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FRESH Study; Acute HIV-1 Infection in Cohort of High-risk Women in KZN, South Africa

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BACKGROUND

The HIV epidemic in KwaZulu-Natal (KZN), South Africa (SA), continues unabated among young at-risk women. Seroprevalence data collected in 2009, at an antenatal clinic in KZN, showed that without intervention 66% of women became HIV-infected by age 23 (Figure 1). The majority of these women live in poverty, are victims of abuse, have few if any role models, and limited opportunity to improve their lives.

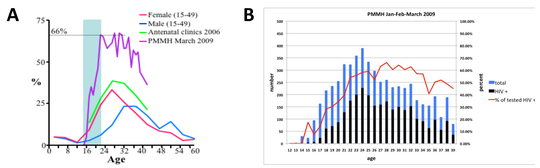


Figure 1. A. South Africa HIV seroprevalence at Prince Mshiyeni Memorial Hospital (PHHM) Antenatal Clinic in Durban (2009) and antenatal clinics nationwide (2006). B. Number and ages of antenatal attendees at PMMH (Jan-Mar 2009).

Need for a Vaccine. While anti-retroviral therapy (ART) in SA has increased steadily since 2004, the magnitude of the epidemic underscores the need for a vaccine. The underlying hypothesis in this study is that adaptive and innate immune responses (1) decrease rates of HIV acquisition and (2) influence viral control in chronic infection. These two factors directly influence HIV disease progression, and understanding them is key to developing an HIV vaccine.

Importance of Acute Infection. Previous studies of chronically infected cohorts have been limited by the heterogeneity of the study group, and unknown time of infection. This study follows a cohort of uninfected women at high-risk for HIV infection, enabling characterization of immune responses just prior to, and in the earliest stages of infection. In addition to understanding disease progression and its implications for vaccine development, understanding factors that influence the establishment of viral reservoirs may be important in guiding approaches to viral eradication and functional cure.

A Unique Cohort. In order to study key events occurring during the earliest stages of HIV infection (Fiebig stage I), research must be designed to ensure high participant retention and adherence to very frequent monitoring. To achieve this, the FRESH study uniquely combined a basic science research protocol with a poverty alleviation program. Though an atypical pairing of efforts, poverty and HIV are two things that young women in KwaZulu-Natal have in common.

RESULTS

Phase I: Surveillance of High-risk Uninfected

- 500 women screened
- 298 eligible women enrolled
- 197 currently enrolled and adhering to twice-weekly finger-prick monitoring and attending life-skills/empowerment classes.
- 1500-2000 HIV PCRs/month
- 51 women have completed the 1-year life-skills empowerment course and have either been employed, placed in intern/learner ships, started their own small business or returned to school.

Phase II: Monitoring of Acute HIV-Infection

- 11 acute HIV infections identified
- 9 of 11 experienced flu-like illness consistent with acute viral syndrome
- Mean time to infection 141 days (39-284)
- Incidence of 6.9 (95% CI: 3.1-13) per 100 person-years
- All 11 acute infections were identified at Fiebig Stage I; detectable by viral RNA (PCR) with negative p24 antigen (ELISA)

Table 2. Basic Characteristics of Cohort

Average age	20.1	[18-23]
Age of boyfriend	23.4	[18-42]
Sex acts past 7 days	1.02	[0-7]
Number of regular partners past 7 days	0.86	[0-11]
% women who never or only sometimes use condoms:	79%	
% women on hormonal contraception:	49%	
% women who use drying agents:	11%	

The majority had 1 regular sexual partner who was close to their age. Condom use was infrequent and only half used reliable contraception. Drying agents, which are often abrasive, are inserted in the vagina to enhance their partners' pleasure.

Figure 2. Duration of Surveillance Preceding Acute HIV Infection

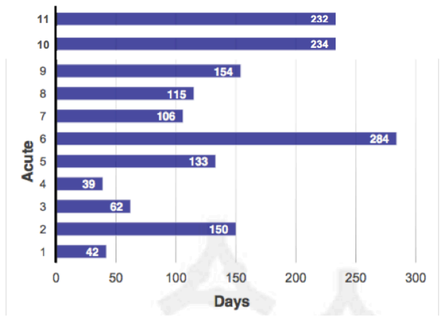


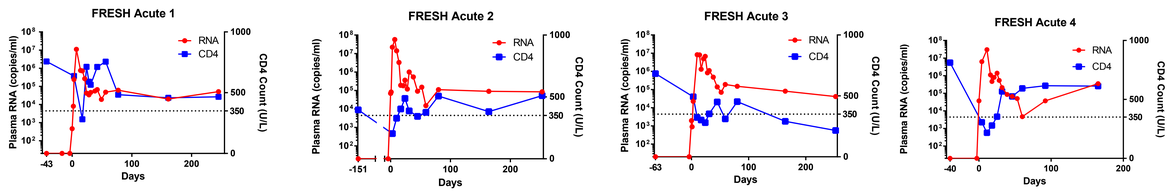
Figure 2. At 13 months after study launch, 9 acute infections were identified for an incidence rate of 6.9 per 100 person years for a 95% CI (3.1 – 13.0). At 14 months, 11 acute infections were identified. Mean duration of surveillance until acute HIV infection was 141 days (range: 39–284).

