Towards an HIV Cure
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Krista L Dong, MD / Ragon Institute of MGH, MIT & Harvard

Session 4: Collaboration for a cure - Cure everywhere, for everyone

The FRESH Cohort

10 years of Acute HIV Research in South Africa

DISCLOSURE: I have no relevant financial relationships with ineligible companies

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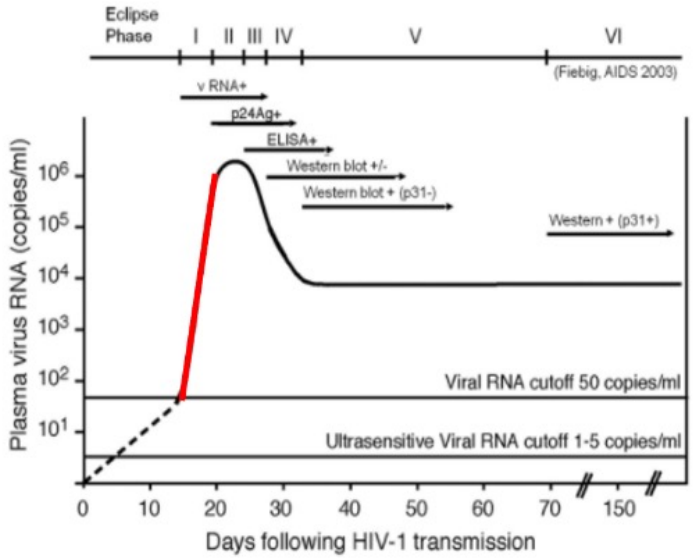
Aim: Detect Acute HIV Infection during Fiebig I prior to peak viral load during viral upswing.



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

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Enrolled in 9-month Program

Females Rising through Education, Support and Health

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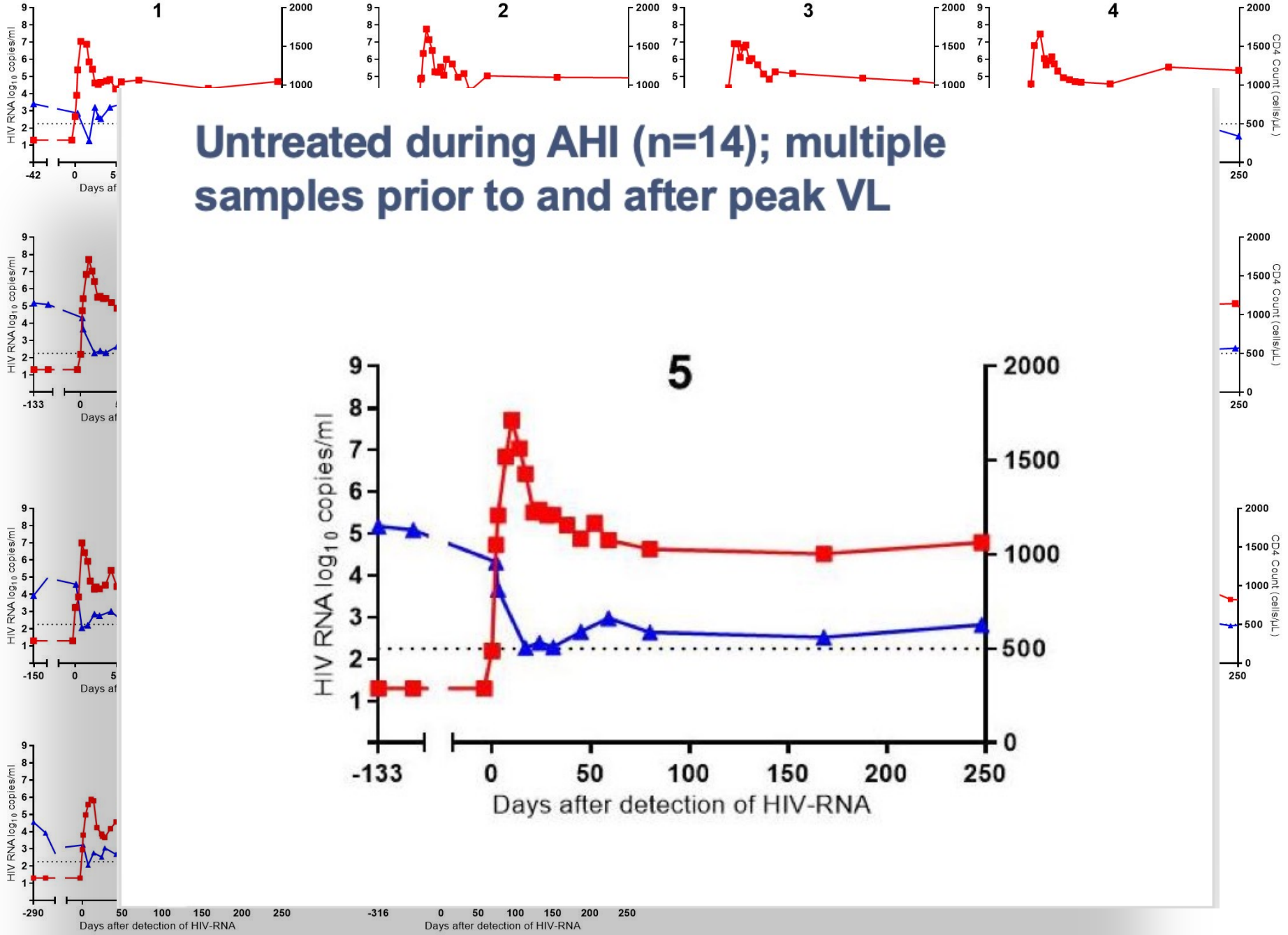
HIV-RNA twice per week (Finger-prick)

