Workshop ~ 8 March 2025

IAS2025: 2664

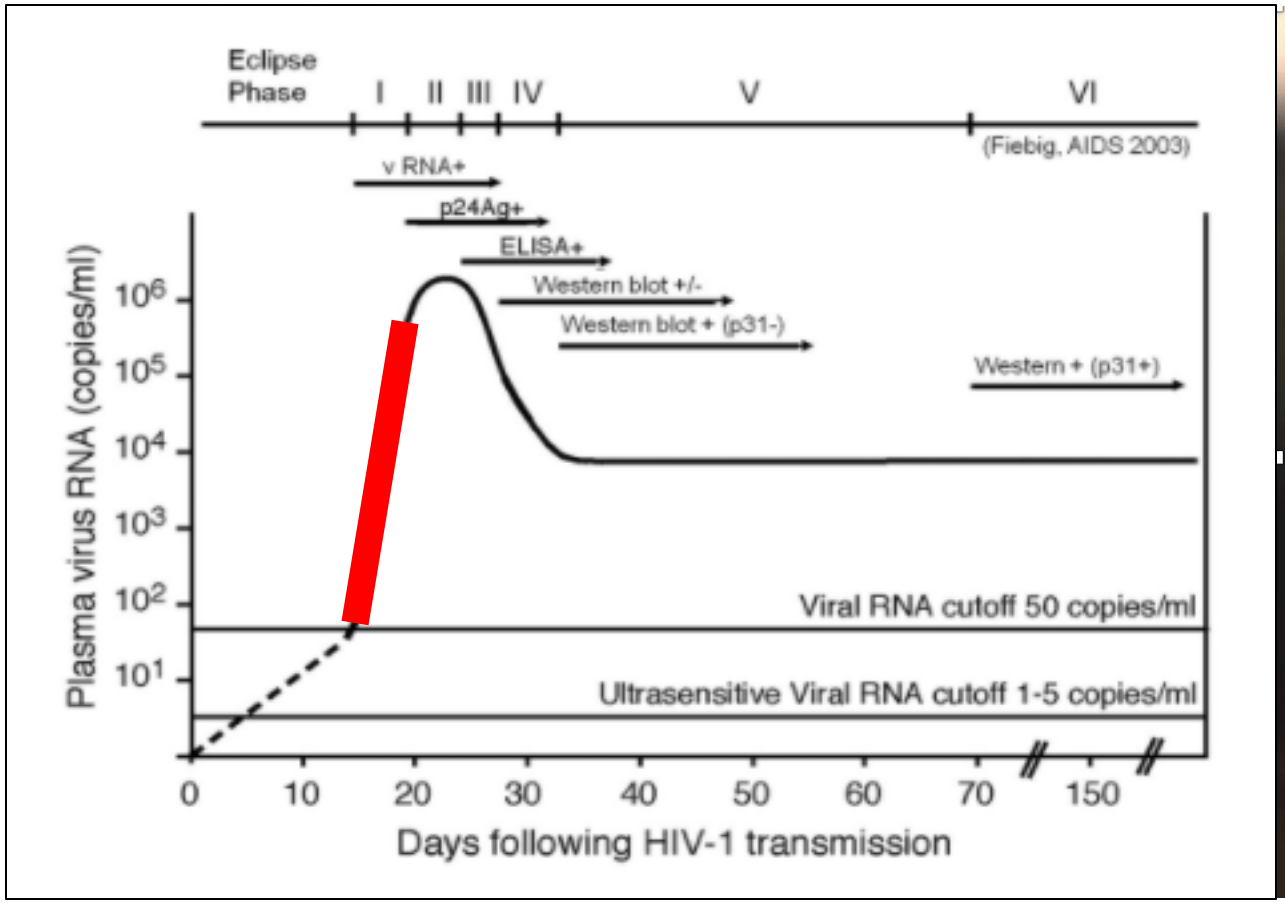
Perspectives of Partners and Families on the Psychosocial Impacts of Analytical Treatment Interruptions in HIV Cure Research in Durban, South Africa

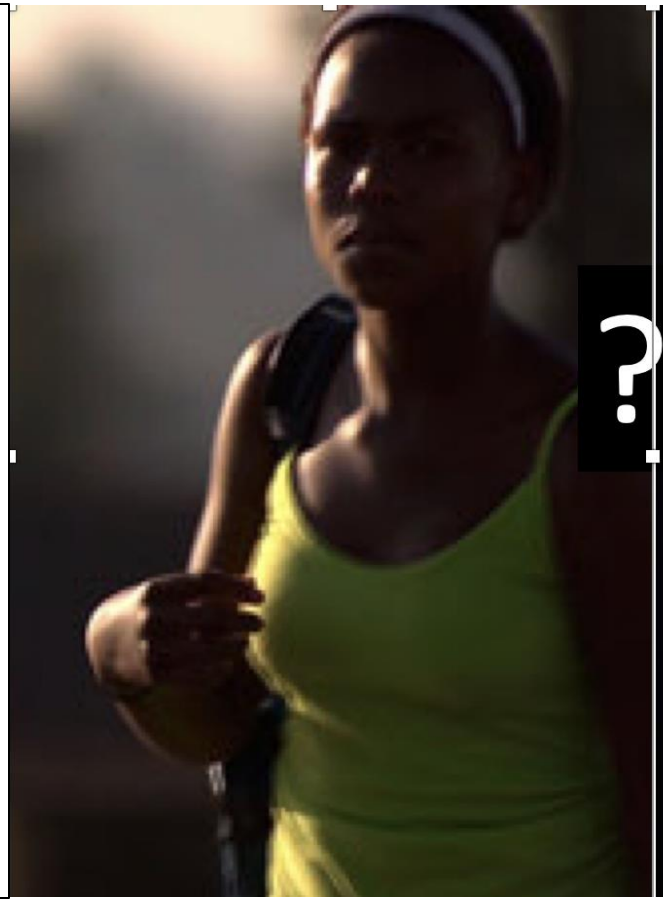
K. Dong[1,2,3], M.W. Ngcobo[4], D. Mthimkhulu[4], N. Langa[4], A. Zulu[4], L. Maphalala[5], V. Pillay[5], M. Mthembu[6], W. Tran[7], R. Lau[7], A. Miall[5], D. Mindry[8], A. Ahmed[7], T. Ndung'u[9,10,11], K. Dube[7]

