Acute HIV Infection and Opportunities for Early Intervention

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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.
Thai Red Cross Anonymous Clinic (April 2009 to 10 August 2013)

80,557 sensitive HIV EIA (Ag-Ab combo assay)

- 5,523 positive
- 75,034 negative

Less sensitive HIV EIA

- 5,443 positive
- 80 negative

Chronic HIV

Pooled NAT

- 59 positive
- 74,975 negative

139 acute HIV

Not infected

HIV RNA diagnosed HIV earlier than sensitive EIA by 5 days
SEARCH 010/RV 254 study: Acute HIV enrollment/compartment studies/new drugs

Real-time screening of 80,557 samples in Bangkok by pooled nucleic acid and sequential EIA

Acute HIV infection (AHI) confirmed (n=139)

114 AHI enrolled

51% F I/II

Main protocol (n=114)
- Clinical characterization
- Phlebotomy

Optional procedures
- Sigmoid biopsy (n=80)
- Leukapheresis (n=70)
- Lumbar puncture (n=69)
- MRI/MRS (n=103)
- Genital secretion (n=107)
- Inguinal LN biopsy (n=2)

ARV protocol (n=111)
- MegaHAART (n=60)
- HAART (n=51)

3 days

2 days

Updated from Ananworanich J, PLoS ONE 2012
www.clinicaltrials.gov 00796146

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Distribution of CD4+ and CD4+CCR5+ T lymphocytes in the gut mucosa of patients with acute HIV infection

- p=0.04* (HIV- vs Fiebig I)
- p=0.006** (HIV- vs Fiebig II)
- p<0.001*** (HIV- vs Fiebig III)

- p=0.002** (Fiebig I vs Fiebig II)
- p<0.001*** (Fiebig I vs Fiebig III)

% CD4+ and % CD4+CCR5+
Almost all Fiebig I subjects had undetectable integrated HIV DNA in PBMC.
Lower total and integrated HIV DNA in the sigmoid colon in Fiebig I subjects

- Median Total HIV DNA in sigmoid colon copies/10^6 cells:
  - Fiebig I (n=8)
  - Fiebig III (n=13)

- Median Integrated HIV DNA in sigmoid colon copies/10^6 cells:
  - Fiebig I (n=8)
  - Fiebig III (n=10)

The % is the % undetectable.
HIV RNA between megaHAART vs. HAART

<table>
<thead>
<tr>
<th>Time</th>
<th>MegaHAART n</th>
<th>HAART n</th>
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Integrated HIV DNA in PBMC
Total HIV DNA in PBMC

Mean Total HIV DNA copies/10^6 PBMC

Chronic 5 yrs. ART
FCs

Fiebig I n: 24 23 22 20 15 11 7 4
Fiebig III n: 36 34 31 27 18 18 13 9

Mean Integrated HIV DN.
copies/10^6 PBMC

Fiebig I n: 24 23 22 20 16 11 7 4
Fiebig III n: 36 34 31 27 18 18 14 9

ber 2013
Almost all subjects treated during acute HIV had undetectable integrated HIV DNA after 1 year of ART.
Objective 1
Is early ART alone sufficient to cure in patients treated during Fiebig I?

Objective 2
Will therapeutic HIV vaccine + early ART result in better viremic control vs. early ART alone?

Objective 3
Will HDACi + early ART result in depletion of reservoir/cure vs. early ART alone?

Objective 4
Will anti-inflammatory drugs or broadly neutralizing mAb + early ART = less activation and reservoir vs. early ART alone?

Where we are now
in RV254/SEARCH 010
ART initiated during acute HIV restricted infection in PBMCs and TCM

Goal
Functional cure (Viremic control without ART)

A series of randomized trials are being developed
Objective 1: Is early ART alone sufficient to cure in patients treated during Fiebig I?

11 patients
- Initiated ART during Fiebig I and viral suppression for ≥ 2 years with no viral blip for the past 1 year

Step-wise interruption
- Step 1: 6 subjects
  - If at least 1 out of 6 is a success (viremia < 100 copies/ml at week 24), go to step 2
- Step 2: 5 subjects

ART resumption criteria
- VL > 1000 copies/ml or a rapid rise in VL
- Persistent low level viremia above 100 copies/ml
VRC mAb 01 administered during acute infection

Two recent publications provide proof of concept –

Shingai et al – mAb reduced SHIV viremia to undetectable in 3 days

Barouch et al – mAb reduced SHIV viremia 3 logs in 7 days and in a minority of cases established durable control of viremia

Primary Objectives

1) Safety of VRC01 in acutely HIV infected individuals

2) Impact of VRC01 on viral dynamics during AHI

3) Impact of VRC01 on HIV reservoir seeding during AHI

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VRC mAb 01 administered during acute infection

Enrollment among RV 217 participants
1) Aptima reactive at SBV and visit 1 of phase IB
2) EIA negative, ie Fl to FlIII

Interventions

1) Study agent VRC-HIVVRC01060-00-AB (VRC01) monoclonal antibody, 40 mg/kg IV

2) ART: TDF/FTC/EFV in daily fixed dose combination

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VRC mAb 01 administered during acute infection

**Design**

Group 1 (n=6) start ART alone in AHI on day 0

Group 2 (n=6) start ART with single infusion of 40 mg/kg VRC01 in AHI on day 0

Group 3 (n=6) single infusion of 20 mg/kg VRC01 in AHI on day 0 followed by ART initiation on day 7

All groups will subsequently be followed for 24 weeks.

Consider ATI?
HIV RNA between megaHAART vs. HAART
A special thanks to all RV217 and RV 254 volunteers!

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