodeficiency virus-1 infection. *Infect Dis Clin North Am* 2014; **28**: 633–650.
- Karr J, Das B, Dobrowski C *et al*. Estrogen blocks HIV re-emergence from latency and points to gender-specific differences in HIV reservoirs. *IAS Towards an HIV Cure Symposium*. Vancouver, Canada.
- Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol* 2004; **44**: 499–523.
- Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol* 2001; **2**: 349–351.
- UNAIDS. *The Gap Report*. 2014. Available at: [www.unaids.org/sites/default/files/media\\_asset/UNAIDS\\_Gap\\_report\\_en.pdf](http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf) (accessed December 2015).
- Mills E, Wilson K, Rachlis B *et al*. Barriers to participation in HIV drug trials: a systematic review. *Lancet Infect Dis* 2006; **6**: 32–38.
- Loutfy MR, V LK, Mohammed S *et al*. Recruitment of HIV-positive women in research: discussing barriers, facilitators, and research personnel's knowledge. *Open AIDS J* 2014; **8**: 58–65.
- Schonfeld TL, Gordon BG. Contraception in research: a policy suggestion. *Irb* 2005; **27**: 15–20.
- Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. *Obstet Gynecol* 2013; **122**: 1077–1081.
- Gwadz MV, Leonard NR, Cleland CM *et al*. The effect of peer-driven intervention on rates of screening for AIDS clinical trials among African Americans and Hispanics. *Am J Public Health* 2011; **101**: 1096–1102.
- Ives NJ, Troop M, Waters A *et al*. Does an HIV clinical trial information booklet improve patient knowledge and understanding of HIV clinical trials? *HIV Med* 2001; **2**: 241–249.
- Volkman ER, Claiborne D, Currier JS. Determinants of participation in HIV clinical trials: the importance of patients' trust in their provider. *HIV Clin Trials* 2009; **10**: 104–109.
- Freedberg KA, Sullivan L, Georgakis A *et al*. Improving participation in HIV clinical trials: impact of a brief intervention. *HIV Clin Trials* 2001; **2**: 205–212.
- Gwadz MV, Cyler K, Leonard NR *et al*. An exploratory behavioral intervention trial to improve rates of screening for AIDS clinical trials among racial/ethnic minority and female persons living with HIV/AIDS. *AIDS Behav* 2010; **14**: 639–648.
- Corbie-Smith G, Odeneye E, Banks B *et al*. Development of a multilevel intervention to increase HIV clinical trial participation among rural minorities. *Health Educ Behav* 2013; **40**: 274–285.
- el-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *JAMA* 1992; **267**: 954–957.
- Berlin JA, Ellenberg SS. Inclusion of women in clinical trials. *BMC Med* 2009; **7**: 56.
- Merkatz RB. Inclusion of women in clinical trials: a historical overview of scientific, ethical, and legal issues. *J Obstet Gynecol Neonatal Nurs* 1998; **27**: 78–84.
- Blehar MC, Spong C, Grady C *et al*. Enrolling pregnant women: issues in clinical research. *Womens Health Issues* 2013; **23**: e39–45.
- Schonfeld T. The perils of protection: vulnerability and women in clinical research. *Theor Med Bioeth* 2013; **34**: 189–206.
- Westreich D, Rosenberg M, Schwartz S, Swamy G. Representation of women and pregnant women in HIV research: a limited systematic review. *PLoS One* 2013; **8**: e73398.
- Frew PM, Saint-Victor DS, Isaacs MB *et al*. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. *Clin Infect Dis* 2014; **59** Suppl 7: S400–407.
- Haas DM, Wunder K, Wolf JG, Denne SC. Women's health care providers' attitudes toward research in pregnancy. *J Reprod Med* 2010; **55**: 108–114.
- Stone VE, Mauch MY, Steger KA. Provider attitudes regarding participation of women and persons of color in AIDS clinical trials. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **19**: 245–253.
- Mikesell L, Bromley E, Khodyakov D. Ethical community-engaged research: a literature review. *Am J Public Health* 2013; **103**: e7–e14.
- Barnett J, Aguilar S, Brittner M, Bonuck K. Recruiting and retaining low-income, multi-ethnic women into randomized controlled trials: successful strategies and staffing. *Contemp Clin Trials* 2012; **33**: 925–932.
- Corbie-Smith G, Isler MR, Miles MS, Banks B. Community-based HIV clinical trials: an integrated approach in underserved, rural, minority communities. *Prog Community Health Partnersh* 2012; **6**: 121–129.
- Tucker JD, Rennie S. Social and ethical implications of HIV cure research. *AIDS* 2014; **28**: 1247–1250.
- Brizay U, Golob L, Globberman J *et al*. Community-academic partnerships in HIV-related research: a systematic literature review of theory and practice. *J Int AIDS Soc* 2015; **18**: 19354.
- Rhodes SD, Malow RM, Jolly C. Community-based participatory research: a new and not-so-new approach to HIV/AIDS prevention, care, and treatment. *AIDS Educ Prev* 2010; **22**: 173–183.
- Seifer SD, Michaels M, Collins S. Applying community-based participatory research principles and approaches in clinical trials: forging a new model for cancer clinical research. *Prog Community Health Partnersh* 2010; **4**: 37–46.
- Community Recommendations Working Group of Community Partners. *Recommendations for Community Involvement in National Institute of Allergy and Infectious Diseases HIV/AIDS Clinical Trials Research*. 2009. Available at: <https://www.niaid.nih.gov/about/organization/daids/Networks/Documents/cabrecommendations.pdf> (accessed December 2015).
- Falcon R, Bridge DA, Currier J *et al*. Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. *J Womens Health* 2011; **20**: 1043–1050.
- Coleman-Phox K, Laraia BA, Adler N *et al*. Recruitment and retention of pregnant women for a behavioral intervention: lessons from the maternal adiposity, metabolism, and stress (MAMAS) study. *Prev Chronic Dis* 2013; **10**.
- National Institutes of Health. *NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October 2001*. 2001. Available at: [http://grants.nih.gov/grants/funding/women\\_min/guidelines\\_amended\\_10\\_2001.htm](http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm) (accessed December 2015).
- Taylor HA. Implementation of NIH inclusion guidelines: survey of NIH study section members. *Clin Trials* 2008; **5**: 140–146.
- Handibode J, Aidarus N, Fisher K. Women in HIV cure trials: a chance to reverse the historical paradigm of underrepresentation of women in HIV treatment trials. *Strategies for an HIV Cure*. October 2014. Bethesda, MD.
- Currier J, Squires K, Bridge D. GRACE (Gender, Race And Clinical Experience): 48-week outcomes of darunavir/ritonavir-based therapy in women compared with men. *Ann Intern Med* 2010; **153**: 349–357.