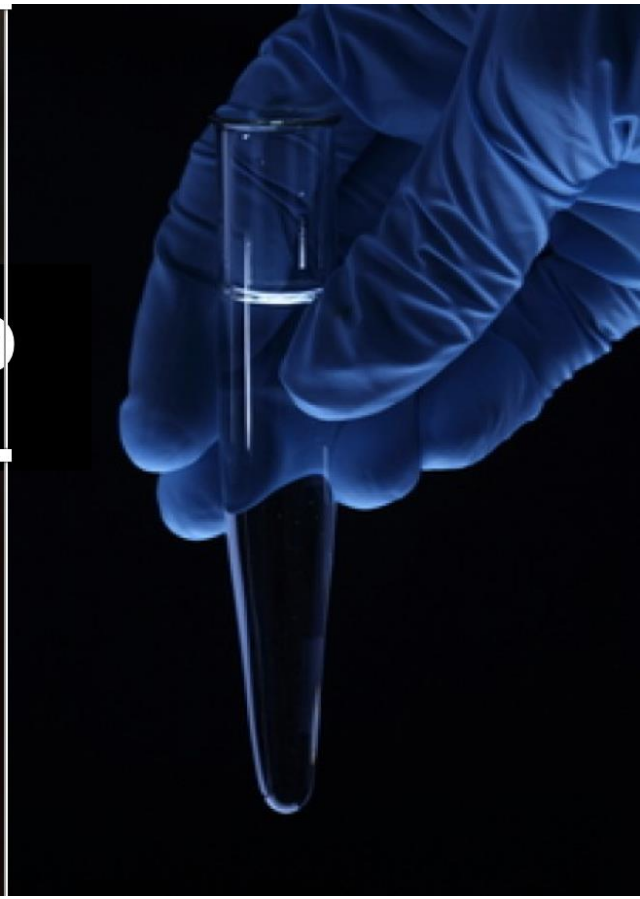
Implementing an ATI-inclusive HIV Cure Trial in South Africa; *Lessons the FRESH Cohort*

Krista L Dong, MD
Associate Professor, Harvard Medical School
Clinical Director, FRESH Clinical Research Site
Director, Integration of TB in Education and Care for HIV/AIDS
Core Member, Ragon Institute of Mass General, MIT and Harvard

Original aim of the FRESH cohort







Fiebig Stage I

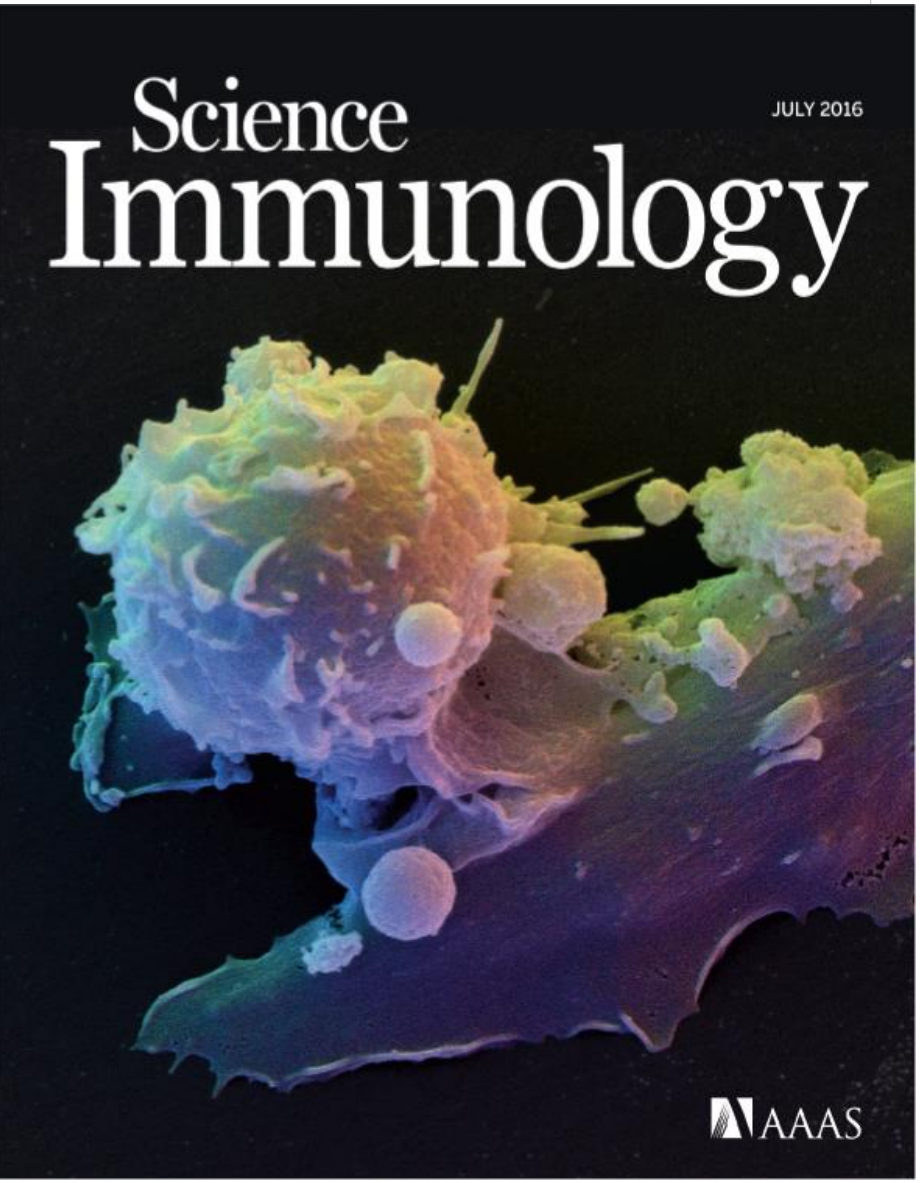
9-months, HIV-RNA twice per week (Finger-prick)

Detect acute HIV infection at earliest timepoint

Empowerment, job-life skills

Work, return to school or start a small business

Translation



HIV

A FRESH approach: Combining basic science and social good

by [illegible]

FRESH and socioeconomic empowerment

The FRESH program has been operational for more than 5 years, during which time HIV incidence in the cohort has remained more than 8% per 100 person-years (*1*), which is consistent with reported incidence rate in South Africa among women in the target age group. Adherence to the FRESH study visits and blood and vaginal mucosal sampling has been outstanding and likely heightened by integration with the socioeconomic empowerment curriculum and the continual iterative development of the curriculum so as to ensure a high level of relevance and perceived benefit by participants. Of those completing the program, a greater than 85% rate of placement in jobs or internships, starting a small business, or returning to school has been sustained (*1*).

