Diagnosing and treating acute HIV infection
Implications for HIV cure

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SEARCH, The Thai Red Cross AIDS Research Centre
APACC 2019
Nothing to disclose.
Diagnosing and treating acute HIV infection

Possible Implications for HIV cure

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SEARCH, The Thai Red Cross AIDS Research Centre
APACC 2019
▪ Defining and Diagnosing Acute HIV Infection
▪ Remission and Cure prospects
▪ Impact of acute HIV treatment: reservoir and beyond
Defining and Diagnosis Acute HIV Infection

Cells are Infected & Depleted of CD4 cells

Tissue is Infected & Depleted of CD4 cells

Immune System is Exhausted

HIV Mutates & Evades Immunity

HIV is Transmitted

Plasma HIV RNA (copies/mL)

Days following HIV Transmission

Eclipse

1 2 3 4 5

Fiebig, AIDS 2003; Adapted from CURIEculum

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Acute HIV Diagnosis Algorithm at Thai Red Cross Anonymous Clinic, Bangkok April 2009-present

4th generation immunoassay (n=333,713)

Reactive (n=21,274)

Non-reactive (n=312,439)

3rd or 2nd generation Immunoassay

Reactive (n=585)

Non-reactive (n=185)

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

Positive (n=770)

Negative (n=185)

Chronic HIV (n=20,689)

Acute HIV (n=312,254)

HIV uninfected

Updated from de Souza M, AIDS 2015

“Inclusion of pooled NAT in the testing algorithm increased the number of acutely infected patients detected, from 81 to 112 (38%), relative to 4thG HIV antigen/antibody immunoassay at an increase in screening costs of 22% per individual screened.”
### Acute Retroviral Syndrome (ARS)

Number of ARS symptoms [Median (IQR)]: 7 (5-9)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence among ARS cases (N=335/430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>93%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>79%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>67%</td>
</tr>
<tr>
<td>Headache</td>
<td>64%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>57%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>54%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41%</td>
</tr>
<tr>
<td>Rash</td>
<td>39%</td>
</tr>
</tbody>
</table>

### Acute Retroviral Syndrome (ARS)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No ARS (N=95)</th>
<th>ARS (N=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fiebig I/II (IgM - )</strong></td>
<td>73%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Fiebig III/IV/V (IgM + )</strong></td>
<td>27%</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Time since HIV exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Median days (IQR)]</td>
<td>15 (11-21)</td>
<td>20 (16-26)</td>
</tr>
</tbody>
</table>

Main aims of the RV254/SEARCH 010 cohort in Bangkok, recruiting since April 2009 (610/770 AHI identified):

1. Describe clinical, immunological, and virological characteristics of AHI

2. Limit HIV reservoir with very early antiretroviral therapy (ART)

3. Identify volunteers for (future) HIV remission and cure protocols.
HIV Remission and Cure Prospects

Circulating virus

ART

STOP

< 2 months

Boston A
3 months

Boston B
8 months

Mississippi child
28 months

Bone marrow transplantation

Early ART

Limit of detection

Berlin (London, Düsseldorf) patient

SEARCH, The Thai Red Cross AIDS Research Centre
Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión, Charline Bacchus, Laurent Hoqueloux, Véronique Avettand-Fenoel, Isabelle Girault, Camille Lecouroux, Valérie Potard, Pierre Versmisse, Adeline Melard, Thierry Prazuck, Benjamin Descours, Julien Guergnon, Jean-Paul Viard, [ ... ], the ANRS VISCONTI Study Group

Published: March 14, 2013 • https://doi.org/10.1371/journal.ppat.1003211
- 24 post-treatment controllers (originally 14) are now in the VISCONTI cohort
- Started ART during primary infection
- Do not resemble elite controllers
- Interrupted after a median of 3.5 years of treatment
- Now median follow-up of 12 years
- 5 (21%) have restarted ART, 4 for viral load increases; 1 for head and neck cancer diagnosis

The 5 who restarted ART were among 7 who experienced ≥ viral load 400 copies/ml
None of the 17 who remained below this viral load level restarted ART

