Viral reservoirs and insights for HIV cure in adults and children

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Outline

• Background on cure research

• 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

• Conclusions and implications for HIV cure research in resource-limited settings
Barriers to a cure

- Lifelong treatment is probably unsustainable
- People of ART who are fully suppressed have lower life expectancy
- cART use is associated with significant morbidity

Barriers to cure: latently infected T-cells

HIV Viral load

HAART
Barriers to cure: residual viral replication

HIV Viral load

HAART

HAART
Barriers to cure: anatomical reservoirs
Strategies for cure

• Eliminate latently infected cells

• Make cells “resistant” to HIV

• Optimise HAART
  – Intensification
  – Early treatment
HIV remission is rare but possible

ART started early in infection

- Mississippi child 28 months
- Visconti, French Teenager
- Timothy Brown

Can study of acute HIV-1 infection be a pathway to cure?

**Key questions:**
- Characteristics of the transmitted/founder virus?
- Immune responses in acute HIV-1 infection- why do they fail? What is the impact of T/F virus? Impact on reservoir? Impact of early treatment?
- Can we mimic effective immune responses or augment ineffective immune responses for better vaccines or cure?

**Viral set point is a predictor for:**
- Rate of disease progression
- Risk of transmission
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.
- Empowerment and training program coincides with twice per week HIV RNA testing for 9 months. Serial pre-and post-infection samples (blood, FGT and lymph nodes) are collected.
- Study host and viral factors associated with acquisition and disease progression- T/F virus, antiviral immune mechanisms.
Acute infections detected (N = 54)

As of May 10, 2017:

- 14 untreated, 11/14 (79%) Fiebig I
- 40 treated early, 32/40 (84.2%) Fiebig I
- **Incidence 8.2** (95% CI=5.8-12.0) per 100 p/y
Typical treated and untreated acute HIV-1 infection

FRESH Acute 1

FRESH Rx Patient 1

Treatment: TDF/FTC/EFZ
Raltegravir intensification reduces time to full suppression

- Untreated (n=13)
- Early ART (n=8)
- Early ART + RAL (n=15)

**Median HIV RNA log_{10} copies/ml**

- Sampling timepoints after detection of HIV-RNA

- Early ART

\[ p < 0.0177 \]
Early ART blunts peak viremia in Fiebig I treated patients.
Early cART in Fiebig I preserves CD4 T cells
Participants treated in Fiebig stage I do not seroconvert*

*WB- Biorad GS kit
Markers of reservoirs and latency

Forms of intracellular HIV DNA

1. Non-integrated linear DNA
2. Integrated provirus
3. 2-LTR circles
4. DNA sequencing
5. p24 antigen
HIV persistence measurements

Proteinase K cell lysate: ACH-2, PBMCs

Pre-amplification from cell lysate

Single well pre-amplification of HIV and CD3

Frequency of cells harbouring HIV DNA

HIV copy number

2 X CD3 copy number

TaqMan Probes
(sensitivity: 1 HIV DNA copy)

Real-time nested PCR of pre-amplified products

Total HIV DNA

Integrated HIV DNA

HIV CD3

Real-time nested PCR of pre-amplified products

adapted from Vandergeeten et. al., 2014, JVI
Early establishment but steady decay of the reservoir in early treated participants

527 (Fiebig stage I treated) SK-141 (chronically infected patient)

Reservoir measurements according to Vandergeeten et al, 2014, JVI
Higher total DNA reservoir in Fiebig stage I compared to chronically infected untreated patients
Total HIV DNA correlates with peak viral load

- Total HIV DNA (log copies/10^6 cells)
- Viral Load (log copies/ml)

p=0.0012, r=0.942
Reduced but still detectable viral reservoir at 52 weeks for Fiebig I treated participants.
A list of all HIV DNA sequences detected in FRESH (n=4)

Patient 1

Days post-detection
10
46
161
165

Patient 2

Days post-detection
2
42
164

Patient 3

Days post-detection
7
42
164

Patient 4

Days post-detection
18
42
161
332
Longitudinal monitoring of HIV reservoir size in FRESH patients

Treatment initiated immediately post-detection

No treatment
HIV Gag p24 detectable in early treated fully suppressed subjects

HIV+ Chronic  HIV+ ET  HIV Negative

Gag-p24: Brown  Nucleus: Blue
p24+ cells co-localize with BCL6+ cells in the germinal centers

**PID:** 053 (127-33-0942-683)
Early Tx
**Age:** 19
**VL:** <20 cps/ml
Conclusions

- Acute HIV infections- novel insights into characteristics of T/F virus, immune responses and reservoir establishment mechanisms for vaccine and functional cure strategies

- FRESH study participants initiated on cART may have higher quality CTL immune responses but reservoir is established very early, decays slowly

- Understanding of T/F viruses, immune responses and reservoirs following may be useful for future intervention studies

- Suitable platform for future interventions aimed at cure?
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