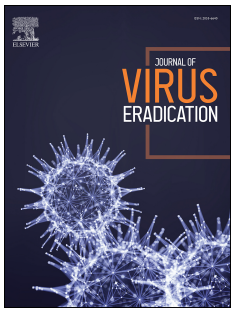

Bringing social context into global biomedical HIV cure-related research: An urgent call to action

Annie Miall, Rio McLellan, Krista Dong, Thumbi Ndung'u, Parya Saberi, John A. Sauceda, Karine Dubé

PII: S2055-6640(21)00035-2

DOI: https://doi.org/10.1016/j.jve.2021.100062

Reference: JVE 100062

To appear in: *Journal of Virus Eradication*

Received Date: 18 October 2021

Accepted Date: 27 December 2021

Please cite this article as: A. Miall, R. McLellan, K. Dong, T. Ndung'u, P. Saberi, J.A. Sauceda, K. Dubé, Bringing social context into global biomedical HIV cure-related research: An urgent call to action, *Journal of Virus Eradication* (2022), doi: https://doi.org/10.1016/j.jve.2021.100062.

Bringing Social Context into Global Biomedical HIV Cure-Related Research: An Urgent Call to Action

Authors
Annie Miall[1]*, Rio McLellan[1]*, Krista Dong[2,3,4], Thumbi Ndung'u[3,5,6,7], Parya Saberi[8], John A. Sauceda[8], Karine Dubé[9]

*Annie Miall and Rio McLellan are joint first authors.

Author Affiliations
1. Harvard College, Cambridge, MA, USA
2. Harvard Medical School, MA, USA
3. Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA
4. Massachusetts General Hospital, MA, USA
5. Africa Health Research Institute (AHRI), Durban, South Africa
6. HIV Pathogenesis Programme, The Doris Duke Medical Research Institute, University of KwaZulu-Natal, Durban, South Africa
7. Division of Infection and Immunity, University College London, London, UK
8. Center for AIDS Prevention Studies (CAPS), Division of Prevention Sciences, University of California San Francisco (UCSF), San Francisco, CA, USA
9. UNC Gillings School of Global Public Health, Chapel Hill, NC, USA

Corresponding Author
Karine Dubé, DrPH, MPhil
UNC Gillings School of Global Public Health
4108 McGavran-Greenberg Hall
Chapel Hill, NC, USA
Email: karine_dube@med.unc.edu

Viewpoint

Advances in science have ushered in a wave of new potential curative and control strategies for HIV that could eliminate the current requirement for life-long antiretroviral therapy (ART) for people living with HIV (PLWH) (Deeks et al. 2016). These strategies, proposed to be applied mostly as combination therapies include early treatment initiation to reduce the size of the HIV reservoir and preserve antiviral immune responses, latency reversal agents, HIV transcriptional silencing ("block and lock"), immunotherapies to enhance existing immune responses, and gene therapies to engineer HIV-specific immunity in T-cells or alter cellular susceptibility to HIV infection (Peterson and Kiem 2018). With the advent of new biomedical therapeutic strategies, there emerges a parallel need for consideration of acceptability, accessibility, and scalability of these potential curative strategies (Dubé, Auerbach, et al. 2019).