Hocqueloux et al., AIDS 2018
The Control of HIV After Antiretroviral Medication Pause (CHAMP) Study: Posttreatment Controllers Identified From 14 Clinical Studies

Golnaz Namazi, Jesse M Fajnzylber, Evgenia Aga, Ronald J Bosch, Edward P Acosta, Radwa Sharaf, Wendy Hartogensis, Jeffrey M Jacobson, Elizabeth Connick, Paul Volberding ... Show more


Published: 06 August 2018  Article history ▼
CHAMP Study

Post-treatment controllers identified in 14 studies with treatment interruption. Definition: viral loads ≤400 copies/mL at > 2/3 time points for ≥24 weeks

Results

67 post-treatment controllers identified of whom 38 initiated ART during early HIV infection (early 13% vs chronic 4%, \( P < .001 \))

55% maintained HIV control for 2 years, 20% for ≥5 years.
5/22 African women (22.7%) who initiated ART in PHI maintained VL less than 400 copies/ml over a median of 188 weeks following treatment interruption.
Impact of acute HIV treatment: reservoir and beyond

After 24 weeks:
- 98% HIV RNA <200 copies/mL
- 93% HIV RNA < 20 copies/mL
Significant Decline in Total HIV DNA with Early ART

After treatment initiation, in all Fiebig stages there is a rapid decrease in the frequency of cells harboring total HIV DNA, but it remains near stable in chronic infection.

Leyre, Chomont, CROI 2017 (948) RV254 and RV304 Thai studies
**Blood**

![Blood chart](chart1.png)

**Colon**

![Colon chart](chart2.png)

**Lymph node**

![Lymph node chart](chart3.png)

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Leyre and Chomont (U Montreal, unpublished)

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Early ART Reduces Chronic Inflammation

Levels of inflammatory markers do not universally normalize to those seen in uninfected comparators

**ART started during chronic infection**

- HIV-uninfected

**PCR positive/4th generation IA negative**

**4th generation IA positive/3rd generation IA negative**

**3rd generation IA positive/Western Blot negative or indeterminate**

*Sereti, CID 2017*
Lymph Node Collagen deposition in Thai HIV negative and HIV positive volunteers after 1-2 years of ART

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV negative</td>
<td>avg. 9.8%</td>
</tr>
<tr>
<td>ART start &lt; 2 weeks</td>
<td>avg. 13.3%</td>
</tr>
<tr>
<td>ART start 2-4 weeks</td>
<td>avg. 24.9%</td>
</tr>
</tbody>
</table>

Timothy Schacker, CROI 2018
RV411, ATI in Fiebig I
Expansion of HIV-specific CD8\(^+\) T Cells after Treatment Interruption

Memory HIV-specific CD8 T cells

<table>
<thead>
<tr>
<th>Time</th>
<th>CD8 A11 Nef T cells</th>
<th>HLA-A11 Nef Tetramer(^+) CD8(^+) T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5yrs</td>
<td>4617</td>
<td>0.01</td>
</tr>
<tr>
<td>4.5yrs</td>
<td>7010</td>
<td>0.004</td>
</tr>
<tr>
<td>2.6yrs</td>
<td>4320</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Takata, Trautmann, CROI 2017
RV411, ATI in Fiebig I
Sequences sampled during acute HIV1 infection and after viral rebound were intermingled in phylogenetic trees

- Sequences sampled during acute HIV-1 infection
- Sequences sampled after HIV-1 rebound

• Similar sequences between acute infection and post rebound suggest lack of viral replication during therapy and possibly clonal expansion of latently infected cells

Rolland, Tovanabutra, 2017 CROI
RV411: Time to VL Rebound in Fiebig I Treated Individuals

Time to viral load rebound >20 copies/ml
Median 26 days
Range 13 to 48 days

Colby, Ananworanich, Nature Med 2018
Initiation of ART in Fiebig I, but not in Fiebig III, prevents loss of sigmoid mucosal CD4+ T Cells

