Identification & Treatment of Acute HIV infection

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Topics

- Detection of acute HIV-1 infection
  - Point of care tests to diagnose acute HIV-1
- Treatment of acute HIV-1 infection
  - Benefits of early therapy
    - Results of randomized clinical trials
    - Reservoir size
    - GALT and CD4 depletion and immune reconstitution
Acute HIV infection
Is it Flu (is it Ebola?)

HIV: Manifestations of Primary Infection

**Most Common Symptoms: N = 160**

- **Fever**: 86%
- **Myalgias**: 59%
- **Headache**: 55%
- **Adenopathy**: 44%

Or malaria! Prospective detection and description of acute HIV infection in a high risk cohort of women in LIC

- Prevalence – 34%; Incidence – 2.56%
- 42 cases of AHI identified (35 before detectable antibodies)
- Mean age at acquisition 24.4 yrs (18-34)
- Symptoms were elicited at least once during the AHI window in 84% of volunteers; Of 302 visits evaluated, at least one symptom was reported in only 75 visits (24.8%)
- About 38% presented with clinical features suggestive of malaria (blood smear negative); 19% had flu-like symptoms; while the rest had 1-2 (21.5%) or no (21.5%) symptoms
- Physical examination abnormalities were detected in 74% of volunteers
- Lymphadenopathy was reported in only 5% of the volunteers
- 9 cases of pregnancies identified during phase IB
Many missed opportunities to diagnose early

So Who is doing the testing and diagnosing?
HIV transmission risk according to the stages of HIV disease and viral load

Galvin et al., Nat Rev Microbiol, 2004
Unawareness of HIV infection in France and transmission of HIV

Supervie et al. HIV in Europe Conference 2012, Copenhagen

(adapted from Marks et al. AIDS 2006, with French estimated data)
Factors associated with acute HIV infection diagnosis in MSM

ANRS-Opportunity study

Who intiated the test leading to HIV diagnosis?

*Others: relatives, friends, NGOs, etc…

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>IC95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient himself</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>The physician</td>
<td>1.69</td>
<td>[1.07-2.68]</td>
</tr>
<tr>
<td>Others*</td>
<td>0.31</td>
<td>[0.07-1.38]</td>
</tr>
</tbody>
</table>

Champenois IAS KL 2013
History of HIV testing

- Tested never or rarely: 1
- Tested occasionally: 1.52 [0.75-3.08]
- Tested regularly: 3.73 [1.78-7.82]
- Tested very frequently: 5.91 [3.01-11.56]

OR IC95%  

- Tested never or rarely: 1  
- Tested occasionally: 1.52 [0.75-3.08]  
- Tested regularly: 3.73 [1.78-7.82]  
- Tested very frequently: 5.91 [3.01-11.56]  

Champenois IAS KL 2013
### Benefit of Routine Screening for Acute HIV Infection

<table>
<thead>
<tr>
<th>Location, reference</th>
<th>Testing population</th>
<th>No. of subjects</th>
<th>Antibody-positive HIV prevalence, %</th>
<th>Increased yield with AHI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Carolina [22]</td>
<td>All public testing</td>
<td>109,250</td>
<td>0.5</td>
<td>3.6</td>
</tr>
<tr>
<td>San Francisco, California [23]</td>
<td>STD clinic</td>
<td>3075</td>
<td>3.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Los Angeles, California [23]</td>
<td>STD clinic</td>
<td>1712</td>
<td>0.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Seattle, Washington [27]</td>
<td>MSM only</td>
<td>3525</td>
<td>2.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Atlanta, Georgia [24]</td>
<td>VCT and STD clinic</td>
<td>2202</td>
<td>3</td>
<td>6.1</td>
</tr>
<tr>
<td>Johannesburg, South Africa [28]</td>
<td>VCT and STD clinic</td>
<td>1906</td>
<td>35.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Lilongwe, Malawi [25]</td>
<td>STD clinic; male</td>
<td>929</td>
<td>46.8</td>
<td>5</td>
</tr>
<tr>
<td>Lilongwe, Malawi [26]</td>
<td>STD clinic All</td>
<td>1450</td>
<td>40.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Porto Alegre, Brazil [29]</td>
<td>VCT clinic</td>
<td>933</td>
<td>19.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Los Angeles, Florida, and New York [30]</td>
<td>STD clinic and MSM clinic</td>
<td>99,111</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Cohen 2010 JID
Should we trace all sexual contacts?
How to make the diagnosis of AHIV infection

