MHRP Studies in Early Treatment and The Journey towards HIV Remission

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The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.
Why is Acute HIV Infection Important?

The first 4 weeks of infection

More cells are infected
CD4 depletion
Tissue infection
Exhausted immune system
Mutated HIV evades immunity

Transmission of HIV

Plasma Viral RNA (copies per ml)

Days following HIV-1 Transmission

The first 4 weeks of infection
Two Ways to Achieve HIV Remission
(Undetectable Viral load in Blood without ART)

From Nicolas Chomont, 2015 IAS Plenary, Vancouver
MHRP/Thai Red Cross Acute Infection Studies

**RV217**
Prospective acute infection study in high risk individuals

- Twice weekly testing in E. Africa/Thailand of 2555 uninfected persons
- Acute HIV infection (n=124)

*Robb ML, NEJM 2016*

**SEARCH010/RV254**
Acute infection cohort with early ART

- Real-time screening of 200,000 samples in Thailand
- Acute HIV infection (n=430)

*de Souza M, Ananworanich J, AIDS 2015*

Fiebig I/II: RNA+, HIV IgM-
RV217 Population

- Participants from East Africa, Thailand
- High risk behavior determined by an audio-computer assisted self interview
- Twice weekly finger sticks performed to identify HIV RNA
- Regular risk reduction counseling
- All receive HAART since 2014-2015
Viral Load during Acute HIV Infection (RV217)

Symptoms and signs in 86%
Generally few, mild, brief
No one with CD4<350

Robb ML, NEJM 2016
Acute HIV Diagnosis Algorithm in RV254 Study

4th generation immunoassay
(n=213,589)

Reactive
(n=14,873)

Non-reactive
(n=198,716)

Pooled nucleic acid testing
(3-30 samples/pool)

3rd or 2nd generation Immunoassay

Reactive
(n=405)

Non-reactive
(n=128)

Positive
(n=533)

Negative
(n=198,588)

Chronic HIV
(n=13,849)

Acute HIV
(n=533)

HIV uninfected
(n=198,588)

433 AHI enrolled

- HIV prevalence: 11%
- Incidence of AHI: 2.2 per 100 person-years.

Updated from de Souza M, AIDS 2015
What can early treatment do and not do to help reach HIV remission?
Key Questions

- What can **early treatment** do and not do to help reach HIV remission?
  - Data from RV217 and RV254 acute HIV infection studies

- Does **early treatment** in RV254 delay time to viral load rebound after treatment interruption?

- What might HIV remission treatment look like?
Plasma HIV RNA in RV217 untreated and RV254 treated acute HIV infection participants

- In RV217 untreated group: peak viremia is at week 2 and set-point is at week 4
- In RV254 treated group: 97% with HIV RNA < 50 at week 144

Stark Differences in HIV Reservoir in Untreated vs. Treated Acutely HIV-Infected Thai Adults

Reservoir “set-point” is established early in acute infection and determines reservoir size in chronic infection

Window of opportunity to significantly alter reservoir size is with early ART

Ananworanich, Robb, Ebiomedicine 2016
High Seronegativity in Very Early Treated Thais

4th generation antigen-antibody combo immunoassay 6 months after ART

Very early treated individuals can remain HIV antibody negative more than 6 months from onset of infection

RV254 adults: Baseline DNA values in memory CD4 predict their reservoir after ART

Nicolas Chomont (U Montreal)
Limited CD4 Recovery in the Lamina Propria of Gastrointestinal tract

Elevated plasma sCD14 after early ART

†p<0.05 compared to HIV-

Diagnosis of Acute HIV Infection

Urgency to initiate ART as soon as possible

- Reduce HIV reservoirs
- Preserve immunity
- Prevent HIV transmission
What can early treatment do and not do to help reach HIV remission?

- **Reservoir**: Reduce but not eliminate
- **HIV-specific Immune responses**: Partially reverse immune damage
- **Immune activation**: Partially reduce activation
Does Early ART in RV254 Delay Time to Viral Load Rebound after Treatment Interruption?
Viral Load Rebound post-Treatment Interruption

Median (range) time to viral load rebound: 14 (5-29) days

Rothenberger, Schacker et al, PNAS 2014
Data provided by Timothy Schacker (University of Minnesota)
Viral Load Rebound post-Treatment Interruption

Median (range) time to viral load rebound

Chronic: 14 (5-29) days
Fiebig III/IV: 22 (21-77) days

SEARCH 019: Chloroquine + Maravoric + Vorinostat

p=0.002
Rates of Viral Load Rise following Treatment Interruption

<table>
<thead>
<tr>
<th>HIV Reservoir</th>
<th>HIV-specific responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Magnitude</td>
</tr>
<tr>
<td>Fiebig III/IV</td>
<td>++</td>
</tr>
<tr>
<td>Chronic</td>
<td>+++</td>
</tr>
</tbody>
</table>

Immune therapeutics will be needed in addition to early ART for durable remission.