Table 3. Acute Infection, STIs, Contraception and Use of Vaginal Drying Agents

Acute No.	STI	Genital symptoms	No. Sex Acts (last 7 days)	No. Regular partners	Hormonal Contraception	Use of Vaginal drying agents	Condom use
11	(+)N gonorrhea (+)HSV-2	None	1	1	Depo	No	Never
10	none	None	n/a	n/a	Depo	No	n/a
9	*pending*	None	0	1	none	Yes	Sometimes
8	(+)Chlamydia (+)N gonorrhea	None	1	1	Depo	No	Never
7	(+)Chlamydia	None	1	1	Loop	Yes	Always
6	(+)T vaginalis	None	0	1	Nur-iserate	No	Never
5	(+)Chlamydia (+)N gonorrhea	None	1	1	Nur-iserate	Yes	Sometimes
4	(+)N gonorrhea (+)T vaginalis	None	1	1	Nur-isterate	No	Always
3	(+)N gonorrhea	None	1	1	OCP	Yes	Never
2	(+)N gonorrhea	None	1	1	Nur-isterate	Yes	Never
1	(+)Chlamydia	None	3	1	Nur-iserate	Yes	Sometimes
	90%	0	1	1	80% of acutes	55% of acutes	80% never or sometimes

Table 3. Sexually transmitted infections (STIs) were detected in 90% (9 of 10) of acutely infected participants at the time of first +RNA. Of the 9 acutes with a +STI, all denied genital symptoms. STIs were detected in ~30% of the HIV-uninfected cohort. The number of sex acts reported during the 7 days preceding acute infection was variable (0 to 4), with 10 of 10 reporting only one regular sexual partner at the time of infection. Use of hormonal contraception was comparable in HIV infected and HIV-uninfected. Condom use was infrequent in both HIV-infected (80%) and HIV-uninfected (79%).

Figure 3. Pre- and Immediately Post-Infection Viral Load (HIV RNA) and CD4



Frequent monitoring enabled both pre- and immediately post-infection sampling, revealing rapid rise of HIV RNA (shown in red) with multiple samplings prior to peak viremia and marked decline of CD4 count (shown in blue). All 11 acutes were identified during Fiebig stage I (HIV RNA positive, p24/ELISA negative). CD4 count in 7 of 11 (63%) dipped below 350 cells/mm^3, at least transiently, with almost all dropping below 500 cells/mm^3. CD4 in "Acute 3" dropped below 350 cells/mm^3 within 10 days after +RNA PCR, with transient rebound before dropping again below 350 cells/mm^3 at 164 days. No further rebound was consistent with rapid disease progression.

METHODS

Groups of 30 women were enrolled monthly to reach a cohort target of 300 HIV-negative sexually active women aged 18 to 23 years of age. Participants were co-enrolled in an intensive 1-year life skills, poverty-alleviation intervention with classes scheduled twice-weekly to coincide with the frequency of Phase I surveillance with HIV RNA PCR via finger prick blood collection. Large volume blood draw and vaginal mucosal sampling was performed 3-monthly during Phase I to obtain PBMCs and mucosal tissue via cervical and vaginal swab, cervical cytobrush and cervicovaginal lavage . Participants identified with acute HIV infection where immediately shifted to the Phase II sampling schedule (See Table 1.) with continued frequent RNA PCR.

Table 1. Phase II. Acute Infection Sampling Schedule

Week	0	1	2	3	4	6	8	12	24	36	48	100	152
Plasma/ PBMC (ml)	X	X	X	X	X	X	X	X	X	X	X	X	X
Mucosal swabs, CVL, cytobrush	X	X	X	X	X	X	X	X			X	X	X

CONCLUSIONS

1. Pairing a basic science research protocol with a poverty alleviation intervention is a unique and effective means of conducting clinical research in an underserved community. This approach may **increase study adherence** while providing direct and sustained **benefit to participants**.
2. This study confirmed that it is feasible to identify **acute HIV infection during Fiebig stage I** through surveillance of a cohort of high risk HIV-negative young women, performing HIV RNA PCR twice-weekly on blood obtained by finger prick. This resulted in a short "eclipse period", or time between infection and first detection of viral RNA in the plasma.
3. Sampling at **multiple time points prior to peak viremia** showed peak viral levels are achieved rapidly (7.6 days, range: 7-11 days) after initial +RNA PCR.
4. **Drop in CD4 count was rapid** following acute infection, with nadirs reached within less than 2 weeks (13 days, range: 3-24 days) and dipping below current SA guidelines for ART initiation (350 cells/mm^3) prior to modest rebound.
5. **Higher rates of STIs** (90%) were observed at the time of HIV acute infection, compared with uninfected participants (~30%), despite similar sexual risk behavior (age and number of partners, condom and hormonal contraception use). Use of vaginal drying agents was higher in the acute cohort and requires further study.
6. **The FRESH cohort presents a unique opportunity** to study acute HIV infection during the period between transmission and peak viremia, prior to massive CD4$^+$ T cell destruction and establishment of viral reservoirs. This may be ideal for early treatment and HIV cure research.

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