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A Community Call to Action to Prioritize Inclusion and Enrollment of Women in HIV Cure-related Research

In diversity there is beauty
and there is strength
—Dr. Maya Angelou

To the Editors:

In the spirit of the words of late author, poet, and civil rights activist, Dr. Maya Angelou, global communities of advocates for diversity and equity in HIV clinical research took a moment to rejoice at the results of a late breaker abstract submitted by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1107 study team at the 2022 Conference on Retroviruses and Opportunistic Infections (CROI). It was revealed that a fourth individual, a US mixed-race Black woman, achieved HIV viral remission 37 months after an analytic treatment interruption (ATI) using a CCR5Δ32/Δ32 haplo-cord transplant for the treatment of acute myelogenous leukemia (AML).[1] She joins Timothy Ray Brown (1966–2020), the Düsseldorf patient, Adam Castillejo, and a potentially fifth cured individual, all of whom received an allogenic hematopoietic stem cell transplantation (HSCT) from a donor homozygous for the CCR5Δ32 deletion to treat hematologic malignancies, with subsequent sustained remission from HIV (The authors acknowledge the limitations of terms like "sustained viral remission" and how these terms may create a false sense of hope for an HIV cure among people with HIV. We recognize the desires of the Global Community for consistent use of less stigmatizing language when discussing HIV cure-related research. This discussion, although critical, is beyond the scope of our article).[2–4]

We as Community of women living with and/or affected by HIV (herein referred to as Community) believe the news of a woman FINALLY being included among the complex global discourse involving an HIV cure after an HSCT is one step in the right direction away from the historical and paternalistic practices that have unjustly limited women's participation in HIV clinical research broadly, and HIV cure-related research specifically.[5,6] Unfortunately, women screen-out of HIV research studies at higher rates than men for reasons that include desire for future pregnancies, ongoing breastfeeding, and strict contraception requirements.[5] These practices directly infringe on women's sexual and reproductive rights by limiting access to research based on current or potential pregnancy or imposing strict contraceptive requirements (above and beyond standard practice). In addition, many women may be unwilling to participate because of sociostructural barriers that include stigma and limited logistical support from sites including childcare, inconvenient transportation, and site hours of operation.[7]

The drastic underrepresentation of women in HIV cure-related research is particularly concerning. Women represented a paltry 11.1% of participants in HIV cure studies,[8] despite comprising more than half of people with HIV worldwide[9]; a statistic that in part reflects the disconnect between where most women with HIV live and the resource-rich settings where most HIV cure-related trials are taking place.[10] There has been extremely limited participation of transgender women in HIV-cure related research, and few studies have examined transgender women's perceptions about HIV cure-related research.[11] This reflects both the historic underrepresentation of transgender women and the common and harmful practices of sex and gender misclassification.[12]

Women can be meaningfully included in HIV cure studies. For example, the landmark A5366 study (Selective Estrogen Receptor Modulators to Enhance the Efficacy of Viral Reactivation with Histone Deacetylase Inhibitors), conducted by AIDS Clinical Trials Group (ACTG) investigators, was the first and the only HIV cure-related research study conducted exclusively among women.[13] Although the study did not include an analytical treatment interruption (ATI), it did include a pharmacologic intervention. Investigators were able to complete enrollment within 3 months of study initiation with overall positive feedback from most study participants.[14] More research needs to be conducted to better understand how to support women's participation in trials that include challenging procedures such as ATIs.[15]

It is also important to reference 2 recent reports of HIV "cure" in women without an intervention. The Esperanza Patient[16] and Loreen Willenberg[17] (San Francisco patient) are examples of exceptional elite controllers who achieved HIV remission without the benefit of antiretroviral therapy (ART). These cases underscore how the inclusion of women can advance HIV cure science in novel ways.