Biologic factors that affect HIV acquisition risk in FRESH

The FRESH study design has provided key mechanistic insights into the biological factors that predispose women to HIV infection. Consistent with data from other South African studies, we found a high prevalence of asymptomatic sexually transmitted infections (*2*), which calls for a reevaluation of the current syndromic approach to the diagnosis and treatment of sexually transmitted infections in South Africa. The availability of longitudinal follow-up data and pre- and post-infection biological samples enabled key insights regarding biological determinants of HIV acquisition. For example, we identified

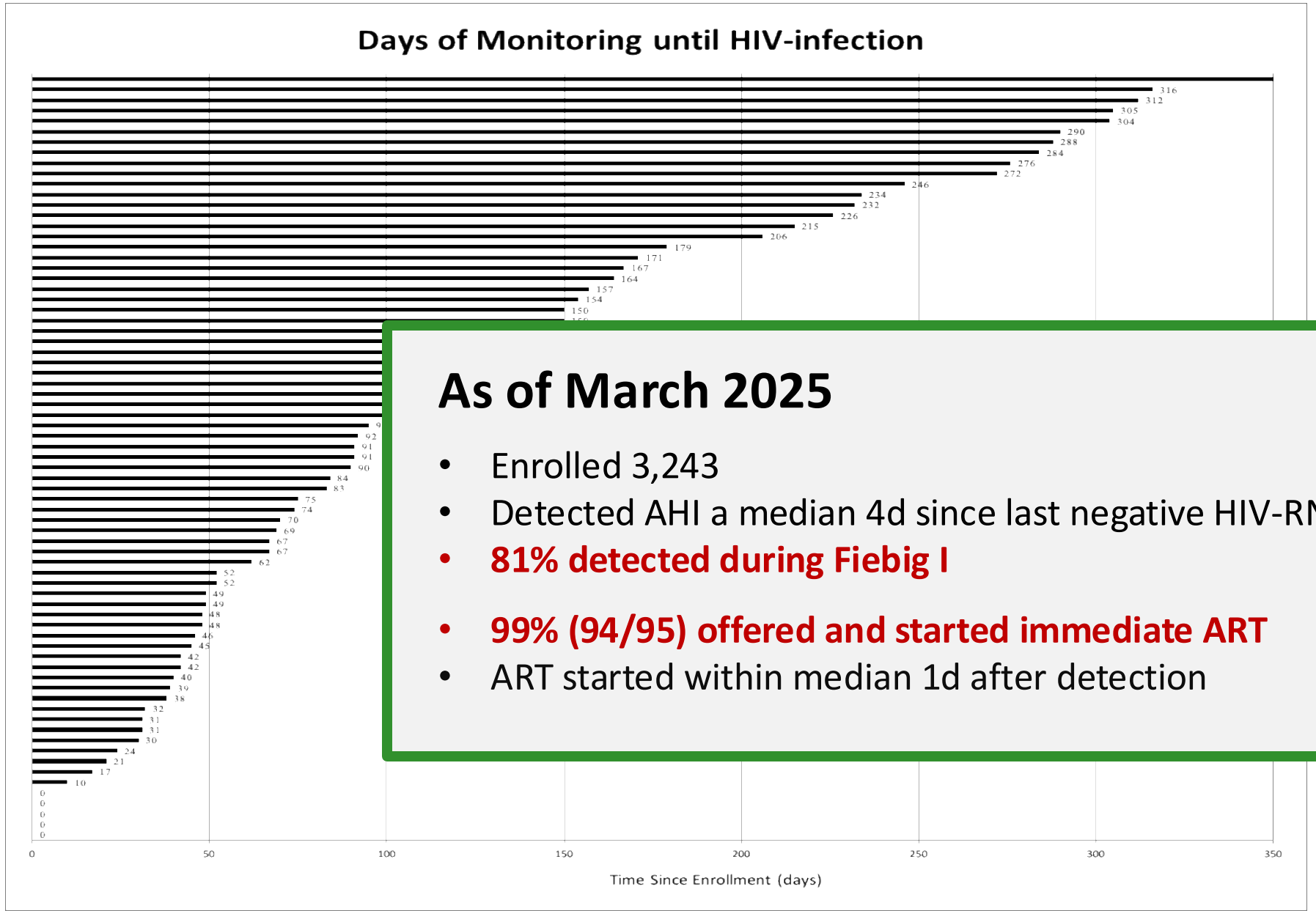
Investigators share results with FRESH team

Allow investigators learn from Study Participants

MGH/Ragon Investigators
(Caroline Mitchell)

South African Investigators
(Thumbi Ndung’u)

109 hyper-acute infections detected



As of March 2025

- Enrolled 3,243
- Detected AHI a median 4d since last negative HIV-RNA
- **81% detected during Fiebig I**
- **99% (94/95) offered and started immediate ART**
- ART started within median 1d after detection

A Platform for Conducting **[patient-centered]** HIV Cure-related Research

health Department: Health PROVINCE OF KWAZULU-NATAL | HEALTH SYSTEMS TRUST | WITTEN FAMILY FOUNDATION | Mass General Brigham | UNIVERSITY OF KWAZULU-NATAL INYUVESI YAKWAZULU-NATALI | HIV PATHOGENESIS PROGRAMME | ITEACH | Ragon Institute MASS GENERAL I MIT I HARVARD