Detect acute HIV infection at earliest timepoint

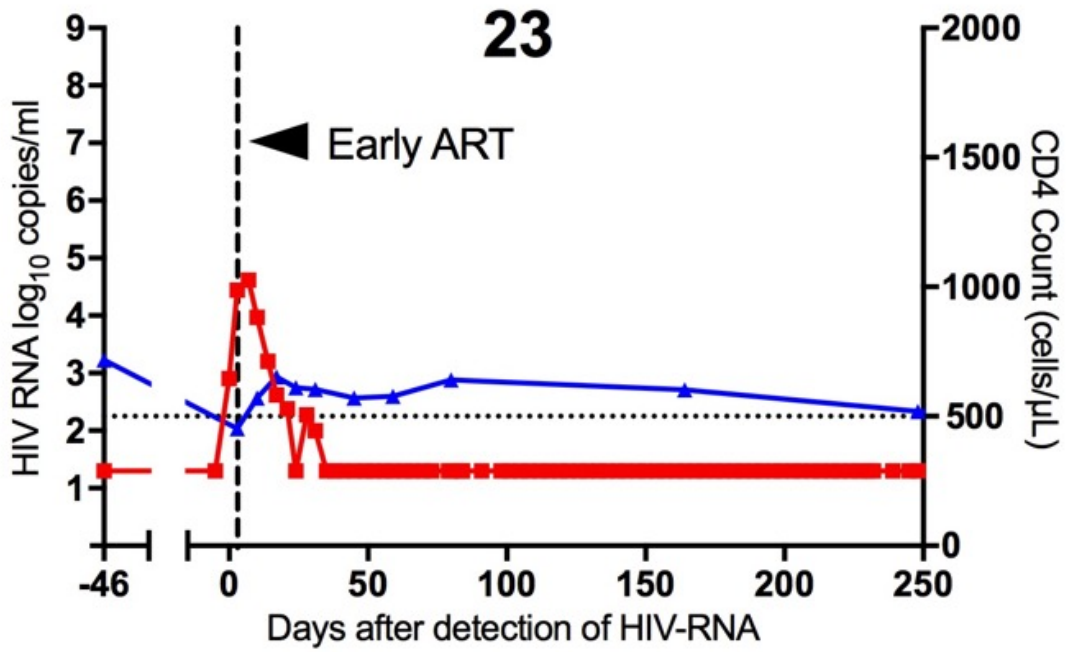
N=14 Hyperacute Infections

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



Immediate Treatment

Immediate ART; blunting peak VL and duration of viremia.



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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

SCIENCE IMMUNOLOGY | EDITORIAL

HIV

A FRESH approach: Combining basic science and social good

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96 Acute Infections Detected

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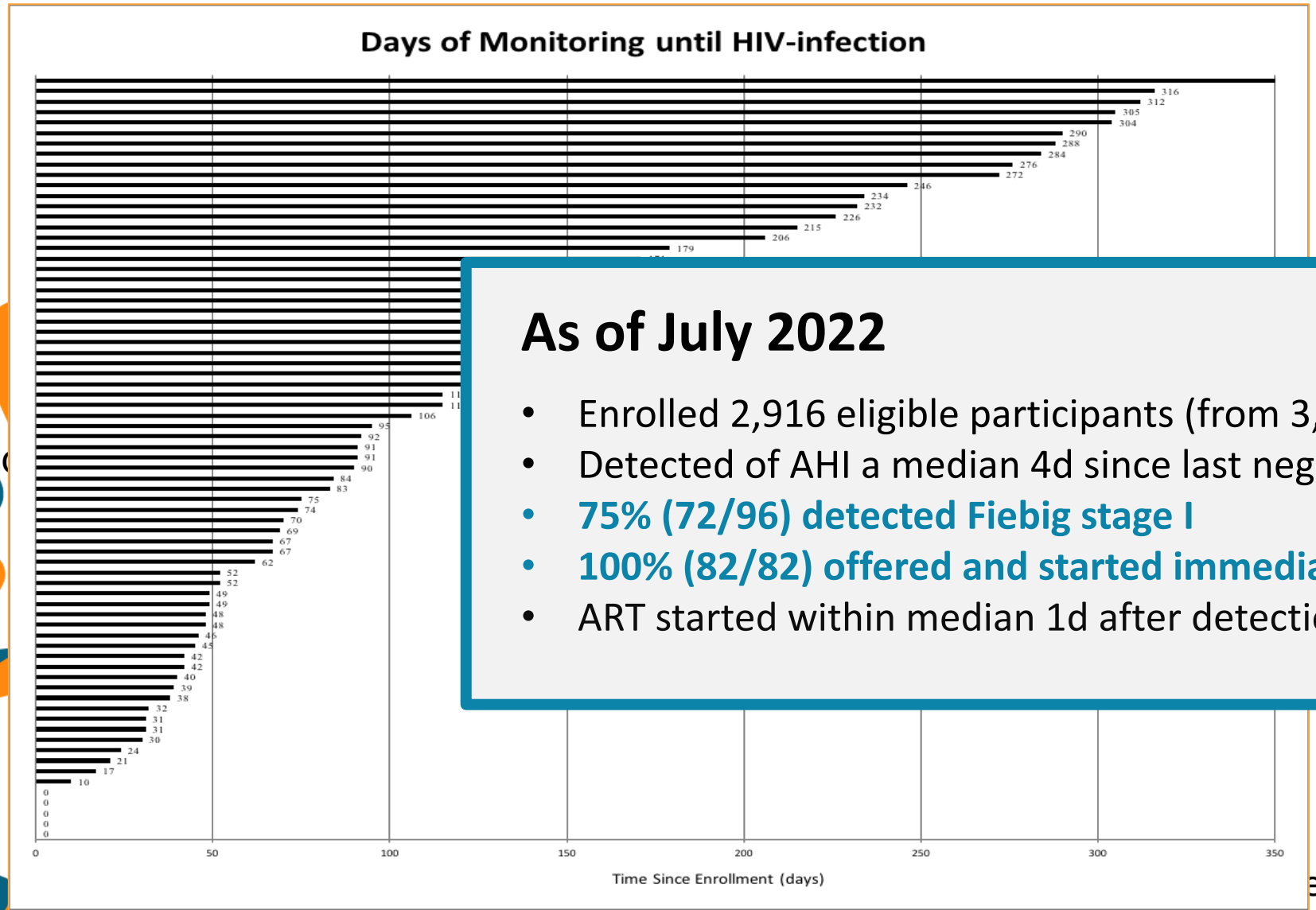