• P24
• EIA
• NAT

• Detuned assays-incidence
• Viral diversity
• Cytokines/immune activation markers
The stages of acute human immunodeficiency virus infection as characterized by detection of viral particles and evolving antibody responses

Natural History and Laboratory Staging of HIV Infection


© 2010 by the Infectious Diseases Society of America
### Fiebig Stage Classifications for Substages of Human Immunodeficiency Virus Type 1 Primary Infection, with Durations.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Defining finding and/or marker</th>
<th>Duration, mean (range), days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Individual phase</td>
</tr>
<tr>
<td>Eclipse</td>
<td>...</td>
<td>10 (7–21)</td>
</tr>
<tr>
<td>I</td>
<td>vRNA positive</td>
<td>7 (5–10)</td>
</tr>
<tr>
<td>II</td>
<td>p24 antigen positive</td>
<td>5 (4–8)</td>
</tr>
<tr>
<td>III</td>
<td>ELISA positive</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>IV</td>
<td>Western blot positive or negative</td>
<td>6 (4–8)</td>
</tr>
<tr>
<td>V</td>
<td>Western blot positive, p31 antigen negative</td>
<td>70 (40–122)</td>
</tr>
<tr>
<td>VI</td>
<td>Western blot positive, p31 antigen positive</td>
<td>Open-ended</td>
</tr>
</tbody>
</table>

**NOTE.** ELISA, enzyme-linked immunoassay; vRNA, viral RNA.
Can we diagnose really early?

Staging of Acute and Early HIV-1 Infection

Modified from Cohen et al NEJM 2011; 364:20 p 1943-54
## What We Have

### HIV Testing Assays and Window Periods

<table>
<thead>
<tr>
<th>HIV Test</th>
<th>Assay Method</th>
<th>Approximate Window Between Infection and Positive Test Result, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation EIA</td>
<td>Disrupted viral particles used to bind patient HIV antibody, detected by marker conjugated to anti-human IgG antibody</td>
<td>35–45</td>
</tr>
<tr>
<td>Second-generation EIA (including most rapid tests)</td>
<td>Synthetic or recombinant HIV antigen used to bind patient HIV antibody; detected by marker conjugated to anti-human IgG antibody</td>
<td>25–35</td>
</tr>
<tr>
<td>Third-generation EIA (also some rapid tests)</td>
<td>&quot;Antigen sandwich&quot;: synthetic or recombinant HIV antigen used to bind patient HIV antibody; detects IgM and IgG antibody; detects additional HIV antigen</td>
<td>20–30</td>
</tr>
<tr>
<td>Fourth-generation EIA</td>
<td>Third-generation EIA method to bind patient antibody to HIV plus monoclonal antibody to bind p24 antigen; detects IgM and IgG antibodies and p24 antigen</td>
<td>15–20</td>
</tr>
<tr>
<td>RNA</td>
<td>Extraction of HIV nucleic acid, amplification by PCR or other methods; detects HIV RNA</td>
<td>10–15</td>
</tr>
</tbody>
</table>

Branson and Steckler J. Inf. Dis. 2012; 205:521-524
Rapid POC Tests
CDC AHI Study

Optimizing a dried blood spot-based pooled RT-PCR technique for identification of acute HIV infection in Mochudi, Botswana
Incident HIV infection
Diversity intra host