HIV Cure Trial with an ATI

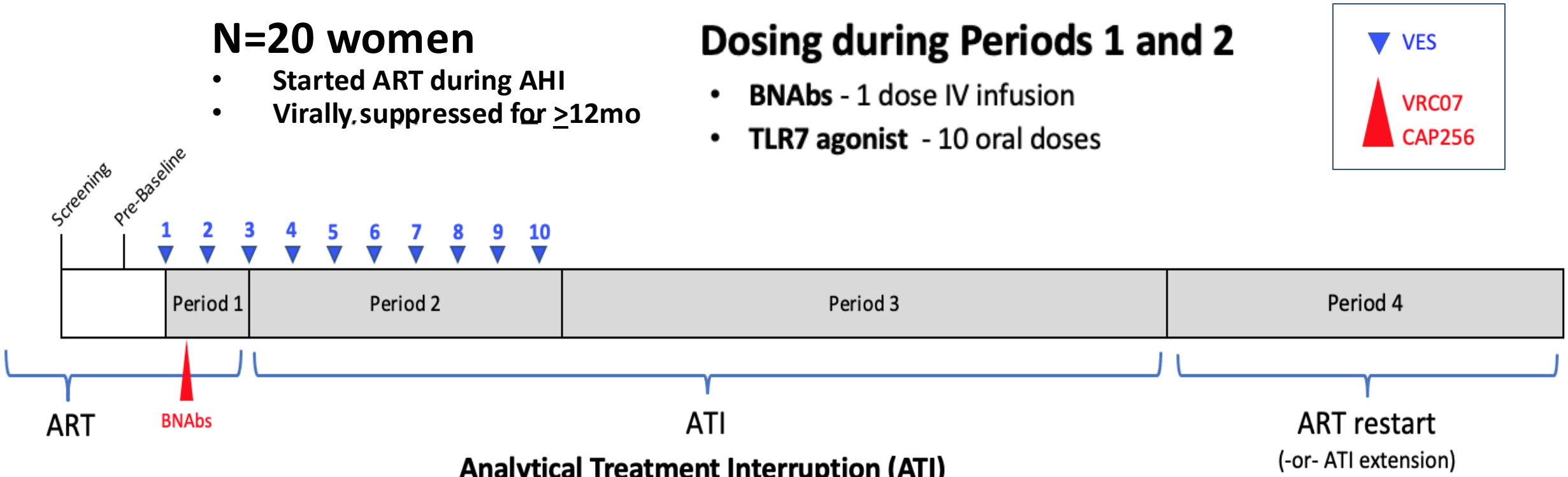
A Phase 2a Study to Evaluate the Safety and Tolerability of a Regimen of Dual Anti-HIV Envelope Antibodies, VRC07-523LS and CAP256V2LS, in a Sequential Regimen with a TLR7 Agonist, Vesatolimod, in Early Antiretroviral-Treated HIV-1 Clade C-Infected Women

N=20 women

- **Started ART during AHI**
- **Virally suppressed for ≥12mo**

Dosing during Periods 1 and 2

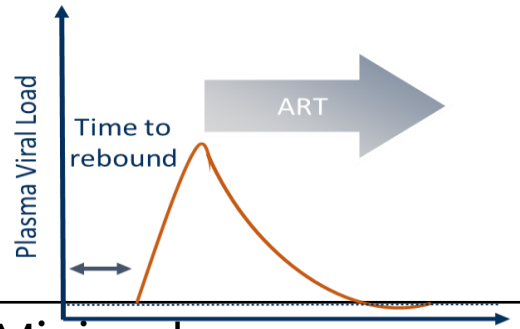
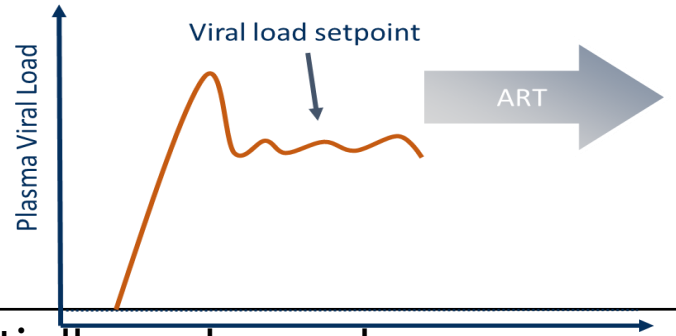
- **BNAbs** - 1 dose IV infusion
- **TLR7 agonist** - 10 oral doses



Analytical Treatment Interruption (ATI)

- Up to 44w

Two ATI Designs: *Time to rebound vs. Set point*

	ATI DESIGN	
	Time to rebound	**Set point**
ART restart	Resume ART immediately once VL detectable 	Resume ART if agreed set point not reached 
Duration of viremia	Minimal	Potentially prolonged
Risks Transmission Inflammation Reservoir reseeding	 • Low • Low • Negligible	 • Possible • Possible • Unknown
Knowledge gained	Limited • Size of the reservoir (?)	Significant • Insights into post-treatment control. • Viremia needed for some immunotherapies (?)

Things we didn't know

1. First in Africa / first in women dual-bNAb-ATI trial
2. BNAb sensitivity (mono vs dual)
3. Enrolment target - uptake/availability/retention
4. Disclosure
5. Optional LN and gut
6. ATI harms
7. Impact of ATI on family and *partners (living with and without HIV)*
8. Acts of god – floods, civil unrest, pandemic

Why was this ATI-inclusive trial at FRESH Important?

Most trials

- White men
- US/Europe
- HIV Clade B
- Resource abundant settings

HIV cure has emerged as a global research priority requiring the field to look beyond trials conducted to date;

Women remain critically underrepresented in cure research globally. Despite representing over half of HIV infections worldwide, women represent only 13% of HIV cure research participants.

We expect a lot from participants. Frequent, complex visits. Long follow-up duration. Trusts us – stop your ART during an ATI (biological risk, but also social, emotional and ethical challenges)

There is so much we don't ask or know.

Understanding barriers in high-HIV burden low- and middle-income countries (LMIC), particularly for marginalized groups, is critical to designing protocols that promote enrollment of those in greatest need of innovations in HIV cure and treatment.

Women represent over half (53%) of the global HIV burden but make up **only 17% of HIV cure trial participants**, and 18% of participants in ACTG studies.

- Barr et al. *J Virus Erad* 2019
- Smeaton et al. *Clin Infect Dis* 2020

Women, especially adolescent girls and young women who are at disproportionate risk, **must be prioritized** as a part of equitable enrolment in **HIV cure research**.

Smeaton et al. *Clin Infect Dis* 2020
Campbell et al. *J Acquir Immune Defic Syndr* 2022;

Complex HIV Cure Trial Protocols – *involved real people*

VES

VRC07
CAP256

Screening
Pre-Baseline
1 2 3 4 5 6 7 8 9 10

Period 1 | Period 2 | Period 3 | Period 4

ART
BNAbs

Analytical Treatment Interruption (ATI)