Previous research that included women as study participants has highlighted the effects of sex assigned at birth on HIV pathogenesis, persistence, and treatment response[18] and how sex differences may affect the HIV reservoir and immune response to therapeutic

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approaches being investigated as cure strategies.[19] Sex-based analyses are imperative at all stages of clinical research to understand the crucial differences in HIV reservoir dynamics. The National Institute of Health (NIH) Policy on Sex as a Biological Variable asserts that biological sex, "may be critical to the interpretation, validation, and generalizability of research findings."[20] Furthermore, a 2001 Institute of Medicine report the significance of sex as a variable in both human and experimental studies.[21] These considerations support the scientific rationale to include women and fundamentally all sexes and genders in HIV cure research. Other policy-related frameworks that highlight the importance of gender diversity in research should also be considered. For example, the NIH Revitalization Act of 1993 provided a federal level mandate that all NIH supported research must include women and minority populations. Additionally, tenets of the Universal Declaration of Human Rights (UDR) (1948) and Article 15 of the International Covenant on Economic, Social and Cultural Rights (ICESCR) (1996) affords the right to the benefits of scientific progress to all people.[22] Meaningful inclusion of women in HIV clinical research, a critical health justice consideration, was reaffirmed in the Consensus Study Report by the National Academies of Science, Engineering, and Medicine, "Improving Representation in Clinical Trials and Research."[23] Notwithstanding these policy frameworks, and despite clear guidelines to include information about sex and gender (and other demographic variables), presentations and posters at major HIV-related conferences, such as Conference on Retroviruses and Opportunistic Infections (CROI), still do not consistently and accurately report sex and gender findings.[24]

In its current state, HIV cure research does not equitably engage the full spectrum of people disproportionately affected by HIV. In addition to women, other racial, ethnic, and gender minority populations are also systematically underrepresented in cure research (ie, Black, Latinx, and transgender people).[15] Researchers should affirm the NIH's commitment to stand against structural and systemic racism and other practices that perpetuate racial inequalities in biomedical research.[25] Until then, any promise of an HIV cure will not be accessible to all populations affected by HIV other than white men who are consistently oversampled as participants in HIV cure research.

We as Community offer several action steps to support an HIV cure research infrastructure that is inclusive of women.

We call for:

- Full support of women's bodily autonomy and decision-making processes to freely decide whether to participate in an HIV cure study
- Consideration of women's sexual and reproductive freedoms that intersect with their ability to meaningfully participate in research
- The end of overly restrictive contraception requirements and documentation as part of inclusion criteria for HIV cure studies
- Provide no-cost, easily accessible contraception as part of study participation
- Targeted representation and enrollment of women in HIV cure research at all phases, not only those in phase 2b or higher
- Engagement of community and other women early in study development
- Meaningfully involve women from resource-limited settings to lead HIV cure research and advocacy related efforts
- Conduct of HIV cure trials in resource-limited settings for women from resource-limited settings, where the burden of the HIV epidemic lies
- Inclusion of sociobehavioral sciences research to understand and address barriers to women's enrollment and retention in clinical trials
- Clinical trial protocols to specifically state the minimum percent enrollment for women; clinical research sites should be given adequate time, resources, and support to enroll women
- Clinical trial protocols to be written to include sex-based comparisons, when appropriate, so that necessary information can be collected as trials are conducted
- Scientific conferences and journals to enforce requirements for the inclusion of sex and gender data or at least a concrete plan to collect these data in a future follow-up study
- Accurately report sex and gender (ie, to avoid misclassifying transgender women and/or nonbinary individuals)
- Publications to report numbers of women enrolled, even when it is zero
- Identification of the sex of cell lines and animals (in preclinical studies), in addition to sex and gender of human participants.

As a Community of women with HIV and affected by HIV and a concerned group of global women's health and HIV advocates, activists, educators, scientists, ethicists, mothers, and daughters, we stand in solidarity to offer these final remarks: a time of reckoning within the field of HIV cure research is seriously needed if women are to be equal beneficiaries of the scientific advances related to a cure. Acclaimed author and activist, Malala Yousafzai reminds us, "We cannot all succeed when half of us are held back."[26] Let us all abide these words as we rebuild a research enterprise that truly embraces

FIGURE 1. Graphic representation of diverse groups of women.

intentionality and sex and gender diversity in HIV cure research while we finally lay to rest current research paradigms and social practices that reinforce women's inequality. It is BEYOND time we support women's bodily autonomy while prioritizing women's inclusion and enrollment in HIV cure research. Without women, there will be no cure (Fig. 1).

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