Figure 2 | A hypothetical example of changes in replicative fitness and viral load during HIV-1 disease progression. An individual is typically infected by a few HIV-1 clones (depicted by a small green circle), which dramatically increase in copy number but not in genetic diversity during the first 1–2 months of infection. Following this acute infection period, viral load is reduced partly as a result of strong HIV-specific cell-mediated immunity. The virus population is thought to oscillate between expansion of HIV-1 populations owing to immune escape from existing HIV-specific cytotoxic T-lymphocyte (CTL) clones and contraction caused by new genetic bottlenecks that are induced by newly emerging CTL clones. The replicative fitness and genetic diversity of the HIV-1 population seem to track closely together and, following early disease (purple box), both increase at a relatively linear rate with the length of infection. This increase in replicative fitness correlates with increases in viral loads (right axis) and decreases in CD4+ T-cell counts (not shown). The scale for replicative fitness is arbitrary but is derived from the relative HIV-1 fitness values, that is, the ability of one HIV-1 isolate to out-compete another in an in vitro dual-virus competition experiments.
So what do the CDC recommend?

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens

HIV-1/2 antigen/antibody combination immunoassay

(+)  (−)

HIV-1/HIV-2 antibody differentiation immunoassay

HIV-1 (+)  HIV-1 (−)  HIV-1 (+)  HIV-1 (−) or indeterminate
HIV-2 (−)  HIV-2 (+)  HIV-2 (+)  HIV-2 (−)

HIV-1 antibodies detected  HIV-2 antibodies detected  HIV antibodies detected  HIV-1 NAT

(+): indicates reactive test result  
(−): indicates nonreactive test result  
NAT: nucleic acid test

HIV-1 NAT (+): Acute HIV-1 infection  
HIV-1 NAT (−): Negative for HIV-1
Conclusions: 1

• Improvements in technology do allow for earlier diagnosis
  – “the window is closing, but still remains open”
• However, point of care tests have not performed well in field testing to date
• Finding those at risk and testing them is a challenge
• Supports continued use of nucleic acid amplification testing in conjunction with serologic testing
  – Studies support cost effectiveness
Treatment of Acute HIV-1 Infection

Potential benefits:

• Beneficial effect on laboratory markers and disease progression
• Decrease severity of acute disease
• Alter initial viral set point, which can affect disease progression rates
• Reduce rate of viral mutation as a result of suppression of viral replication
• Reduce risk for viral transmission

Potential risks:

• Drug toxicities
• Development of ART drug resistance
• Need for continuous therapy and strict adherence
• Adverse effect on quality of life

DHHS Guidelines, 2012
Early ART limits persistence of HIV reservoir in Long-lived CD4+ T cell subsets (RV254/SEARCH010)

Nicolas Chomont (VGTI-Florida)

Updated from Ananworanich J, 2013 CROI

Duration of HIV at ART initiation

- **≤ 2 weeks**
- **2-4 weeks**
- **≥ 24 weeks**

Long-lived central memory CD4+ T cells

Integrated HIV DNA (copies/10^6 cells)
Severe depletion of CD4 cells in lamina propria in early infection (Douek et al.)

Implications? - microbial translocation, LPS and chronic immune inflammation
Immune reconstitution in mucosal CD4+CCR5+ T cells in GALT

Ananworanich et al. PLOS One 2012: 7(3);e33948
Figure 4: Estimated proportion of incident HIV infections attributable to contact with individual with early HIV infection.

The solid line is the proportion of incident HIV infections attributable to sexual contact with an individual with early HIV infection (EHI), as estimated by the mode set of input parameters in our model. The dashed lines correspond to the simulations producing the 2.5th and 97.5th percentile values in 2010.