Kroon, Ananworanich, de Souza et al. 2016 IAS
MHRP-related HIV Remission Trials

RV254 Cohort

Acute HIV Infection

- ART
  - VL suppression
  - ART +
    - VRC01 (RV398)

  or with
  - Telmisartan (RV408)

Low frequency of latently infected cells in blood/tissue
Preserved HIV-specific immune responses

Analytical treatment interruption

No additional intervention
- Treated Fiebig 1 (RV411)

Single interventions
- VRC01 (RV397)
- Ad26/MVA (RV405)

Combination interventions
- Vorinostat +hydroxychloroquine +maraviroc (SEARCH 019)
- Ad26/MVA/TLR 7
MHRP-related HIV Remission Trials

To limit the establishment of the reservoir
- Early ART
- Acute cohorts Fiebig I ATI

To reduce the size of the reservoir
- Latency Reversing agent
- Immune therapies
- Anti-inflammation
  - Vorinostat
  - Ad26/MVA, DC VRC01
  - Telmisartan
RV 411: Treatment interruption of treated Fiebig I participants

**Volunteers from Thai Red Cross**
- ≥18 years old
- Started on ART during **Fiebig 1**
- Prescribed ART for ≥24 mo
- HIV-1 RNA <50 copies/mL for ≥12 mo
- CD4 >400 cells/mm$^3$

*4-week* PI substitution for subjects prescribed NNRTI

**Intermediate Endpoint (Futility):**
- Virologic control (RNA <50 copies/mL)
- 1 of first 8 subjects must meet this endpoint

**Primary Endpoint:**
- Virologic control (RNA <50 copies/mL)

!I = HIV RNA Assessment

Any positive HIV RNA prompts repeat quantitative testing at least every 3 days until negative or ART resumed
Criteria for ART Resumption

- HIV-1 RNA >1,000 copies/mL on 2 consecutive determinations at least 1 day apart
- Any HIV-1 RNA > 10,000 copies/mL
- CD4 < 350 cells/mm$^3$ twice over 2 weeks
- CD4 decline > 50% from baseline prior to ATI
- Clinical progression to CDC Category B or C disease
- Acute retroviral syndrome
- Pregnancy
Possible new proposals of combination strategies

- TLR7+ Ad26MVA (2017)
  - Treated acutes with ATI

- TLR7+ 2bNAb (2017)
  - At acute HIV Without ATI
  - Treated acutes with ATI

- TLR7+ vaccine +2bNAb (2018)
  - Treated acutes with ATI
Broadly Neutralizing Monoclonal Antibody (bNabs) Targets

V2
(PGDM1400, CAP256)

CD4bs
(VRC01, 3BNC117)

V3
(PGT121, 10-1074)
Broadly Neutralizing Antibody Studies in Early Treated Individuals

RV398

RV397

NIAID-funded studies [PI: J Ake (RV398), J Ananworanich (RV397)]
**NHP SIV-MAC251 Challenge**

<table>
<thead>
<tr>
<th>Group</th>
<th># Challenges for 50% Infection</th>
<th>P-Value vs Sham*</th>
<th>Hazard Ratio (95% Conf. Interval)</th>
<th>Per-Exposure Risk of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA/MVA</td>
<td>2</td>
<td>0.0055</td>
<td>0.186 (0.057-0.611)</td>
<td>0.269</td>
</tr>
<tr>
<td>MVA/MVA</td>
<td>1</td>
<td>0.5587</td>
<td>0.725 (0.247-2.129)</td>
<td>0.615</td>
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<tr>
<td>Ad26/MVA</td>
<td>3</td>
<td>0.0037</td>
<td>0.174 (0.053-0.567)</td>
<td>0.250</td>
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<tr>
<td>MVA/Ad26</td>
<td>3</td>
<td>0.0062</td>
<td>0.198 (0.062-0.632)</td>
<td>0.269</td>
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<tr>
<td>Sham</td>
<td>1</td>
<td>N/A</td>
<td>1</td>
<td>0.727</td>
</tr>
</tbody>
</table>

*Chi-square test, proportional hazard model
Figure 2b

Sham

DNA/MVA

MVA/MVA

Ad26/MVA

MVA/Ad26

Days Following Infection

Log SIV RNA

MEAN

5.85

5.36

6.39

5.36

4.77

3.53

4.77

Days Following Infection

Log SIV RNA

MEAN

5.85

5.36

6.39

5.36

4.77

3.53

4.77

N=1

N=3

N=1
SIV RNA Following ART Initiation on day 7

Day Following Initiation of Study

Log SIV RNA

Copies / ml

Sham

TLR7

Ad26/MVA

Ad26/MVA+TLR7

Borducchi, Robb, Michael, Barouch, Nature 2016
CD8+ T Cell Activation Following TLR7 Agonist

**Sham**

**TLR7**

**Ad26/MVA**

**Ad26/MVA+TLR7**
TLR7 Agonist+Ad26MVA Vaccine Reduced Viral Load in Monkeys after ART Discontinuation

Borducchi, Robb, Michael, Barouch, Nature 2016
Delay of Viral Rebound and Reduction of Setpoint Viral Loads by Ad26/MVA Vaccine + TLR7 Agonist Following ART Discontinuation

- **Days to Viral Rebound Following ART Discontinuation**
  - **P = 0.04**
  - **P = 0.003**
  - **P = 0.01**
  - **P = NS**

- **Setpoint SHIV RNA Copies / mL**
  - **P < 0.0001**
  - **P = 0.0003**
  - **P = NS**
  - **P = 0.004**
What might HIV remission strategies look like?
What might HIV remission treatment look like?

Viral Load

Time

Suppressive ART

Latency modifying agents

Repeat doses of immunotherapeutics

Biomarkers

ART

ART
Lessons Learned So Far from the MHRP Studies

- **Delayed in time to viral load rebound with early ART**
  - Statistically significant but not clinically meaningful (Fiebig III/IV vs. chronic)

- **Treatment interruption can be conducted safely**
  - Frequent viral load monitoring and ART resumption at 1000 copies/ml

- **Designing treatment interruption trials with immunotherapeutics**
  - Benefits may be missed with the current designs
    - SIV models showing viremic control after rebound events
  - Risks and benefits must be weighed very carefully
    - Stronger scientific rationale is needed
    - Step-wise approach with gate keeper endpoints to indicate responses to interventions before allowing longer and higher viremia
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