Globally, many vulnerable populations are disproportionately affected by HIV. It is therefore critical to consider social contexts in the development of HIV cure trial protocols. This will ensure optimal recruitment, retention, fidelity to the protocol (e.g., adhering to treatment and other trial requirements), and efficacy at scale within current HIV endemic areas. For example, in the United States (US), gay, bisexual, and other men in same gender relationships are the most affected demographic by HIV ("U.S. Statistics" 2021). However, 70% of the global HIV burden is borne by sub-Saharan Africa (SSA) with the highest rates of infection occurring in adolescent girls and young women (AGYW) who are up to six times more likely to have HIV compared to their male peers (Abdool Karim, Havlir, and Phanuphak 2020). Most current HIV cure clinical trial designs and related social support strategies (emotional, informational, instrumental) included to improve study success, are aimed at US demographics and may not translate to those in low and middle-income countries (LMICs) given the disparities between affected populations (Qiao, Li, and Stanton 2014). For example, men in the same gender relationships in the US may experience different relationship dynamics than women in SSA face with their male partners. Many women report not feeling comfortable or safe disclosing their status or seeking treatment due to fear of gender-based violence (GBV) or discrimination (Beesham et al. 2021; Mthembu et al. 2021). Implementing a generalized approach in supporting adult men in same gender relationships in the US versus AGYW trial participants in SSA may have consequences on research participation and patient/partner safety differential effects due to regional-specific challenges, beliefs, resources, HIV-associated stigma, and other factors related to setting, age, or social context.

Biological and behavioral risk factors for HIV acquisition by AGYW in SSA are inseparable from the social context in which these young women live (Gosmann et al. 2017). This environment presents regional-specific challenges for AGYW including heightened poverty risk compared to their male counterparts, GBV, and unequal gender-power dynamics (Abdool Karim, Havlir, and Phanuphak 2020). For instance, exposure to intimate partner violence (IPV) and poor partner communication are key deterrents governing a woman's ability to negotiate condom usage. Adolescent pregnancy and domestic responsibilities additionally limit the ability to complete secondary education which further impacts health, options for employment, and ability to achieve economic independence (Ahinkorah et al. 2021). Challenges such as these serve as barriers to enrolling in and completing clinical trials while contributing to intergenerational cycles of poverty, low levels of education as well as unemployment (Ahinkorah et al. 2021). Failing to consider the social contexts that AGYW lives within limit the ability to include them in HIV cure research studies. Therefore, in developing interventions and designing the structure of trials to assess them, the inclusion of socio-behavioral research to identify AGYW-specific concerns may inform future HIV cure-related research on the feasibility, acceptability, and tolerability of participation.

An example of a cohort established to further HIV cure research that included social context in its design is the FRESH Acute HIV study (Ndung'u et al. 2018). FRESH, *Females Rising through Education, Support and Health,* was launched in 2012 in KwaZulu-Natal South Africa, in a community with one of the highest HIV infection rates in the world (Dong et al, 2018). The study recruits young sexually active women who are at high risk of HIV acquisition to undergo frequent HIV testing and biological sampling. Enrolled in groups of 20-30 women from a community where teen pregnancy, food insecurity, school drop-out, and limited access to jobs is the norm, study participants are co-enrolled in a 9-month life skills and empowerment program that coincides with their study visits. In groups designed to promote a sense of belonging, participants learn about self-esteem, communication, budgeting, basic computer skills, resume writing, interview strategies, and go on field trips to explore work options. At the same time, routine monitoring of mental health, sexual risk behavior, and risk perception for HIV infection are evaluated while providing pre-exposure prophylaxis (PrEP) to reduce the risk of HIV infection, and PrEP is provided along with intensive prevention counseling. The FRESH program has an over 80% placement rate of participants in jobs, internships, return to school, or starting their own business within 1 year of completing the program. To date, this approach has enabled the identification of 94 acute HIV infections, mostly during Fiebig stage I, within a median of 4 days since the last negative HIV RNA test and initiation of ART within 1 day of detection (Ndung'u et al, 2018). The FRESH approach of incorporating a social intervention within the clinical research protocol has been effective at addressing participant needs that would otherwise present as barriers to enrollment in clinical trials. It also contributed toward the establishment and successful long-term follow-up of a cohort of women living with HIV who have limited viremia, reservoir size, and viral diversity due to early detection and treatment, who are ideal candidates for HIV cure-related clinical trials (Ananworanich, Dubé, and Chomont 2015). This model provides investigators with a real-world test ground for HIV prevention, treatment and cure-related interventions in an area of the world where the need continues to be disproportionately high.