Acute HIV infection
Transmission
Beyond week 2:
If blood plasma VL < detection, also seminal plasma VL < detection
Prevent diversity

Figure 3. Model of HIV-1 Transmission.
A genetically and phenotypically diverse quasi-species of virus is present in the semen, cervicovaginal secretions, or blood of persons with chronic HIV-1 infection, but most often, only a single virion or virally infected cell is transmitted and leads to productive clinical infection. Other viruses may breach the mucosal or cutaneous surfaces, but they generally do not result in productive infection or contribute to it, presumably because such viruses are defective or less fit or simply fail to come into contact with susceptible target cells. $R_0$ represents the basic reproductive ratio, which corresponds to the number of secondary infections caused by one infected cell. If this number falls below 1, infection is extinguished. In acute infection, the number of productively infected cells and the concentration of free virus in the plasma increase exponentially, with an estimated $R_0$ of 8.
The role of mutational robustness in RNA virus evolution

Adam S. Lauring¹,², Judith Frydman³ and Raul Andino⁴

Figure 1 | Viral populations as mutant networks. a | The consensus sequence (grey line) is the average sequence of a population and might not be represented on any individual genome because of the extremely high genetic diversity of RNA virus populations. Low-fidelity replication, which is a characteristic feature of RNA viruses, results in a diverse population of unique genotypic variants while maintaining the same consensus genome sequence. Mutations acquired in each replication cycle are represented by differently coloured triangles. b | RNA virus populations can be depicted as networks in which the genetic variants (circles) of varying fitness are connected by mutational pathways (black lines).
Figure 4. Population diversity is a virulence determinant. Results of experiments described in Vignuzzi et al. [76]. A neurovirulent clone of poliovirus was isolated from the brains of mice that had been infected with a wild-type strain. Naive mice were then reinoculated with this clone as part of either a genetically constrained (top) or diverse population (bottom). Although all mice received the neurovirulent clone, only those infected with a diverse quasispecies developed disease. Subpopulations within the diverse quasispecies cooperated with the neurovirulent clone to facilitate its entry into the CNS.

doi:10.1371/journal.ppat.1001005.g004

Summary of Studies on the Effects on Virologic Control and/or Disease Progression of Early Antiretroviral Therapy (ART) during Acute or Early Infection with Human Immunodeficiency Virus (HIV) Followed by Treatment Cessation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Study type</th>
<th>Study details</th>
<th>Outcomes</th>
<th>Main study effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell et al.</td>
<td>2010</td>
<td>USA</td>
<td>Prospective</td>
<td>61 males infected with HIV-1, randomized to 52 weeks of lamivudine monotherapy followed by 20 weeks of no therapy</td>
<td>Limited virological control</td>
<td>No difference in virologic control or disease progression between the two groups.</td>
</tr>
<tr>
<td>Saag et al.</td>
<td>2009</td>
<td>USA</td>
<td>Randomized controlled trial</td>
<td>39 patients randomized to 13 weeks of atazanavir/ritonavir plus stavudine/didanosine followed by 6 weeks of no therapy</td>
<td>Improved virologic control</td>
<td>Improved virologic control and disease progression in the treatment group compared to the control group.</td>
</tr>
<tr>
<td>Fried et al.</td>
<td>2009</td>
<td>USA</td>
<td>Retrospective</td>
<td>89 patients infected with HIV-1, treated with stavudine and lamivudine for 3 weeks, then randomized to stavudine plus tenofovir disoproxil fumarate or stavudine plus didanosine</td>
<td>Improved virologic control</td>
<td>Improved virologic control in the group treated with tenofovir disoproxil fumarate.</td>
</tr>
<tr>
<td>Katinger et al.</td>
<td>2008</td>
<td>USA</td>
<td>Prospective</td>
<td>72 patients infected with HIV-1, randomized to 4 weeks of atazanavir/ritonavir plus stavudine/didanosine followed by 6 weeks of no therapy</td>
<td>Limited virological control</td>
<td>Limited virological control in both groups.</td>
</tr>
<tr>
<td>Katinger et al.</td>
<td>2008</td>
<td>USA</td>
<td>Prospective</td>
<td>72 patients infected with HIV-1, randomized to 4 weeks of atazanavir/ritonavir plus stavudine/didanosine followed by 6 weeks of no therapy</td>
<td>Improved virologic control</td>
<td>Improved virologic control in the group treated with atazanavir/ritonavir.</td>
</tr>
</tbody>
</table>

NOTE: CD4 cell, CD4 T lymphocytes, CD80, Data Safety and Monitoring Board, HIV: Human immunodeficiency virus.
### What treatment works best?