As of July 2022

- 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

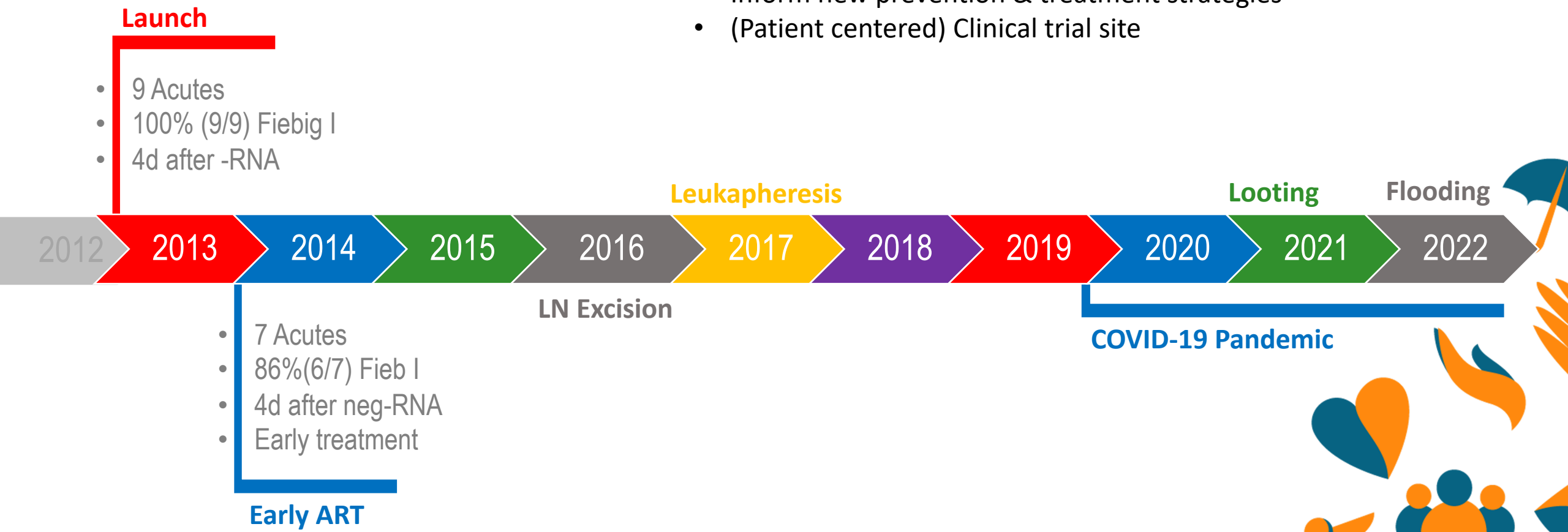
Click ic

ent

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



Optimize Biological Sampling

2017 - Partnered with SANBS to introduce Leukapheresis

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Consented				Results		
No.	Acute #	PID	Date	Yield (billion cells)	Viability	Failure
1	62	1368	3-Dec-18			No show
2	59	1401	4-Dec-18			Venapuncture
3	74	1491	5-Dec-18	4.2	100%	
4	38	631	6-Dec-18	2.0	89%	
5	44	922	10-Dec-18			Venapuncture
6	47	852	11-Dec-18	6.6	100%	
7	33	515	13-Dec-18	1.0	100%	
8	75	1685	20-Dec-18	7.4	100%	
9	76	1663	8-Jan-19	5.4	99%	
10	35	701	1-Apr-19			Venapuncture
11	24	541	2-Apr-19	5.9	98%	
12	73	1512	3-Apr-19	8.0	99%	
13	48	1088	4-Apr-19	5.5	99%	
14	75	1685	5-Apr-19	5.7	100%	
15	78	1750	18-Apr-19			Collection failure
16	40	704	13-May-19			Collection failure
17	29	479	14-May-19	2.7	100%	
18	79	1918	15-May-19	4.9	100%	
19	18	442	16-May-19	4.2	100%	
20	11	208	17-May-19	7.0	100%	
21	81	1875	7-Jun-19	1.2	100%	
22	80	1946	10-Jun-19			Collection failure
23	82	2040	19-Jun-19	2.3	99%	
24	83	2020	1-Jul-19	2.4	100%	
25	84	2077	1-Aug-19	3.5	99%	
26	79	1918	15-Aug-19	1.3	100%	
27	85	1952	4-Sep-19			Collection failure
28	86	2113	17-Sep-19	10.0	100%	
29	8	309	18-Sep-19	3.6	100%	
72%				**4.3**	**99%**	**27%**