Participation in HIV cure studies includes additional psychosocial and biological risks and ethical challenges. An example is a need for analytical treatment interruption (ATI) – or the temporary stopping of ART – to determine whether HIV cure interventions are effective. ATIs risk negative health and personal outcomes in requiring the stopping of treatment, disclosure of HIV and ATI status to partners/family members, and negotiation of protection measures with sexual partners while participants are off ART (e.g. referral for PrEP) to prevent HIV transmission (Julg et al. 2019; Peluso et al. 2021). In negotiating issues of disclosure and partner protections, attention must be paid upfront to gender and relationship power dynamics, equity, and GBV approaches in the design of these trials (Dubé et al. 2021). This can only be accomplished through the intentional and proactive collection, reporting, and incorporation of socio-behavioral research findings into the design of trials.

In order to adequately address individualized factors influencing research participation by PLWH, HIV cure-related research must expand beyond standard biomedical outcomes to better align ethical risk/benefit ratios with needs and context for AGYW. This alignment will ensure that any potential future community benefits promised by the study outweigh any risks to participant safety and health (Dubé, Barr, et al. 2019). Integration of biomedical and socio-behavioral science positions PLWH and other key stakeholders, such as intimate partners and family members, as active contributors in advancing the cure field. This approach takes into consideration their expertise and lived experience throughout the development pipeline, from conceptualization of interventions, to study design and support strategy development as opposed to a generalized approach where one size does not fit all. Because PLWH live within complex contexts, we must anticipate social-structural factors directly

affecting the successful implementation of clinical trials. Therefore, we make a call to action to include socio-behavioral components as instrumental in future HIV cure trials.

References

Abdool Karim, Quarraisha, Diane Havlir, and Nittaya Phanuphak. 2020. "Putting Women in the Centre of the Global HIV Response Is Key to Achieving Epidemic Control!" *Journal of the International AIDS Society* 23 (3): e25473.

Ahinkorah, Bright Opoku, Melissa Kang, Lin Perry, Fiona Brooks, and Andrew Hayen. 2021. "Prevalence of First Adolescent Pregnancy and Its Associated Factors in Sub-Saharan Africa: A Multi-Country Analysis." *PloS One* 16 (2): e0246308.

Ananworanich, Jintanat, Karine Dubé, and Nicolas Chomont. 2015. "How Does the Timing of Antiretroviral Therapy Initiation in Acute Infection Affect HIV Reservoirs?" *Current Opinion in HIV and AIDS* 10 (1): 18–28.

Beesham, Ivana, Renee Heffron, Shannon Evans, Jared M. Baeten, Jenni Smit, Mags Beksinska, and Leila E. Mansoor. 2021. "Exploring the Use of Oral Pre-Exposure Prophylaxis (PrEP) Among Women from Durban, South Africa as Part of the HIV Prevention Package in a Clinical Trial." *AIDS and Behavior* 25 (4): 1112–19.

Deeks, Steven G., Sharon R. Lewin, Anna Laura Ross, Jintanat Ananworanich, Monsef Benkirane, Paula Cannon, Nicolas Chomont, et al. 2016. "International AIDS Society Global Scientific Strategy: Towards an HIV Cure 2016." *Nature Medicine* 22 (8): 839–50.

Dubé, Karine, Judith D. Auerbach, Michael J. Stirratt, and Paul Gaist. 2019. "Applying the Behavioural and Social Sciences Research (BSSR) Functional Framework to HIV Cure Research." *Journal of the International AIDS Society* 22 (10): e25404.

Dubé, Karine, Liz Barr, David Palm, Brandon Brown, and Jeff Taylor. 2019. "Putting Participants at the Centre of HIV Cure Research." *The Lancet. HIV* 6 (3): e147–49.

Dubé, Karine, John Kanazawa, Chadwick Campbell, Cheriko A. Boone, Allysha C. Maragh-Bass, Danielle M. Campbell, Moisés Agosto-Rosario, et al. 2021. "Considerations for Increasing Racial, Ethnic, Gender, and Sexual Diversity in HIV Cure-Related Research with Analytical Treatment Interruptions: A Qualitative Inquiry." *AIDS Research and Human Retroviruses*, May. https://doi.org/10.1089/AID.2021.0023.