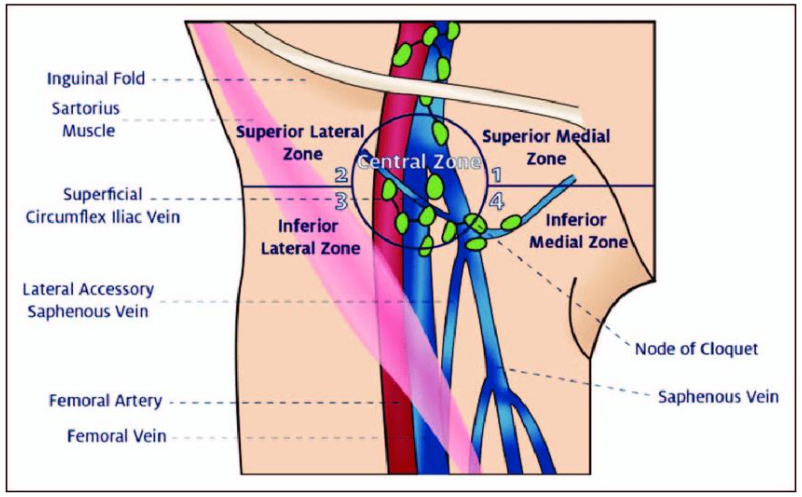
- Up to 44w

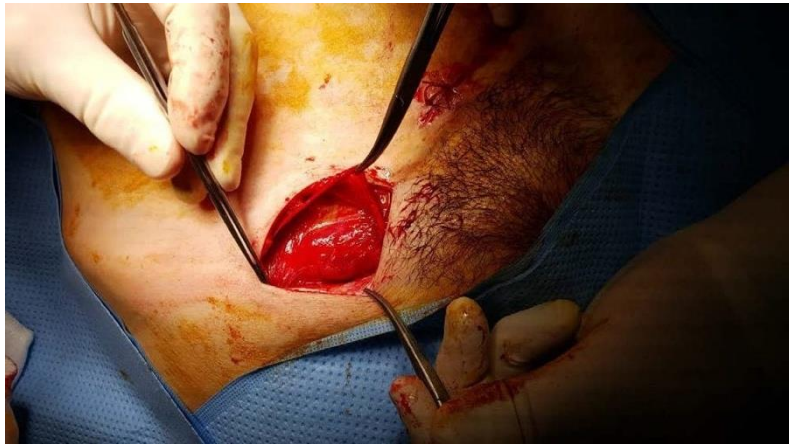
ART restart
(-or- ATI extension)

Advancing our understanding about the HIV Reservoir…

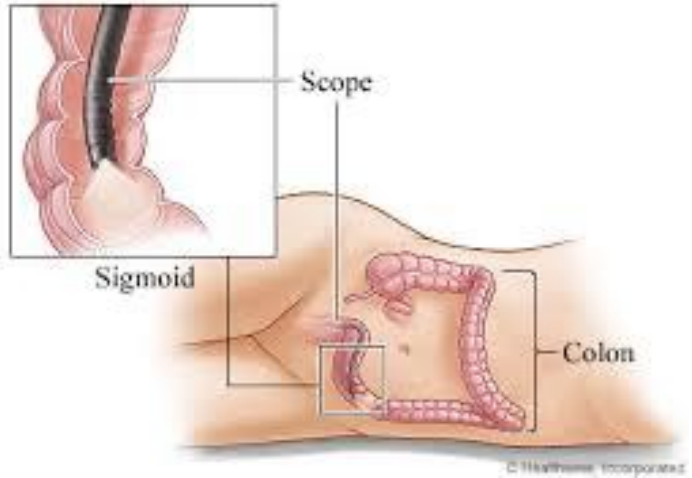
- Repeated LN Excision and GALT biopsies were optional in the FRESH-Gilead trial
- Participants have to arrival early at the clinical site
- Transportation to a private hospital
- Increase risk if elevated BMI
- High level of uptake at FRESH

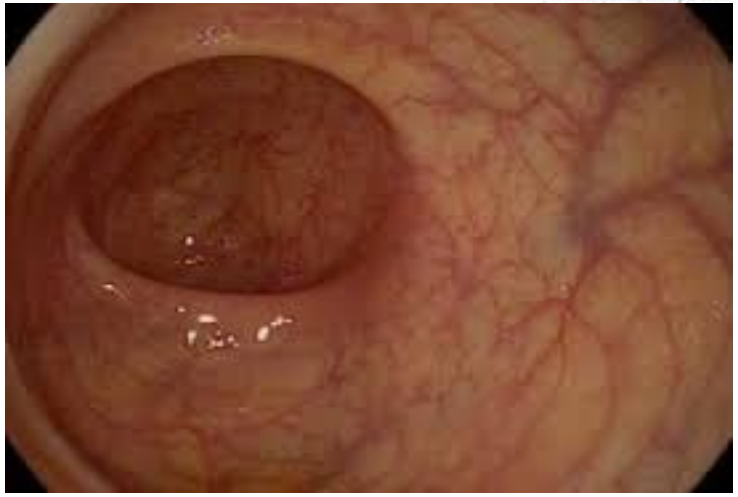
LN Excision





Gut biopsies





Leukapheresis (PBMCs)

- Arrive early at FRESH
- Transportation to tertiary hospital
- Up to 4h with arm straight
- Challenges: access failure, low flow

Leukapacks - Reddy lab (AHRI), Yu/Lichterfeld lab (Ragon)

Centering HIV cure protocols on the patient

Integra… …rc
of You… …ur
Interve… …a
Interru…

- **Ai…** wo… wi…
- **Ai…** th… …s ar…

> “…it is critical to consider social contexts in the development of HIV cure trial protocols. The biological and behavioral risk factors for HIV acquisition by study participants are inseparable from the social context in which these participants live.”

Buil… …ob… research team; trained and mentored to implement quant/qual studies in KZN, South Africa

Journal of Virus Eradication 8 (2022) 100062

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.sciencedirect.com/journal/journal-of-virus-eradication

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

Annie Miall [a,1], Rio McLellan [a,1], Krista Dong [b,c,d], Thumbi Ndung'u [c,e,f,g], Parya Saberi [h], John A. Sauceda [h], Karine Dubé [i,*]

[a] Harvard College, Cambridge, MA, USA
[b] Harvard Medical School, MA, USA
[c] Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA
[d] Massachusetts General Hospital, MA, USA
[e] Africa Health Research Institute (AHRI), Durban, South Africa
[f] HIV Pathogenesis Programme, The Doris Duke Medical Research Institute, University of KwaZulu-Natal, Durban, South Africa
[g] Division of Infection and Immunity, University College London, London, UK
[h] Center for AIDS Prevention Studies (CAPS), Division of Prevention Sciences, University of California San Francisco (UCSF), San Francisco, CA, USA
[i] UNC Gillings School of Global Public Health, Chapel Hill, NC, USA