* $p \leq 0.05$, ** $p \leq 0.01$

Updated from Schuetz et al., PLoS Pathogens, 2014
vRNA+ and vDNA+ Cells in Lymph Nodes from RV254

Total of 83 lymph nodes

vDNA+ cells

vRNA+ cells

- vDNA+ and vRNA+ cells are detected in lymph nodes at acute infection and after viral suppression
- % samples with vRNA+ cells after ART is higher in Fiebig I compared to Fiebig II (p=0.05) and Fiebig III-V (p=0.02)

Tim Schacker, University of Minnesota, CROI 2018

SEARCH, The Thai Red Cross AIDS Research Centre
Viral load rebound post-ATI in RV405

Median (IQR) time to VL > 20 copies/ml for all participants: 20 (11-182) days

- 25 of 26 participants resumed ART and had VL suppression by median of 28 (IQR 19-33) days

Ananworanich, Keystone Symposia, Functional Cures and the Eradication of HIV 2019
Estimated number of onwards HIV transmissions per infected individual during the first year of infection: reduction of 89%

Kroon et al. JIAS 2017
Initiation of Antiretroviral Therapy During Acute HIV-1 Infection Leads to a High Rate of Nonreactive HIV Serology

Mark S. de Souza,1,2,3 Suteerapon Pinyakorn,4,5 Siriwat Akapirat,6 Supanit Pattanachaiwitt,1 James L. K. Fletcher,1 Nitiya Chomchey,1 Eugene D. Kroon,1,2 Sasawimol Ubolyam,2 Nelson L. Michael,5,8 Merlin L. Robb,4,9 Praphan Phanuphak,1,2 Jerome H. Kim,3 Nittaya Phanuphak,1,2 and Jintanat Ananworanich1,4,5, for the RV254/SEARCH010 Study Group.
Decreased seroreactivity in individuals initiating antiretroviral therapy during acute HIV infection.

HIV Ag/Ab combo tested at week 12 and 24 post ART (Bio-Rad GS, Abbott Architect, and Bio-Rad BioPlex 2200):

Non-reactive:
52.2% of Fiebig I (n=23)
7.7% Fiebig II (n=39)
4.5% Fiebig III/IV (n=22)

Seroreversion (reactive to non-reactive) in 10 Fiebig II, and 3 Fiebig III/IV.

Geenius and/or HIV-1 Western Blot negative or indeterminate:
73.9% and 69.6% Fiebig I
50.0% and 26.3% Fiebig II
54.5% and 40.9% Fiebig III/IV
PrEP at acute HIV and ART resistance

- 6/7 cases had genotype resistance test results
- 3/6 had FTC resistance (M184I, M184V)
  - PrEP use 29-122 days
- 0/6 had TDF resistance
- 1/6 cases had NNRTI mutation (E138A)
- 0/6 cases had PI mutations
- Comparison to AHI cohort in Bangkok\(^1\):
  - 0/229 (0%) FTC resistance
  - 1/229 (0.4%) TDF resistance

Colby et al. APACC 2019, poster #3
Diagnosis of acute HIV infection at very low HIV RNA levels in RV254

- 54 (12%) participants diagnosed with AHI based on low VL
- HIV RNA at screening (median) 753 (range 29-4865) copies/ml; 57% <1,000 copies/ml.
- Testing W0 after median 3 (range 1-6) days: median change of +1.3 (-0.4 to +3.4) log_{10} copies/ml; 57% had HIV RNA >5,000 cps/mL.
- 3 had drop in HIV RNA: all started PEP on the day of the initial test
- No false positive HIV RNA tests and all tests confirmed by repeat HIV RNA (65% >5,000 copies/ml)
- HIV serology 3rdGIA: HIV Ab seroconversion 87% (46/53) at 12 weeks; 85% (45/53) at 24 weeks
- 4thGIA less sensitive: 58% (31/53) and 47% (25/53) were positive, respectively.
- Only 3 participants, 2 of whom received PEP had both HIV RNA <5,000 copies/ml and negative HIV Ab at 12 weeks.
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Thank you!
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