Addressing key gaps in cure research through identification and treatment of hyperacute HIV infection in a resource-limited setting

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Outline

• Why cure research despite improved prevention and treatment strategies?

• The FRESH cohort- a unique cohort to address gaps in HIV prevention, pathogenesis and cure research

• Impact of treatment during hyperacute HIV infection on virologic and immunologic factors

• Implications for HIV cure research in resource-limited settings
Eastern and southern Africa: high new HIV infections among young women aged 15-24 years

- There is a need to better understand the reasons for high incidence among young women
- Current strategies are suboptimal - new biomedical interventions such as vaccines or a functional cure are needed
Strategies for cure

• **Eliminate latently infected cells** (Ablative chemotherapy, “shock and kill” strategies- reviewed by Siliciano and Siliciano, *JCI*, 2016)


• **Optimise cART**
Acute HIV infections- an opportunity for early interventions?

Viral set point is a predictor for:
- Rate of disease progression
- Risk of transmission

• Can we identify hyperacute HIV infections?
• What will be the impact of early treatment on immune responses and the viral reservoir?
FRESH study cohort

- **FRESH**: Females Rising through Education, Support and Health
- Recruit women 18 to 23 at very high risk of HIV infection
  - Provide an intensive empowerment, life-skills and job readiness curriculum that coincides with the sample collection protocol.
- Identify persons in the earliest stages of acute infection by testing them twice weekly for one year, and collect serial pre- and post-infection samples.
- Study antiviral immune mechanisms
Study setup and sample collection

- **Phase I: Surveillance**
  - Twice weekly HIV RNA PCR testing via finger stick blood draws
  - Quarterly blood and mucosal sampling of the female genital tract

- **Phase II: Acute Infection**

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Acute infections detected (N=42)

As of June 30, 2016:

- 14 untreated, 11/14 (79%) Fiebig I
- 28 treated early, 24/28 (85.7%) Fiebig I
- **Incidence 8.5** (95% CI=5.8-12.0) per 100 p/y

- Median: 124 days; range 0-684
Typical treated and untreated acute HIV-1 infection
Treatment during hyperacute phase blunts peak viremia

Peak Viral Load

Log_{10} RNA copies/ml

Untreated (n=14)  Treated (n=20)
Very early ART limits CD4 T cell loss

**Untreated**

- Preinfection
- Nadir CD4
- Rebound CD4

**Early treated**

- Preinfection
- Nadir CD4
- Rebound CD4

CD4 Count (cell/mm³)
How does timing of cART initiation (Fiebig I/II versus III onwards) or peak viremia affect immune responses?

Viral RNA and/or P24 antigen pos (but antibody neg)
Most treated participants do not seroconvert*

*WB- Biorad GS kit
Some patients started on cART in Fiebig I do not make detectable HIV-specific tetramer CD8+ T cell responses

No tetramer response detected and no memory responses detected by CFSE dilution
CD8\(^+\) T cell responses in early treated subject

PID 442
Fiebig V
HIV-specific CD8 T cells show defects of cytokine secretion and long-term memory during untreated acute HIV infection.
HIV-specific CD8$^+$ T cells in early treated subjects are more functionally competent.
Frequency of individual tetramers+ CD8+ cells is lower in early treated but cells upregulate survival molecules.
Conclusions

• We have demonstrated the feasibility of identifying individuals with acute HIV infection and linking them to care

• FRESH study participants initiated on cART during hyperacute HIV infection may offer new insights on long-term viral remission

• Understanding of immune responses following cART initiation may be useful for future intervention studies

• Ideal platform for future interventions aimed at cure?
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- FRESH study team

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