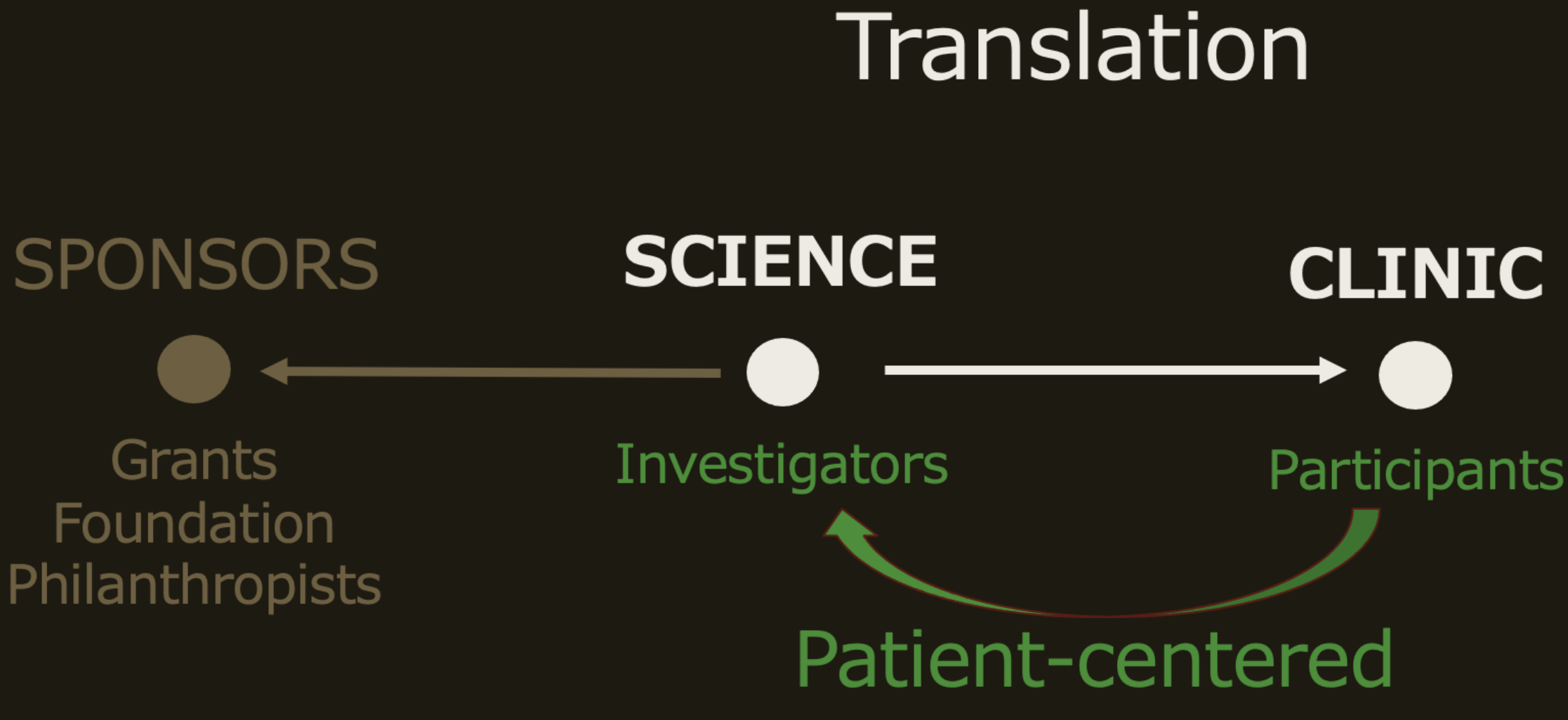
ARTICLE INFO

Keywords:
Social sciences
HIV cure research
Women
South Africa

ABSTRACT

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). In this article, we argue that it is critical to consider social contexts in the development of HIV cure trial protocols. The biological and behavioral risk factors for HIV acquisition by study participants are inseparable from the social context in which these participants live. The article discusses an example of a cohort established to further HIV cure research that included social context, called the FRESH Acute HIV study, which combines a sociostructural intervention while conducting HIV prevention, treatment and cure-related research in Durban, South Africa. We make an urgent call to action to include sociobehavioral components as instrumental in future HIV cure trials in global context.

Dr. Maud Mthembu


Translation
SPONSORS
SCIENCE
CLINIC
Grants
Foundation
Philanthropists
Investigators
Participants
Patient-centered

Socio-behavioral Research

Incorporate within ATI trials when there are important research questions to be answered related to participant experience, and for ATI trials at new sites/regions.

Opinion

Towards Multidisciplinary HIV-Cure Research: Integrating Social Science with Biomedical Research

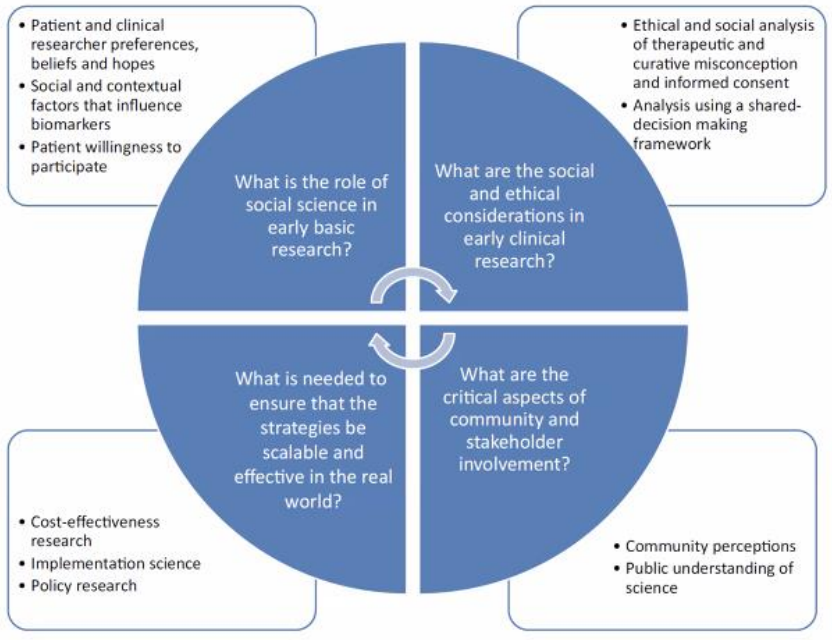


Figure 1. Critical Questions to Address in the Integration of Social Science in the HIV-Cure Research Agenda.

Dubé K et al. Journal of the International AIDS Society 2019, 22:e25404
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25404/full | https://doi.org/10.1002/jia2.25404

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

REVIEW

Applying the Behavioural and Social Sciences Research (BSSR) Functional Framework to HIV Cure Research

Karine Dubé[1,5], Judith D Auerbach[2], Michael J Stirratt[3] and Paul Gaist[4]

[5]**Corresponding Author:** Karine Dubé, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 4108 McGavran-Greenberg Hall, Chapel Hill, NC, 27599. Tel: 919-966-6617 (office). (karine_dube@med.unc.edu)

Abstract

Introduction: The search for an HIV cure involves important behavioural and social processes that complement the domains of biomedicine. However, the field has yet to tap into the full potential of behavioural and social sciences research (BSSR). In this article, we apply Gaist and Stirratt's BSSR Functional Framework to the field of HIV cure research.

