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A FRESH approach: Combining basic science and social good

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Introduction

Over the past decade, there has been considerable progress in the development of new strategies to prevent and treat HIV-1 infection, yet in many areas of the world, new infections continue to occur at an alarming rate. In the hardest hit regions, such as KwaZulu-Natal (KZN), South Africa, incidence rates among young women—a particularly vulnerable population—still approach 10% per year despite successful rollout of treatment and prevention strategies. Contributing to this high incidence rate is economic dependency on male partners, which limits women's ability to negotiate safer sex; gender inequality, including home responsibilities that force early school dropout and block future employment options; and low self-esteem resulting from ongoing female disempowerment. The need for an HIV vaccine to prevent infection and a cure for persons already infected remains paramount.

HIV vaccine and cure efforts would be facilitated by a better understanding of factors that modulate acquisition risk and the early immunologic events after exposure that determine long-term outcome. Given these high rates of transmission, we asked whether one could implement a research project to detect acute HIV infection very early, in order to fill important gaps in biomedical knowledge, and at the same time address risks for HIV infection specific to young women, an understudied group. Here, we describe the establishment and evolution of a longitudinal cohort study termed FRESH (Females Rising through Education, Support and Health) that was created to achieve these aims by combining basic science research with an educational program that addresses poverty alleviation in young African women at high risk of HIV infection.

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Design of the FRESH program

The extremely high incidence of HIV infection in KZN suggested an opportunity to detect infection at the onset of plasma viremia through very frequent testing of individuals at high risk of infection. With incidence rates approaching 10% per year, new infections would likely occur even with implementation of aggressive behavioral interventions. At the same time, we felt that we could not initiate a study among HIV-uninfected women in this setting without addressing additional factors that drive these high rates of acquisition.

Given that poverty and disempowerment substantially contribute to the risk of infection in women, we sought to mitigate these factors by combining a research study with an educational program aimed at reducing HIV risk. On the one hand, FRESH was created as research study of HIV acquisition and acute HIV infection in order to identify biological risk factors that affect HIV acquisition and to address gaps in vaccine and cure research. At the same time, the study was complemented by an educational program for female empowerment and poverty alleviation that was designed to provide a safe environment in which to address emotional and physical health, including abuse and violence, as well as intensive skills development training important to successful entry into the job market or return to school. Although the curriculum included HIV prevention eduation, it was primarily designed as a poverty alleviation program. By combining HIV testing with a twice-weekly socioeconomic empowerment curriculum, we reasoned that these two distinct but complementary goals could be addressed.

To reduce stigma associated with visits to a clinic or hospital, FRESH was set up at a shopping mall in Umlazi, an economically disadvantaged township in KZN, where original retail space was converted into classrooms and exam rooms. After extensive discussions and support from community stakeholders, we began recruitment of women 18 to 23 years of age, the most vulnerable age group in this community. We enrolled women in groups of 30 to 40 who were unemployed and not attending school, which created peer support groups. Criteria for enrollment included being sexually active and able to give informed consent, nonpregnant, nonanaemic, and without other barriers to participation, such as serious chronic illness, enrollment in other studies, or conflicting family responsibilities.

The FRESH educational curriculum was created to provide a sense of community, allowing time during each class for sharing and discussing personal experiences. This was a valued outlet for participants and gave curriculum facilitators a first-hand glimpse into their challenges and unmet needs. Curriculum content, drawing from best-practice poverty alleviation programs, included interactive sessions on self-esteem, relationship- and gender-based violence, stress management, communication, women's health, and HIV prevention and treatment. Additionally, the women engaged in career exploration, including field trips to observe job opportunities at local businesses, lessons about starting a small business, workplace etiquette, computer training sessions, preparation of a resume and cover letter, and mock job interviews. Participants interested in returning to school, either to complete high school or to enroll at a tertiary institution, were assisted accordingly. Impact of the 9- to 12-month educational program was measured by successful placement in work, starting a business, or enrollment in school during the 12 months after completion of the curriculum.

Weekly meetings between the research and curriculum teams fostered a holistic approach to care and support and rapid identification of barriers that affected study participation.

At each twice-weekly visit, participants underwent finger-prick HIV RNA testing before attending class, with results available in less than 24 hours from a local commercial laboratory. Peripheral blood and cervical vaginal samples were obtained and cryopreserved every 3 months during preinfection surveillance, with ongoing behavioral risk assessment. During the first 18 months of the program, combination antiretroviral treatment (cART) was not initiated during acute HIV infection; rather, it was started based on a $CD4^+$ T cell count of less than 350 cells/μL, per the South African guidelines at that time. Institutional Review Board (IRB) approval was eventually obtained to initiate cART immediately after detection of viremia through use of a boosted regiment that included raltegravir until 2 months after viral suppression. IRB approval to provide preexposure prophylaxis (PrEP) was recently obtained and is now available to all FRESH study participants. This intervention is currently recommended but not yet provided in South African public healthcare facilities.

