Effects of Treatment During Acute HIV Infection on HIV Persistence

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On behalf of the RV254/SEARCH010 Study Group

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.
Outline

- Recent published studies and the RV254/SEARCH 010 study
  - How does early ART affect HIV persistence?
  - Are there preferred regimens for early ART?
  - How does early ART affect viremic control after treatment interruption?

- Research gaps
  - Finding acutes
  - Finding biomarkers for HIV remission
How does early ART affect HIV persistence?
Early ART affects the size and composition of the latent HIV reservoir

Ananworanich, Dube and Chomont, Curr Opin HIV/AIDS 2015
Lower levels of cell-associated HIV DNA with early ART

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>ART onset</th>
<th>ART duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laanani M, CID 2015</td>
<td>327</td>
<td>Median 41 d</td>
<td>Median 2.3 yr</td>
<td>• Continued decay of DNA with early ART</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Faster initial decay when ART started by 3 mo post infection</td>
</tr>
<tr>
<td>Jain V, JID 2013</td>
<td>34</td>
<td>&lt; 6 mo</td>
<td>Unk</td>
<td>• 5-times lower DNA in early vs. late ART</td>
</tr>
<tr>
<td>Gianella S, AVT 2011</td>
<td>32</td>
<td>&lt; 2 mo</td>
<td>Median 18 mo</td>
<td>• 0.4 log lower DNA in early vs. late ART</td>
</tr>
<tr>
<td>Koelsch KK, AIDS 2011</td>
<td>8</td>
<td>&lt; 4-6 wk</td>
<td>1 yr</td>
<td>• Lower DNA in PBMCs and colon with early ART</td>
</tr>
</tbody>
</table>
Early ART restricts frequency of replication competent virus in resting CD4

<table>
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<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Archin NM, PNAS 2014</td>
<td>27</td>
<td>&lt;45 d</td>
<td>&gt; 6 mo</td>
<td>• Early ART restricts RCV</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>• Little RCV is generated after ART initiation</td>
</tr>
<tr>
<td>Buzon MJ, JV 2014</td>
<td>9</td>
<td>&lt;6 mo</td>
<td>&gt; 10 yr</td>
<td>• Lower RCV in early vs. late ART</td>
</tr>
<tr>
<td>Strain MC, JID 2005</td>
<td>27</td>
<td>&lt; 6 mo</td>
<td>&gt; 1 yr</td>
<td>• Lower RCV in early vs. late ART</td>
</tr>
</tbody>
</table>

RCV: replication competent virus
Early ART in Thai Adults: RV254/SEARCH010 Study

Real time screening of ~ 130,000 samples at Thai Red Cross Anonymous Clinic

2 days
Enrollment (n= 260)

1 day
Early ART

Optional procedures
- Sigmoid biopsy
- Lymph node biopsy
- Lumbar puncture
- MRI/MRS
- Genital secretion collection

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of infection</td>
<td>18 days</td>
</tr>
<tr>
<td>Fiebig I/II (&lt; 2-3 weeks)</td>
<td>51%</td>
</tr>
</tbody>
</table>
Early ART limits persistence of HIV reservoir in all CD4+ T cell subsets

After 2 years of ART, integrated HIV DNA is undetectable in all subsets of Fiebig I individuals.

Nicolas Chomont (U Montreal)
Decay in integrated HIV DNA in the sigmoid colon after ART

Integrated HIV DNA vanishes quickly in the sigmoid colon of both Fiebig I- and III-treated subjects.

Nicolas Chomont (U Montreal)
Low integrated HIV DNA in lymph node after 6-24 months of ART

**Fiebig I**
- 13%
- Collagen deposition

**Fiebig III**
- 25%

Nicolas Chomont (U Montreal)
Are there preferred regimens for early ART?
Randomized study of 3 vs. 5 drugs for acute/recent HIV infection

3-drug: TDF + FTC + DRV/r
5-drug: TDF + FTC + DRV/r + RAL + MVC

- Markowitz M (JAIDS 2014)
  - 40 enrolled
  - < 4 week HIV onset in most
  - 96-week follow up
  - No differences for
    - HIV RNA (3 copies/ml)
      - 3 VF in 5-drug arm
    - Cell-associated HIV DNA (2.9 log/10^6 CD4)
    - Change in cell-associated HIV RNA
    - Infectious virus in resting CD4+ T cells
    - CD4 and subsets
    - sCD14

- OPTIPRIM-ANRS147 (Cheret A, Lancet ID 2015)
  - 90 enrolled
  - Median 35 days from HIV onset
  - 96-week follow up
  - No differences for
    - HIV RNA
    - But poorer adherence and more VF with 5-drug
    - Cell-associated HIV DNA (2.8 log/10^6 CD4)
    - CD4
    - But lower CD4/CD8 ratio with 5-drug (1.06 vs. 1.24, p=0.04)
HIV RNA decline faster with MegaHAART

HAART: TDF + FTC + EFV
MegaHAART: Intensified with RAL and MVC for the first 24 weeks

Median time to HIV RNA < 50 copies/ml
HAART 83 days vs. megaHAART 55 days (p = 0.04)