First 18 months

- 29 consented
- 72% success rate
- Avg 4.3 (1-10) bill 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

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IMMBASE = Immune Baseline

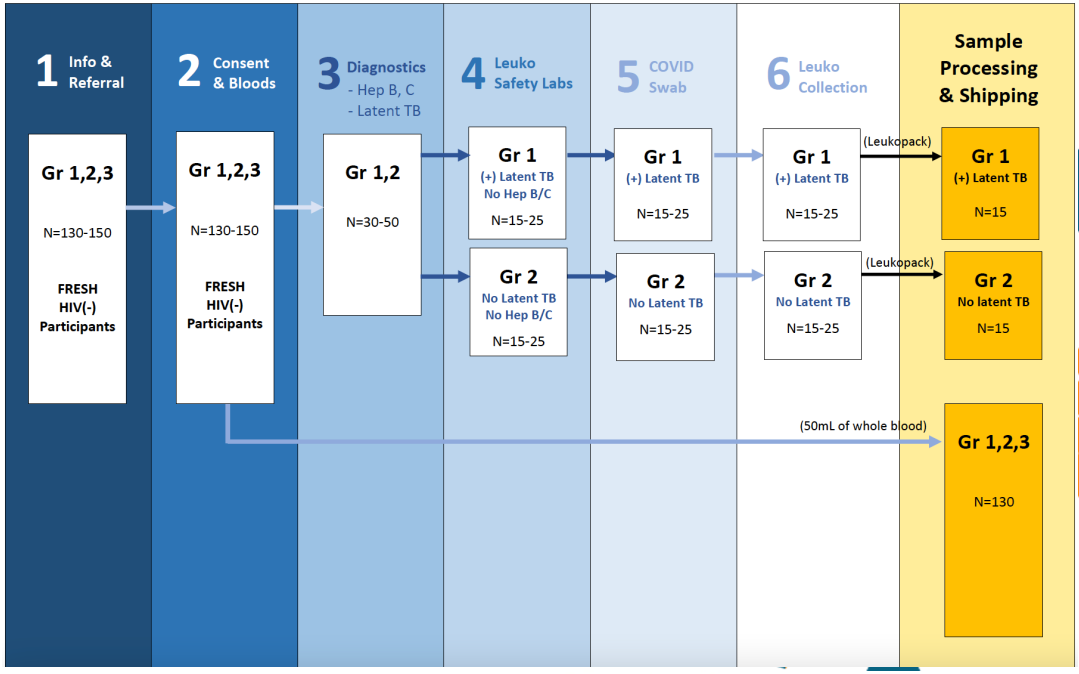
Antibody deep sequencing and characterize antigen-specific naïve precursors in southern African donors

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.



Scripps Research

HPP HIV Pathogenesis Programme
Doris Duke Medical Research Institute
Nelson R Mandela School of Medicine

iavi

Translational Research

Start by listening to investigators

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Lightening Rounds – listen to new ideas from the lab

Allows FRESH to be designed to purpose

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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.

Mike McCune (BMGF) speaks to FRESH staff to assesses potential for HIV cure work

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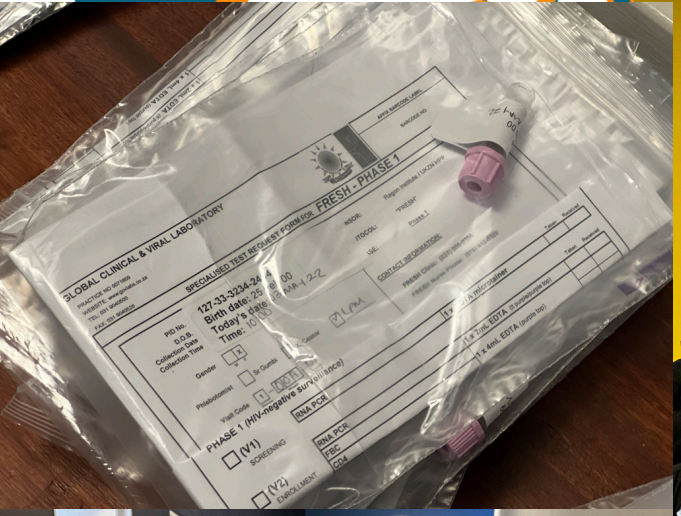
Affiliated Indepen

(Bottom) Chris Dammon (BMGF) met with FRESH participants during development of the foundation's Vaginal Microbiome Consortium (VMRC).


GLOBAL CLINICAL & VIRAL LABORATORY
SPECIALISED TEST REQUEST FORM FOR: FRESH - PHASE 1
PHASE 1 (HIV-negative survivors)
(V1) SCREENING
(V2) ENROLLMENT
RNA PCR
PBC
CT4


Neuberg Global

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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.