Discussion: The BSSR Functional Framework describes four key research domains: (1) basic BSSR (understanding basic behavioural and social factors), (2) elemental BSSR (advancing behavioural and social interventions), (3) supportive BSSR (strengthening biomedically focused clinical trials), and (4) integrative BSSR (building multi-disciplinary combination approaches for real-world implementation). In revisiting and applying the BSSR Functional Framework, we clarify the importance of BSSR in HIV cure research by drawing attention to such things as: how language and communication affect the meaning of "cure" to people living with HIV (PLHIV) and broader communities; how cure affects the identity and social position of PLHIV; counselling and support interventions to address the psychosocial needs and concerns of study participants related to analytical treatment interruptions (ATIs); risk reduction in the course of ATI study participation; motivation, acceptability, and decision-making processes of potential study participants related to different cure strategies; HIV care providers' perceptions and attitudes about their patients' participation in cure research; potential social harms or adverse social events associated with cure research participation; and the scalability of a proven cure strategy in the context of further advances in HIV prevention and treatment. We also discuss the BSSR Functional Framework in the context of ATIs, which involve processes at the confluence of the BSSR domains.

Conclusions: To move HIV cure regimens through the translational research pathway, attention will need to be paid to both biomedical and socio-behavioural elements. BSSR can contribute an improved understanding of the human and social dimensions related to HIV cure research and the eventual application of HIV cure regimens. The BSSR Functional Framework provides a way to identify advances, gaps and opportunities to craft an integrated, multi-disciplinary approach at all stages of cure research to ensure the real-world applicability of any strategy that shows promise.

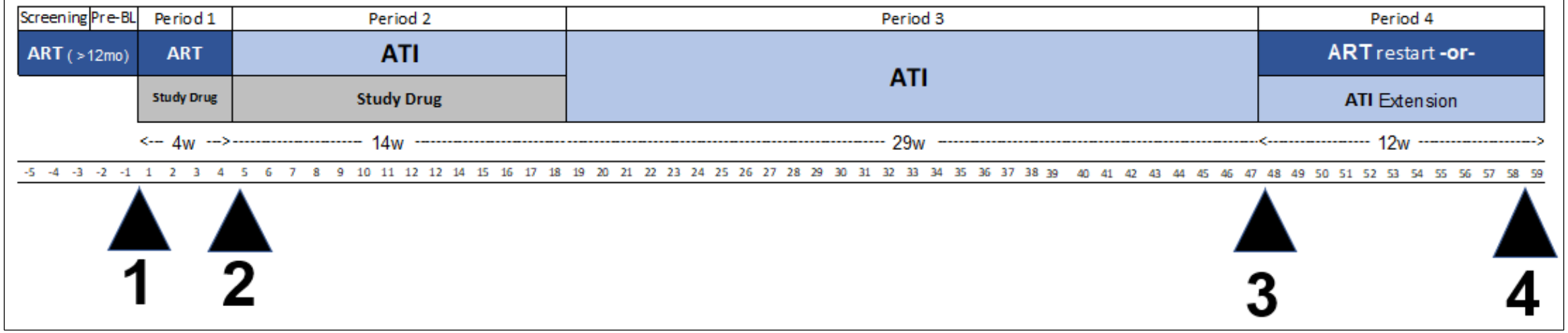
Keywords: Behavioural and Social Sciences Research (BSSR); functional framework; HIV cure research; HIV remission; analytical treatment interruption; people living with HIV

Courtesy of Karine Dube

Group 1: ATI Trial Participants

Longitudinal Assessment – 4 timepoints

1. Entry or Baseline (after trial enrollment)
2. Prior to analytical treatment interruption (pre-ATI)
3. Shortly following the resumption of ART (post-ATI)
4. At the end of the study or early discontinuation