Gosmann, Christina, Melis N. Anahtar, Scott A. Handley, Mara Farcasanu, Galeb Abu-Ali, Brittany A. Bowman, Nikita Padavattan, et al. 2017. "Lactobacillus-Deficient Cervicovaginal Bacterial Communities Are Associated with Increased HIV Acquisition in Young South African Women." *Immunity* 46 (1): 29–37.

Julg, Boris, Lynda Dee, Jintanat Ananworanich, Dan H. Barouch, Katharine Bar, Marina Caskey, Donn J. Colby, et al. 2019. "Recommendations for Analytical Antiretroviral Treatment Interruptions in HIV Research Trials-Report of a Consensus Meeting." *The Lancet. HIV* 6 (4): e259–68.

Mthembu, Jacqueline, Musawenkosi Mabaso, Sarah Reis, Khangelani Zuma, and Nompumelelo Zungu. 2021. "Prevalence and Factors Associated with Intimate Partner Violence among the Adolescent Girls and Young Women in South Africa: Findings the 2017 Population Based Cross-Sectional Survey." *BMC Public Health* 21 (1): 1160.

Ndung'u, Thumbi, Krista L. Dong, Douglas S. Kwon, and Bruce D. Walker. 2018. "A FRESH Approach: Combining Basic Science and Social Good." *Science Immunology* 3 (27). https://doi.org/10.1126/sciimmunol.aau2798.

Peluso, Michael J., Lynda Dee, Shirley Shao, Jeff Taylor, Danielle Campbell, Simon Collins, Monica Gandhi, et al. 2021. "Operationalizing Human Immunodeficiency Virus Cure-Related Trials with Analytic Treatment Interruptions During the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pandemic: A Collaborative Approach." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 72 (10): 1843–49.

Peterson, Christopher W., and Hans-Peter Kiem. 2018. "Cell and Gene Therapy for HIV Cure." *Current Topics in Microbiology and Immunology* 417: 211–48.

Qiao, Shan, Xiaoming Li, and Bonita Stanton. 2014. "Social Support and HIV-Related Risk Behaviors: A Systematic Review of the Global Literature." *AIDS and Behavior* 18 (2): 419–41.

"U.S. Statistics." 2021. June 2, 2021. https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics.

Acknowledgements
The authors would like to thank all participants in the FRESH (Female Rising through Education, Support and Health) cohort, as well as the HIV Pathogenesis Programme (HPP) Community Advisory Board.

Funding
For ensuring that women are represented in HIV cure research, we thank the FRESH study participants, the FRESH clinical research and ITEACH (Integration of TB in Education and Care for HIV/AIDS) teams, the UKZN HPP (University of KwaZulu-Natal HIV Pathogenesis Programme) laboratory staff and members of the Community Advisory Board. The work at FRESH has been made possible by the generosity of Ursula Brunner, Richard and Lisa Witten, Dan and Marjie Sullivan, Mike and Keke McCune, and supported in part by grants from the Bill and Melinda Gates Foundation (OPP1212883), the International AIDS Vaccine Initiative (IAVI) (UKZNRSA1001), Gilead Sciences (PA-HIV-16-0066), the National Institute of Allergy and Infectious Disease (NIAID) (R37AI67073), and the Ragon Institute of MGH, MIT and Harvard.

P.S. and K.D. are supported by the National Institute of Mental Health (NIMH) (award number R21MH122280) to engage diverse young adults living with HIV on cure-related research in the United States. J.S. and K.D. are supported by the NIMH (award number R01MH126786) to investigate the psychosocial aspects of HIV treatment interruptions in the United States.

Conflict of Interest
The authors have no conflict of interest to declare.

Conflict of Interest

The authors have no conflict of interest to declare.