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ART home deliveries

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

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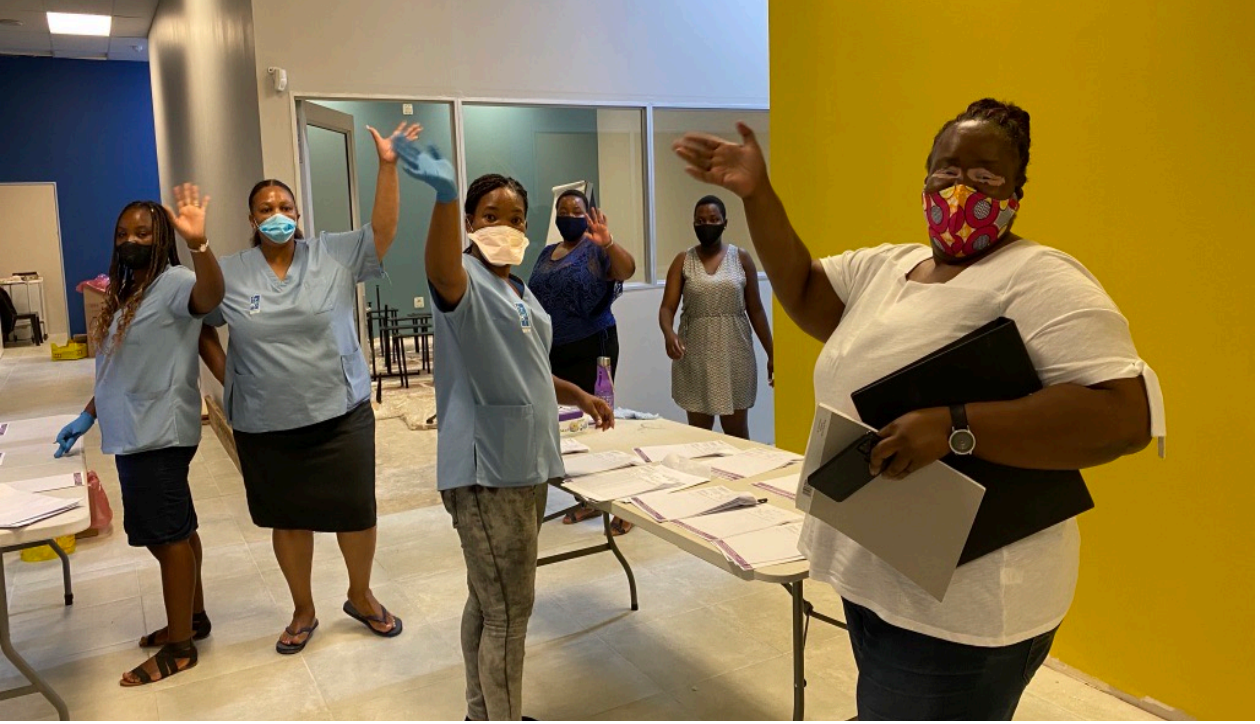
Sept 2020

FRESH outgrew the original site

Needed a space with double the capacity, more centrally located and with space for a trial pharmacy.

November 2020



January 2021

Preparing for a Cure Trial. *Support your most valuable assets.*

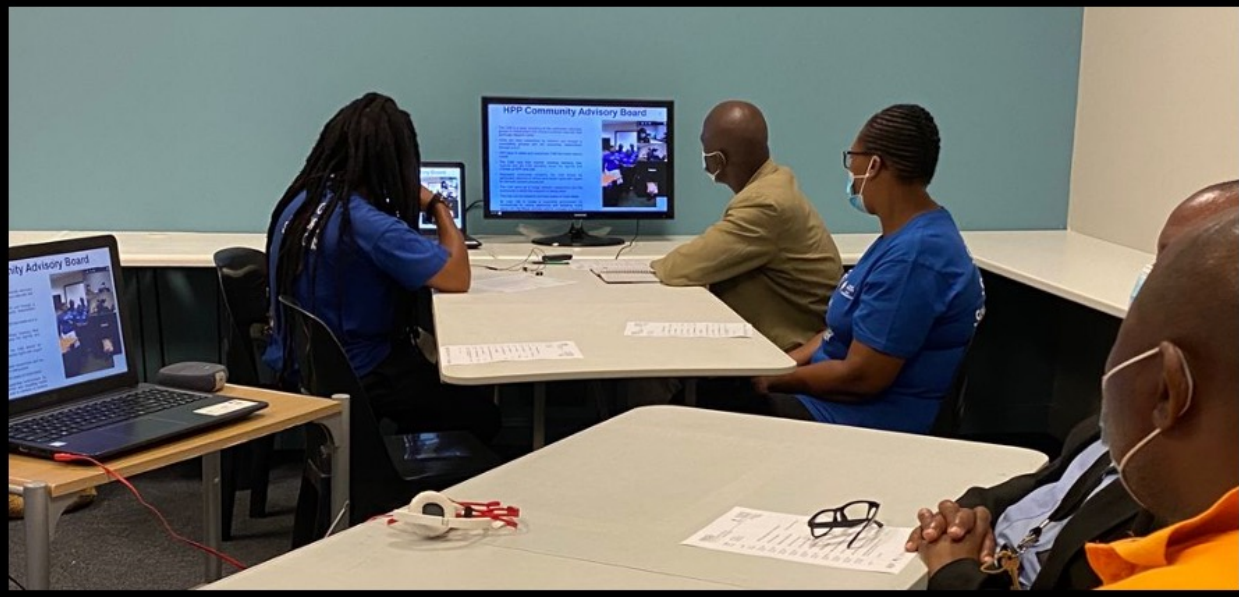
Minimize the reservoir and viral diversity

Achieve rapid and sustain viral suppression, from hyperacute infection until opportunity for enrollment in an HIV 'Cure' or Post-treatment Control trial.

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.

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 overlooks.