Ananworanich J, JVE 2015 (www.viruseradication.com)
No differences in total HIV DNA but higher 2LTR circles with MegaHAART

Ananworanich J, JVE 2015 (www.viruseradication.com)
How does early ART affect viremic control after treatment interruption?
Loss of HIV Suppression post-ATI (ACTG)

Etemad B and Li J, CROI 2015 (Abstract 110LB)
SPARTAC
About 1 in 10 early treated individuals remained virally suppressed at 1 year after interruption

<table>
<thead>
<tr>
<th>VL &lt; 400 after interruption</th>
<th>3 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>26%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>ART 48 wks</td>
<td>32%</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>ART 12 wks</td>
<td>21%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Stohr W, Plos One 2013
# Post Treatment Controllers after early ART

<table>
<thead>
<tr>
<th>Published Studies</th>
<th>Viremic control</th>
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</thead>
<tbody>
<tr>
<td><strong>Optiprim</strong> (n=90)</td>
<td>2 of 90 (2%) had VL &lt; 50 at 2 years</td>
</tr>
<tr>
<td>(Cheret A, Lancet ID 2015)</td>
<td></td>
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<tr>
<td><strong>Spartac</strong> (n=165)</td>
<td>4 of 165 (2%) had VL &lt; 400 at 3 years</td>
</tr>
<tr>
<td>(Stohr W, Plos One 2013)</td>
<td></td>
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<tr>
<td><strong>VISCONTI</strong> (n=14)</td>
<td>15% had VL &lt; 50 for &gt; 6 years</td>
</tr>
<tr>
<td>Saez-Cirion A, Plos Pathogens 2013</td>
<td></td>
</tr>
<tr>
<td><strong>Swiss HIV Cohort Study</strong> (n=32)</td>
<td>3 of 32 (9%) had VL &lt; 50 at 1 year</td>
</tr>
<tr>
<td>(Gianella S, Antiviral Therapy 2011)</td>
<td></td>
</tr>
<tr>
<td><strong>Primo-SHM</strong> (n=173)</td>
<td>4 of 79 (5%) had VL &lt; 100 at wk 24</td>
</tr>
<tr>
<td>(Grijsen ML, PLoS Medicine 2012)</td>
<td></td>
</tr>
<tr>
<td><strong>ANRS CO6 PRIMO</strong> (n=164)</td>
<td>VL &lt; 50 in 11% at 1 year, 8.5% at 2 years</td>
</tr>
<tr>
<td>(Goujard C, Antiviral Ther 2012)</td>
<td></td>
</tr>
<tr>
<td><strong>CASCADE</strong> (n=259)</td>
<td>VL &lt; 50 in 8.2% at 1 year, 5.5% at 2 years</td>
</tr>
<tr>
<td>(Lodi S, Arch Intern Med 2012)</td>
<td></td>
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</tbody>
</table>
Research Gaps

“Finding Acutes”
Edutainment online/offline platform for engaging young MSM into HIV testing and care

Anand T, J Virus Eradication 2015 (www.viruseradication.com)
Comprehensive HIV/AIDS & STI Awareness

HIV/STI transmission, prevention, treatment, and MSM sexual health advise videos

Web board

NAT Testing during the Course of PEP

After reading the webboard message, http://www.adamslong.org/agilery.php?mid=46 I am wondering whether the test results of a NAT test can be false negative if tested white taking a course of emergency anti-viral medication (PEP). I was tested 36 days after taking PEP and was informed that I could be 100% confident in the results. How confident can I be that PEP will work? Please explain this to me again. I am stressed out.

Celebrity gets HIV testing

Club card member and partner for couple HIV testing
AdamsLove Impact

- 1.7 million visitors with 8 million page views
- Thailand, USA, UK are top visiting countries

TemanTeman.org in Indonesia and Malaysia
Adamslove.org in Taiwan and South Korea

Anand T, J Virus Eradication 2015 (www.viruseradication.com)
Research Gaps

“Finding biomarkers for HIV remission”
Biomarkers for longer time to viral load rebound after treatment interruption

- **Clinical parameters**
  - Earlier ART initiation and longer duration of ART
  - High CD4 nadir

- **Low markers of peripheral blood HIV reservoir size**
  - Active reservoirs (Etemad B, CROI 2015, Abs 110LB)
    - Cell-associated HIV RNA and single copy HIV RNA

- **Strong HIV-specific immune responses**
  - Strong HIV-specific CD4+ T cell response (Frater J, AIDS 2014)
  - Low expression of PD-1, Lag-3 and Tim-3 on CD4 and CD8 T cells (Hurst J, CROI 2015, Abs 111LB)
  - Unique NK phenotype and function (Scott-Algara D, CROI 2015, Abs 52)
Low markers of HIV reservoir size in RV254

Intervention/Treatment Interruption

RV409
Latency reversing agent + anti-inflammatory + entry inhibitor

RV411
Treatment in Fiebig I

RV397
Broadly neutralizing antibody

RV405
Therapeutic HIV Vaccine

RV438
Latency reversing agent + broadly neutralizing antibody

HIV Remission

Behavioral Research
Participants’ decision making and expectation
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