Approximately 60/80 interviews transcribed and translated into English

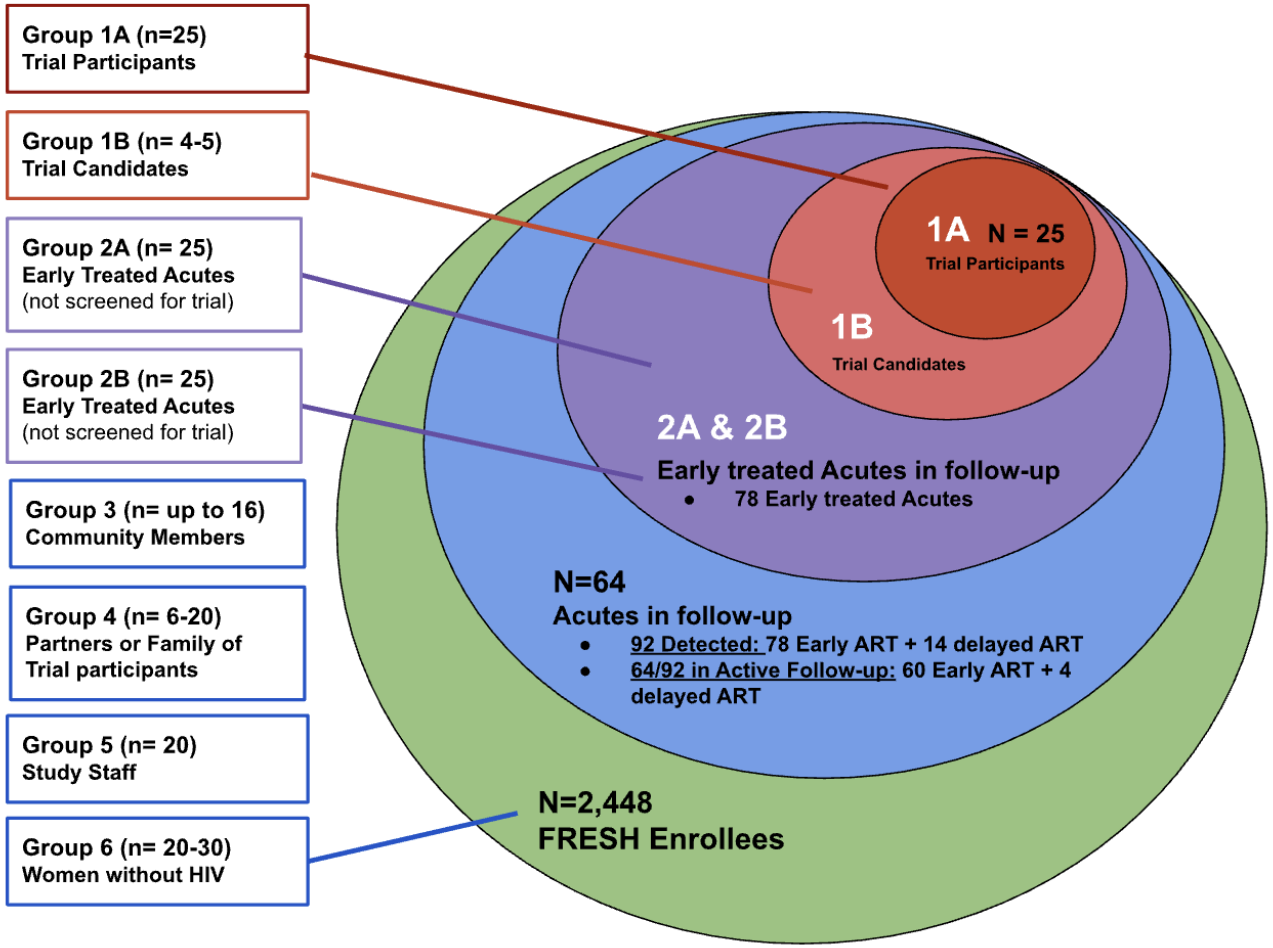
National Institute of Mental Health

Socio-Behavioral Research (SBR)


Karine Dube


Maud Mthembu


Deboarah Mindry



- Gr 1: ATI trial participants
- Gr 2: Non-trial participants
- Gr 3: Community
- Gr 4: Partners and Family Member
- Gr 5: FRESH Clinical Research Staff
- Gr 6: FRESH women without HIV

Group 2 - FRESH Women living with HIV
(Non-trial Participants)

> HIV Res Clin Pract. 2025 Dec;26(1):2455917. doi: 10.1080/25787489.2025.2455917. Epub 2025 Jan 25.

'It is scary to pause treatment': perspectives on HIV cure-related research and analytical treatment interruptions from women diagnosed during acute HIV in Durban, South Africa

Objective: To examine the perspectives of young women diagnosed with acute HIV in a longitudinal study, focusing on their perceptions on ATI-inclusive HIV cure trials and the barriers and facilitators to participation.

Methods. Conduced closed-ended surveys and in-depth interviews with 20 women aged 19-33 living with HIV, who were willing but ineligible or unable to participate in an HIV cure trial.

Conclusions: Understanding women's perspectives on HIV cure research, especially ATI trials, is vital. Building trust and addressing psychosocial challenges through a healing-centered approach can facilitate trial participation. Socio-behavioral research before and during HIV cure trials will be essential to inform participant-centered protocol design.

Group 3 – Community Members

Start early. Can provide insight into local/cultural norms, language, challenges, misunderstanding

HIV Res Clin Pract. 2023 Jul 29;24(1):2243046.

'With this study, we have hope that something is coming': community members' perceptions of HIV cure-related research in Durban, South Africa – a qualitative focus group study

Conclusions: With plans to expand HIV cure trials in Africa, there is a need to better understand and respond to local community needs and preferences and to adopt this as standard practice prior to regional trial implementation.

Participants viewed HIV cure-related research as a way to address the issue of defaulting on (not taking) HIV treatment.

Participants expressed hesitancy around ATIs, since these contradict longstanding treatment adherence messages.

Participants shared concerns around the risk of side effects from experimental interventions balanced against potential efficacy.

They advocated for trial participants to have the right to decide whether to inform their sex partners about their HIV status and ATI participation

Focus group participants also emphasized the importance of using simple language to explain HIV cure-related research.

Viral Rebound and ART Restart

More than viral rebound

- Disappointment and stigma
- Having to disclose
- Removal from U = U
- Possibility of reliving a diagnosis
- An emotional roller coaster

More than restarting meds

- Re-learn to adhere to ART
- Worry about re-filling prescriptions

SANTHE
SUB-SAHARAN AFRICAN NETWORK FOR TB/HIV RESEARCH EXCELLENCE
Transforming African Science, Fighting HIV/AIDS and TB

THE NEWS

MAY 2024 | VOL: 4

Drafting international guidelines for ATI trials

SANTHE and the US Military HIV Research Program (MHRP) held the second Consensus Workshop on Analytical Treatment Interruption in HIV Cure Trials in Nairobi, Kenya, at the Trademark Hotel 8-10 May last week. The event - the first in Africa - brought together participants from five continents - including community advocates, persons living with HIV, scientists, clinicians, and representatives of funding, regulatory, and industry organisations - to draft new international guidelines to facilitate standardisation of analytical treatment interruption (ATI) trials. The benefits of this workshop should extend well beyond the activities of this three-day event, as the consensus guidelines that are developed will influence all future ATI trial design and improve future ATI efforts.


“How does it feel to stop ARVs during an ATI?”

Take home points

Implementing HIV Cure Research and ATI-inclusive Trials

1. Conduct HIV research in regions of the world **where it is needed the most**

2. Basic science and clinical research can be strengthened by integrating social interventions that **address critical challenges** facing participants *(poverty, unemployment, food insecurity, rape/GBV, teen pregnancy, etc.)*

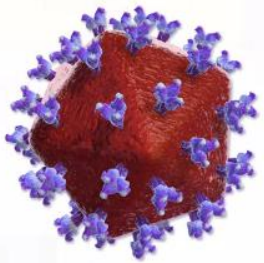
3. Build-in ways for investigators to **engage with participants & the clinical team**

4. Commit to **build capacity** to accelerate and sustain discovery.

Product-Centered Design

VS

Human-Centered Design



Acknowledgements

GILEAD
Creating Possible

- Megha Mehrotra
- Elena Vendrame
- Devi SenGupta

PI / Clinical Specialist

- Dr. Vaneshree Govender
- Dr. Sihle Ngcobo
- Dr. Villeshni Asari
- Dr. Lutchminarian

UKZN Dept of SW
HPP Core Lab
UPL Lab

GS-5445 Trial Participants

10001	10006	10011	10016
10002	10007	10012	10017
10003	10008	10013	10018
10004	10009	10014	10019
10005	10010	10015	10020

FRESH Clinical Team

T Ndung'u
Basic Science

K Dube
Social Science

ITEACH SBR Team

- Mzwakhe Ngcobo
- Deli Mthimkhulu
- Ayanda Zuilu
- Futhi Langa
- Deborah Mindrey

HPP CAB Members

BEAT-HIV DELANEY COLLABORATORY
UPL Universal Pathology Laboratory SA (PTY) LTD
Ragon Institute MASS GENERAL | MIT | HARVARD
Gates Foundation
DURDOC HOSPITAL