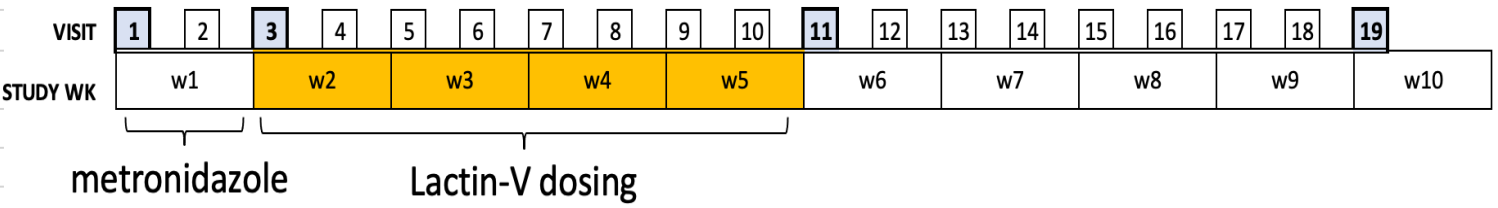
Community Advisory Boards
Meet regularly. Provide research updates.
Review protocols and ICFs during development.

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

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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.

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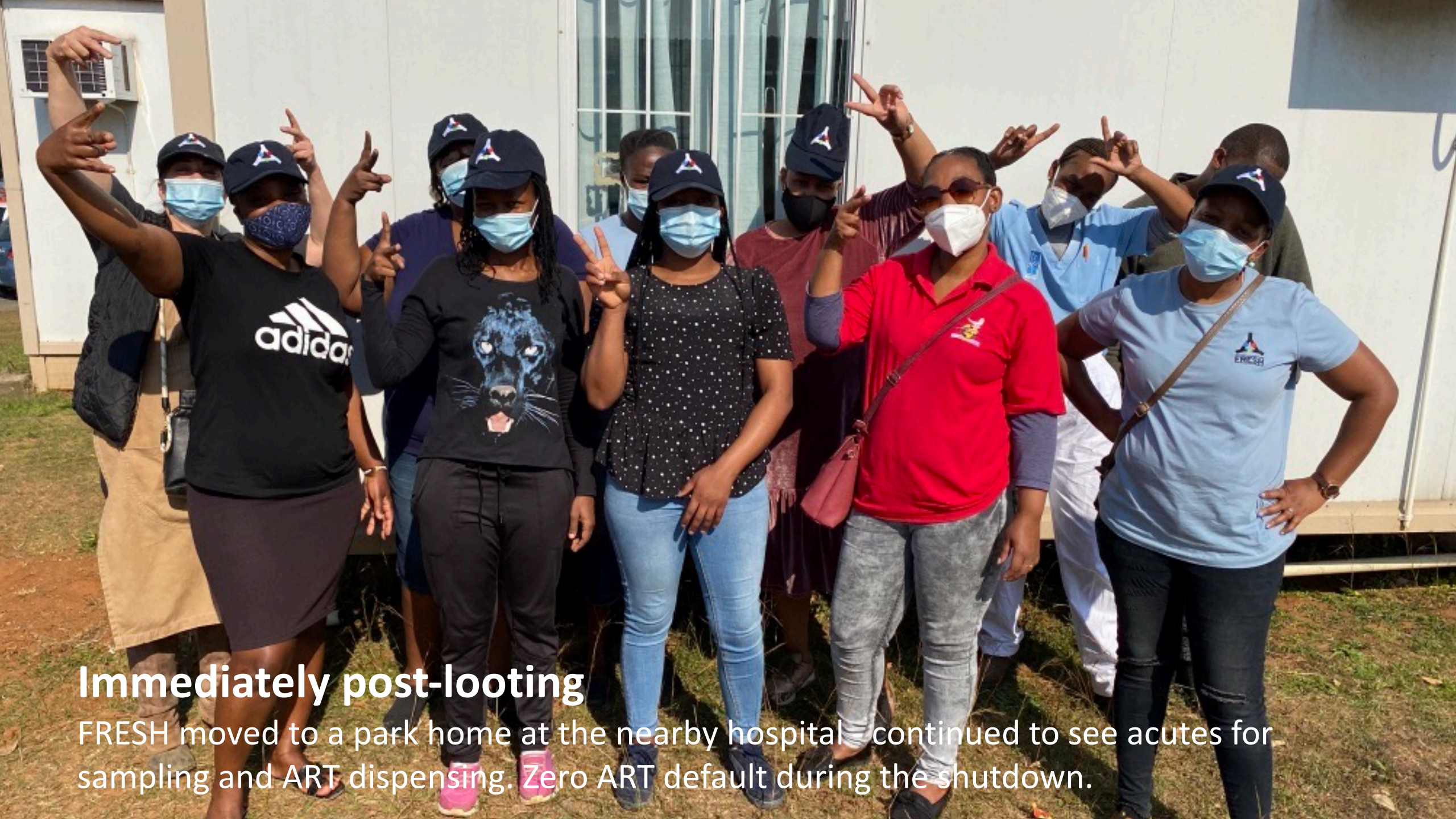
July 2021 – Political unrest / ‘looting’