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 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 followup data and pre- and postinfection biological samples enabled key insights regarding biological determinants of HIV acquisition. For example, we identified the vaginal microbiome as having a substantial impact on HIV risk. Healthy HIV-uninfected women in this cohort have a predominance of highly diverse anaerobic bacterial communities that are strongly correlated with elevated levels of proinflammatory genital cytokines and increased rates of HIV acquisition (2, 3). This is in contrast to the prevalence of *Lactobacillus*-dominant bacterial communities in the female genital tract of women in the United States and Europe. Also crucial to understanding HIV acquisition risk in young women is the demonstration in FRESH that the use of injectable progestin contraceptive and high endogenous progesterone was associated with increased frequency of activated CCR5-enriched HIV target cells in the cervix, providing a biological mechanism for increased HIV acquisition in women with high

progestin exposure (4). Taken together, these findings point to new areas for potential intervention through which to reduce the extraordinarily high rates of HIV infection among women in sub-Saharan Africa.

FRESH and the immunology of "hyperacute" infection

The FRESH study design has successfully identified acute HIV infection at the onset of plasma viremia, with the majority of 72 incident infections detected thus far (June 2018) in Fiebig stage I, some with initial viral loads of less than 100 RNA copies/ml plasma (1, 5). The availability of pre- and postinfection samples revealed the induction of profound $CD8^+$ T cell activation and proliferation in untreated acute infection, involving more than 70% of $CD8^+$ T cells in some individuals, with tetramer staining consistent with the majority of these being HIV-specific. These cells became rapidly proapoptotic and were defective for the production of key antiviral cytokines such as interferon-γ, which may partially explain why the $CD8^+$ T cell response is incompletely effective during the acute phase. Importantly, the rapidity of induction of $CD8^+$ T cell activation and the magnitude of peak activation were associated with a lower viral set point, indicating a key role for these cells in viral control (5). Other findings included very early loss of resting memory B cells after acute HIV-1 infection, which may explain some of the defects seen in response to vaccination in HIV-infected persons, and an irreversible loss of innate lymphoid cells in hyperacute HIV infection, which may partially explain the lymphoid tissue breakdown and persistent immune dysfunction associated with HIV infection.

FRESH and the HIV Cure agenda

As data emerged that suggested improved outcomes with earlier cART initiation, we obtained IRB approval to provide immediate treatment during acute infection, before change in the South African government guidelines. With rapid turnaround of HIV RNA results and careful preparation of study participants, we have been able to initiate treatment less than 24 hours after a positive test. This has resulted in preserved $CD4^+$ T cell counts and lack of seroconversion as determined with both HIV rapid antibody and Western blot testing. These very early treated individuals comprise an ideal cohort for cure research in sub-Saharan African women, who have hitherto been underrepresented in cure research despite their disproportionate burden of HIV infection.

Opportunities and challenges

The FRESH study has been successful in achieving the goals of the education and research components: offering a pathway out of poverty for high-risk disempowered women while providing key insights into HIV transmission and pathogenesis. We consider combining frequent HIV testing with the socioeconomic empowerment curriculum to be a key component for the success of this approach. The sample processing and laboratory investigations have all been performed in KZN, contributing to local capacity building. Key adaptations during program implementation—including approval to initiate treatment during acute HIV infection, providing access to PrEP, and iterative development of the

socioeconomic educational program—all provide direct benefits while contributing to visit adherence and study retention.

However, challenges remain. Whether addition of PrEP will reduce incidence rates in FRESH remains to be seen. The FRESH educational program has empowered women to become employed, but whether this will lead to sustained decreased risk of infection will require further followup. Replication and scale-up of this program, initially funded by private philanthropy and subsequently scaled up with support from the Gates Foundation, is a challenge in terms of cost and time investment. FRESH was designed specifically for young women because of the demonstrated higher rates of infection in this age group compared with men and the relative paucity of data on HIV pathogenesis in women; however, programs that target men are needed in order to gain broader insight into the epidemic.

Despite these challenges, the FRESH approach has been successful in showcasing how basic science research and an educational program that delivers social good can be combined. The continued high acquisition rates underscore the need for expanded research and new interventions to prevent and cure HIV infection. FRESH represents one innovative strategy to address individual and community needs while advancing scientific knowledge.

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