The FRESH Cohort
10 years of Acute HIV Research in South Africa

Krista L Dong, MD / Ragon Institute of MGH, MIT & Harvard
Session 4: Collaboration for a cure - Cure everywhere, for everyone

DISCLOSURE: I have no relevant financial relationships with ineligible companies
Aim: Detect Acute HIV Infection during Fiebig I prior to peak viral load during viral upswing.

A research platform optimized for HIV Cure studies.

1. Enroll groups of young women, 18-23 years old, who are at high-risk of infection.
2. Perform frequent HIV testing (twice weekly finger-prick for HIV-RNA PCR)
3. Integrate with empowerment and life-skills curriculum
FRESH began recruiting in 2012
Young women at high-risk of HIV infection in KZN township
Enrolled in 9-month Program
Females Rising through Education, Support and Health
HIV-RNA twice per week (Finger-prick)
Detect acute HIV infection at earliest timepoint
N=14
Hyperacute Infections

Untreated during AHI (n=14); multiple samples prior to and after peak VL
Immediate Treatment

Immediate ART; blunting peak VL and duration of viremia.
Patient Centered

Integrating an empowerment, job and life skills curriculum

70-80% placed in jobs or internships, return to school or start their own business

A FRESH approach: Combining basic science and social good

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As of July 2022

- Enrolled 2,916 eligible participants (from 3,323 screened)
- Detected of AHI a median 4d since last negative HIV-RNA
- 75% (72/96) detected Fiebig stage I
- 100% (82/82) offered and started immediate ART
- ART started within median 1d after detection
2012-2022

10 years FRESH Cohort

- Establish a cohort of high-risk HIV negative women
- Perform frequent HIV testing and pre-infection sampling
- Study early acute HIV infection and acquisition risk
- Inform new prevention & treatment strategies
- (Patient centered) Clinical trial site

2012
- Launch
  - 9 Acutes
  - 100% (9/9) Fiebig I
  - 4d after neg-RNA

2013-2015
- Leukapheresis
  - 7 Acutes
  - 86% (6/7) Fiebig I
  - 4d after neg-RNA
  - Early treatment

2016-2017
- Early ART

2018-2022
- COVID-19 Pandemic
  - Looting
  - Flooding
Optimize Biological Sampling
2017 - Partnered with SANBS to introduce Leukapheresis

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First 18 months
- 29 consented
- 72% success rate
- Avg 4.3 (1-10) billion PBMCs per collection
- 99% viability

The ability to perform high volume PBMC collections at FRESH allows additional analysis/studies to be performed such as detailed deep sequencing...
**New collaboration: Scripps-HPP-IAVI**

IMMBASE = Immune Baseline
Antibody deep sequencing and characterize antigen-specific naïve precursors in southern African donors

**Primary Aims:**

1. Characterize features of Variable (Diversity) Joining (V(D)J) recombination from South African antibody repertoires to aid rational vaccine design for HIV.

2. Quantify and characterize the antigen-specific naïve B cell precursors that bind to HIV envelope-based antigens, such as eOD-GT8, to predict responsiveness to germline targeting HIV immunogens.

**Secondary Aims:**

1. To survey the antibody repertoire diversity and antibody clonal overlap in South Africa and make comparisons with American antibody repertoires.

2. To establish the impact of tuberculosis infection on the naïve B-cell repertoire and frequencies of naïve B-cell precursors for HIV envelope-based antigens.
Translational Research
Start by listening to investigators

Lightening Rounds – listen to new ideas from the lab
Allows FRESH to be designed to purpose

AIDS 2022
Affiliated Independent Event
Investigators share results with FRESH team
Investigators learn from FRESH participants
Sponsor Engagement
Interactions with the team and participants is a fantastic opportunity to gain insights that are not captured in written reports or summaries.

(Affiliated Independent)

(Bottom) Chris Dammon (BMGF) met with FRESH participants during development of the foundation’s Vaginal Microbiome Consortium (VMRC).
Commit to building local capacity in LMIC. Mentor and share expertise. Conduct investigations in-country. Collaborate.
2020 – COVID Lockdown in SA

For much of May-Jun 2020 (3mo) South Africa was shut down. UKZN closed all research sites – including FRESH. Only essential personnel allowed on the roads.
ART home deliveries

UKZN Lab forced closure. No sampling possible. The FRESH team delivered ART to FRESH participants to maintain VL suppression.
Sept 2020

FRESH outgrew the original site

Needed a space with double the capacity, more centrally located and with space for a trial pharmacy.
Preparing for a Cure Trial. **Support your most valuable assets.**

Minimize the reservoir and viral diversity
Achieve rapid and sustain viral suppression, from hyperacute infection until opportunity for enrollment in an HIV ‘Cure’ or Post-treatment Control trial.

Invest in the Community Education
Community leaders who understand the science of HIV cure will be equipped to inform the community and provide input that investigators may overlook.

*ILAST = Intensive love and adherence support team.*
Each study participant has their own specialized counselor-case manager who sees them at each scheduled visit. Participants feel seen, understood and supported.

**Community Advisory Boards**
Meet regularly. Provide research updates. Review protocols and ICFs during development.
March 2021

Clinical Trial

Phase 2 placebo-controlled randomized trial of LACTIN-V (*Lactobacillus crispatus* CTV-05) among women at high risk of HIV acquisition in Durban, South Africa

• Enrolling: N=60 FRESH participants
• Eligibility: BV+/elevated Nugent score >4, No STI
• Currently enrolled 34 of 60
Gearing up for the Gilead BNAb trial
The FRESH Acute Support group having a (virtual) visit from HIV Cure advocate...
Sustaining the platform. *Inspire and allow for self-support.*

Zoom in the super-charged inspiration! **Moses Supercharger** tunes in to FRESH from Uganda and rocks the house while educating about HIV Cure.
July 2021 – Political unrest / ‘looting’
Throughout KwaZulu-Natal, centered in Durban

FRESH severely affected and had to close for 12 weeks.
Immediately post-looting
FRESH moved to a park home at the nearby hospital and continued to see acutes for sampling and ART dispensing. Zero ART default during the shutdown.
April 10, 2022
Catastrophic Flooding in KZN
April 2022 – the morning after
Roads to FRESH inaccessible. The team drove as close as they could and then walked to site.

- No public transportation. Participants also walked.
- FRESH had no power or water for weeks.
Launched 2022

2\textsuperscript{nd} Clinical Trial at FRESH

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

- N=25 FRESH Acutes (immediate ART)
- Virally suppressed \(\geq 12\)mo, dual-BNAb sensitive
- Sponsor: Gilead
- 1 BNAbs infusions, 10 doses VES, up to 42w ATI
- 18w treatment period (overlapping with ATI)
13-July 2022

First patient
First dose
Leveraging the Platform
Vaginal Microbiome in pregnancy on HIV and Maternal-Child Health

Launching in August

Baby U! - Role of Vaginal and Rectal Microbiota in Preterm Birth. N=200 pregnant women
...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.
Final thoughts from the FRESH Cohort

1. Conduct HIV cure 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 our participants (poverty, unemployment, food insecurity, rape/GBV, teen pregnancy, etc.)

3. Build-in ways for investigators to **engage with study participants** and clinical staff

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

5. Embed social-behavior research to **learn from participants** how to design better protocols and optimal interventions (TPP).
From beyond the pandemic, looting and flooding.

FRESH is back and focused on HIV cure.

Acknowledgements

Thumbi Ndung’u & HPP lab
FRESH Participants
Ursula Brunner
The FRESH Team
Terry and Susan Ragon

[Logos and images of various organizations and people]