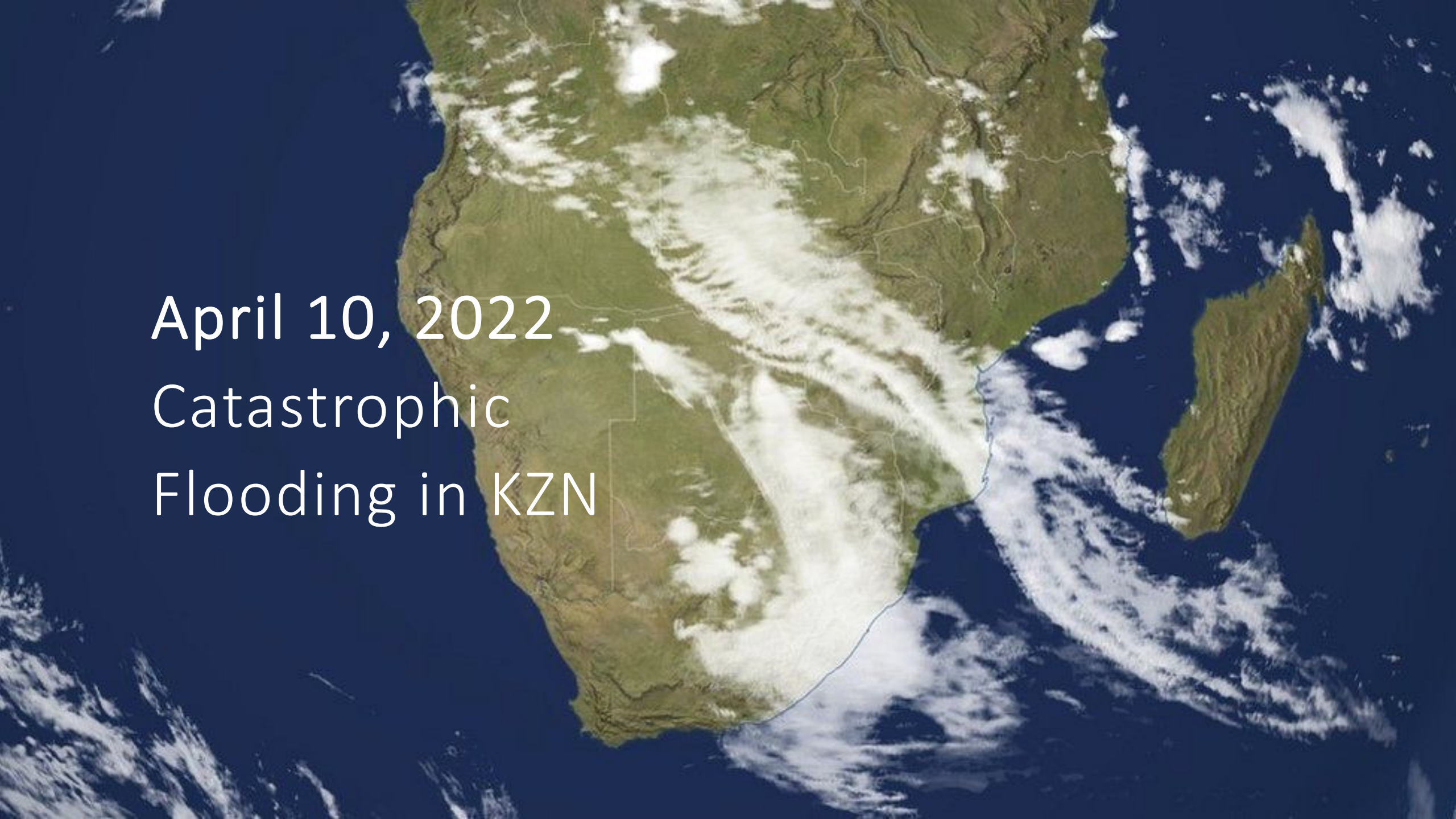
Throughout KwaZulu-Natal, centered in Durban

FRESH severely affected and had to close for 12 weeks.



Immediately post-looting

FRESH moved to a park home at the nearby hospital – continued to see acutes for sampling and ART dispensing. Zero ART default during the shutdown.