Results of randomized clinical trials in acute and early HIV-1 infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Duration of infection</th>
<th>Duration of treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinloch-De Loes 1995</td>
<td>ZDV vs. Placebo</td>
<td>25 days</td>
<td>24 weeks</td>
<td>Reduction in HIV-defining events</td>
</tr>
<tr>
<td>SETPOINT 2011</td>
<td>Immediate PI-based cART vs. delayed</td>
<td>Within 6 months</td>
<td>36 weeks</td>
<td>Delayed time to CD4&lt;350 cells/mm³ after TI; Unable to assess VL effect due to progression</td>
</tr>
<tr>
<td>PRIMO-SHM 2011</td>
<td>Immediate vs. no rx cART 3-4 drugs</td>
<td>Acute and early infection</td>
<td>24 weeks vs. 60 weeks</td>
<td>Transiently decrease VL and delay time to re-start ART after TI; 24 wks = 60 weeks</td>
</tr>
<tr>
<td>SPARTAC 2011</td>
<td>Immediate vs. no rx</td>
<td>Within 6 months</td>
<td>12 weeks vs. 48 weeks</td>
<td>48 week rx delayed time to CD4&lt;350 cells/mm³ post TI- esp. in rx within 12 wks</td>
</tr>
</tbody>
</table>
SPARTAC Trial: Short-Course ART vs No ART in Primary HIV Infection

• 372 patients identified within 6 months of infection randomized to 12 (ART12) or 48 (ART48) wks of therapy, which was then stopped, vs to no immediate ART

• Effect of ART48 in time to CD4 <350 or long-term ART initiation increased when ART started within 12 wks of seroconversion (HR: 0.48; \( P = .003 \))

• HIV-1 RNA setpoint 0.44 log\(_{10}\) copies/mL lower in ART48 arm vs SOC 36 wks after ART interruption

• CD4+ cell count higher over longer-term follow-up with ART48 vs SOC


No impact on AIDS, Death or SAEs
Figure 3. Probability of remaining off treatment in the no treatment and treatment arms.


http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001196
Immune modulators and vaccines
No real benefits seen

• **IL-2**

• **Cyclosporin**

• **Vaccine**
Antiretroviral therapy given during acute HIV infection when compared with no Antiretroviral therapy

Improves short-term CD4 cell count recovery during early HIV infection in this setting

Treatment with a 3- or 4-drug regimen during acute infection reduces HIV RNA levels at least as well as with treatment during chronic infection, but the optimal regimen remains unknown

ART initiated during acute HIV and given for short-term (typically 48 weeks or less) followed by discontinuation has produced mixed results with regard to lowering the viral set point

ART initiated during acute infection slows the rate of CD4 count decline and may prolong the need for subsequent initiation of antiretroviral therapy

Initiating ART during acute (or early) HIV may reduce the short-term incidence of HIV-related complications but does this approach provides a long-term clinical advantage when compared with initiating therapy in patients with chronic HIV infection based on a decline below a CD4 cell count threshold?
The enigma!
VISCONTI Cohort of Post-Treatment Controllers

14 people
ART in first 3 months

Control VL after stopping ART

Why are these patients able to control HIV without ART?

HIV reservoir amount and location?
✔ Low HIV DNA
✔ In shorter-lived CD4 cells

Saez-Cirion A, Plos Pathogens 2013
Conclusions 2

- Randomized clinical trials confirm virologic and immunologic benefits of early therapy
  - Long term benefit yet to be demonstrated

- Very early treatment
  - Limits size of viral reservoirs
  - May protect or allow for reconstitution of GI-tract associated lymphoid tissue
    - sCD14 levels, a marker of microbial translocation, remain comparable to HIV-uninfected individuals
  - Result in normalization of markers of immune activation
  - ? Prevent diversity

- Relative benefits of more intensive therapy during acute infection have yet to be shown in the setting of acute and early infection