April 10, 2022 Catastrophic Flooding in KZN

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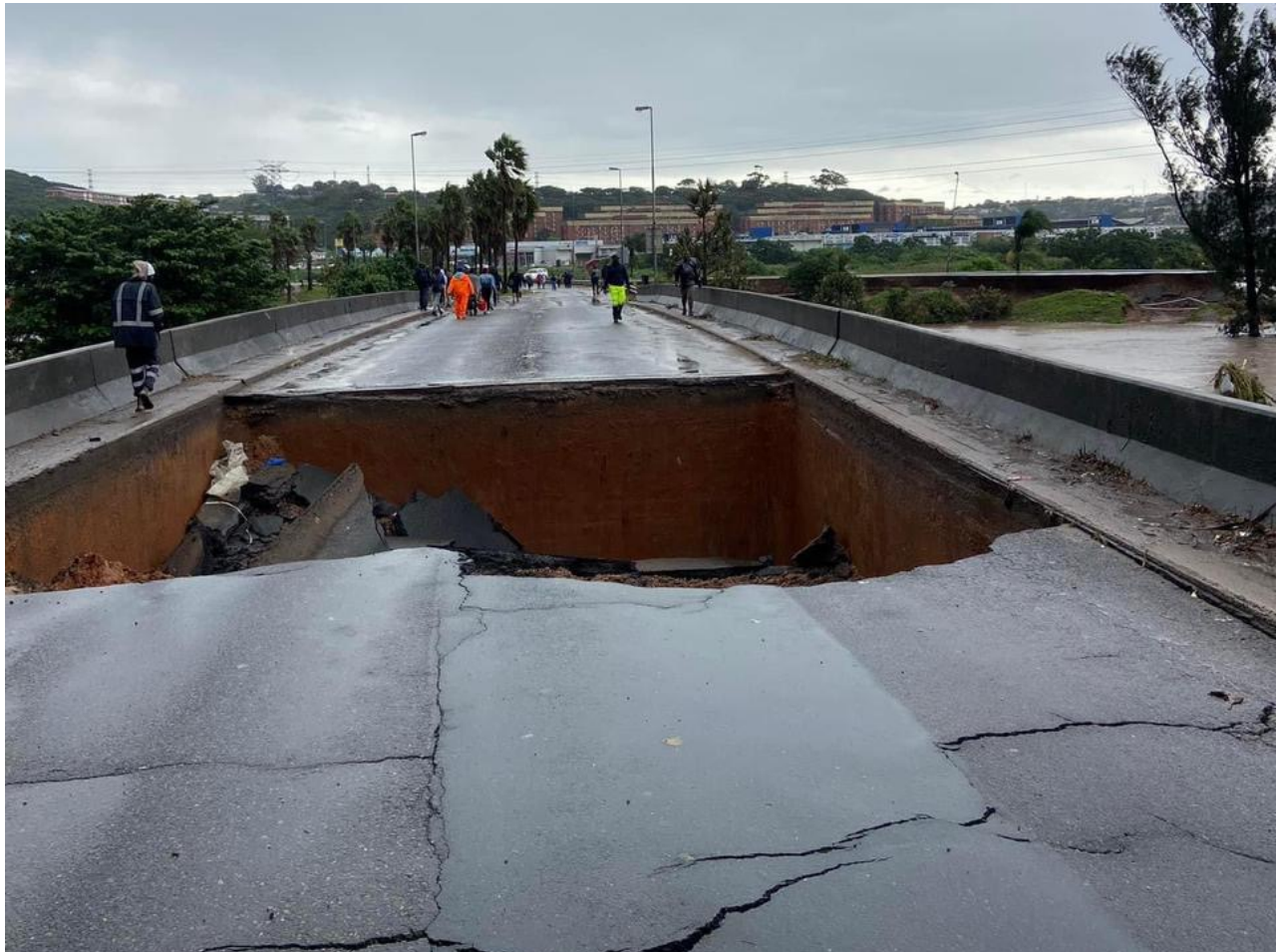
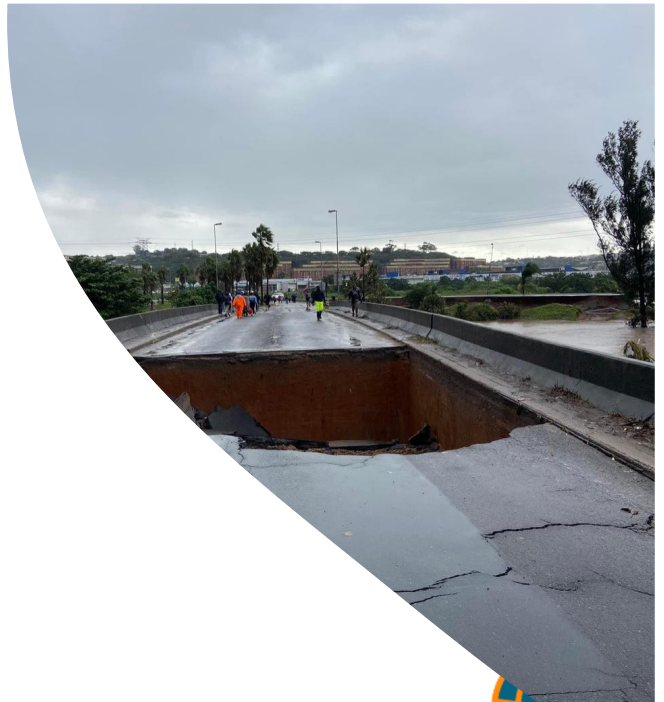
April 2022 – the morning after



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

2nd Clinical Trial at FRESH

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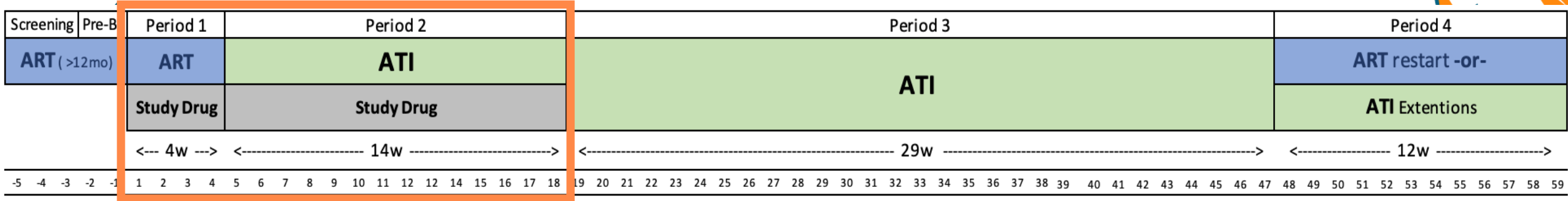
A Phase 2a Study to Evaluate the Safety and Tolerability of a Regimen of Dual Anti-HIV Envelope Antibodies, **VRC07-523LS** and **CAP256V2LS**, in a Sequential Regimen with a TLR7 Agonist, **Vesatolimod**, in Early Antiretroviral-Treated HIV-1 Clade C-Infected Women

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



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13-July 2022

First patient First dose

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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.”

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

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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.

Final thoughts from the FRESH Cohort

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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).

Acknowledgements

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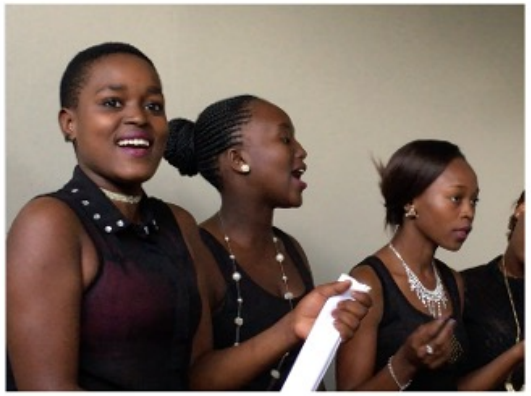
Thumbi Ndung'u & HPP lab



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iavi

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