Acute Retroviral Syndrome

- 40-90% of new HIV infections are symptomatic
- Signs and symptoms typically begin 1-4 weeks following the exposure
- Symptoms can last from days to several weeks, but usually <14 days

Vanhems P et al. AIDS 2000; 14:375-381
## Acute HIV and Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Schacker</th>
<th>Kinloch-de Loes</th>
<th>NC STD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>93%</td>
<td>87%</td>
<td>48%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>93</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>70</td>
<td>48</td>
<td>30</td>
</tr>
<tr>
<td>Headache</td>
<td>55</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>GI Symptoms</td>
<td></td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>

Schacker TW, et al., AIM 1996 125:257-64

## Common Mis-diagnoses

- Mononucleosis
- Rocky Mountain Spotted Fever
- Strep throat
- Influenza
- "Viral illness"
- Secondary syphilis

## AHI Syndrome and Medical Evaluation

- 78% (25/31) with symptoms 3 mo. Prior to 1st positive test
- 65% (20/31) sought medical evaluation
- 50% (10/20) went to ED or Urgent Care
- 20% (4/20) went to private MD
- 30% (6/20) Dx bacterial infection
- 30% (6/20) Dx viral syndrome
- 15% (3/20) Dx AHI
- 18.8% (6/31) aware of AHI prior to Dx

Pilcher, et al. JID 2010:201 (Suppl 1)
Window Periods for HIV Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Time to seroconversion</th>
<th>Window period</th>
<th>Window after infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial 1st generation SIA</td>
<td>2-8 weeks</td>
<td>2-4 weeks</td>
<td>2-6 weeks</td>
</tr>
<tr>
<td>2nd generation SIA</td>
<td>1-6 months</td>
<td>2-6 months</td>
<td>6-9 months</td>
</tr>
<tr>
<td>Third generation SIA</td>
<td>3-12 months</td>
<td>6-12 months</td>
<td>12-18 months</td>
</tr>
</tbody>
</table>

**Rationale for Acute HIV Diagnosis**

- Most Infectious period and Dx often missed
- Individual Perspective
  - Improve prognosis with acute treatment
  - Lowering of viral set point
  - Preservation of CD4 T cells
  - Decrease in rate of progression
  - Early entry into care
  - Short-term behavioral change results in large benefit
  - Management of STIs

**Rational for AHI Diagnosis**

- Recognized previously missed infections
- Avoid transmission to partners with risk reduction
  - 10-100 fold increased transmission risk x 3-6 months
  - May be responsible for 14-50% of all transmission of HIV
  - Quebec AHI/PHI <10% of infection but ~50% transmission
- Networks - leading edge of transmission
  - Identify Transmission networks for intervention
  - Prevent secondary transmission by contact tracing and counseling to modify risk behaviors at risk partners
  - Geographic focus

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Stekler J. et al CID 2007

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STAT Acutes by County (11/1/2002-6/28/2010)

HIV RNA Production during Early Infection
97 pre-Ab samples from 44 plasma donors

HIV RNA Levels, Stages I-VI
N= 322 samples from 51 Seroconverting Plasma Donors

Laboratory Staging of HIV Infection
Evolving Assay Reactivity for:
HIV RNA
p24 Ag
HIV-EIA
HIV-WB
HIV Stage Progression based on 51 Seroconverting Plasma Donors

Fiebig stage classification for sub-stages of HIV-1 primary infection, and the average and cumulative duration of each phase.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration of each phase (days)</th>
<th>Cumulative duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eclipse</td>
<td>10 (7.21)</td>
<td>10 (7.21)</td>
</tr>
<tr>
<td>I (vRNA+)</td>
<td>7 (5.10)</td>
<td>17 (13.28)</td>
</tr>
<tr>
<td>II (p24Ag+)</td>
<td>5 (4.8)</td>
<td>22 (18.34)</td>
</tr>
<tr>
<td>III (EI3S+)</td>
<td>3 (2.5)</td>
<td>25 (22.37)</td>
</tr>
<tr>
<td>IV (Western Blot ±)</td>
<td>6 (4.8)</td>
<td>31 (27.43)</td>
</tr>
<tr>
<td>V (Western Blot -), p31 -</td>
<td>70 (40,122)</td>
<td>101 (71,154)</td>
</tr>
<tr>
<td>VI (Western Blot +, p31+)</td>
<td>Open-ended</td>
<td></td>
</tr>
</tbody>
</table>

Incidence Rate / Window Period (WP) Model Allows Prediction of Test Yields for Direct HIV (p24 Ag, HIV RNA) vs Antibody Assays

Test Yield (per unit) = Incidence Rate (person-years) x Decrease in WP (fraction of year)

Projected WP Closure and Yield of p24 Ag, MP and ID NAT Assays Relative to a Sensitive HIV-1/2 EIA Antibody Test in the Detection of WP HIV Infection

<table>
<thead>
<tr>
<th>Assay</th>
<th>Sensitivity (pEq/mL)</th>
<th>WP Closure (days)</th>
<th>Yield, WP HIV Infections per 1,000 Persons Tested in Various Screening Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>p24 Ag</td>
<td>10,000</td>
<td>6</td>
<td>Blood Donors [2 / 100,000 = 0.002%] STD Clinic [1 / 1,000 = 0.1%] High Risk Clinic [1 / 100 = 1%]</td>
</tr>
<tr>
<td>MP NAT</td>
<td>1,000</td>
<td>9</td>
<td>0.0033 0.016 1.6</td>
</tr>
<tr>
<td>ID NAT</td>
<td>50</td>
<td>13</td>
<td>0.0049 0.025 2.5</td>
</tr>
</tbody>
</table>

Alternative Algorithms for Human Immunodeficiency Virus Infection Diagnosis Using Tests That Are Licensed in the United States


HIV Laboratory Branch, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Malaria, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia. AJ015

Fiebig et al. AIDS, 17:1871-9, 2003
Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection

- 102 acutely infected plasma donor panels
- 3476 complete env sequences from single genome amplifications
- Inferred consensus sequence at estimated time of virus transmission
- 78 donors infected by single virion; 24 by 2-5 virions

Macaque/SIV model

- SIV infection in macaques considered excellent model for HIV in humans for both transmission and pathogenesis research
- "Donor" monkeys repeatedly exposed by intravaginal inoculation of infectious plasma
- Samples taken pre-infection, "blip". Immediately pre-ramp-up, ramp-up and set-point
- Samples "transfused" into naive "recipient" monkeys

High Specific Infectivity of Plasma Virus from the Pre-Ramp-Up and Ramp-Up Stages of Acute Simian Immunodeficiency Virus Infection

Donor group B

Recipient group B

Plasma transfusion from "SIV exposed-eclipse phase" monkeys

Ramp up plasma pool

- 1.3 x10^5 vRNA copies/ml (6.5 x10^4 SIV particles/ml)
- serial dilute to 1-10, 10-100, 100-1000 copies
- 0 TCID50/ml (CEMx174 cells, SEA-stimulated mPBMC)

Ma et al. Journal of Virology 83; 3288-3297, 2009
Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection

Christopher D. Pilcher, George Joaki, Irving F. Hoffman

Fig. A: Amplified transmission of HIV-1. The Aedes aegypti mosquito is highly infectious and can transmit HIV to humans. The amplification of HIV-1 in the mosquito allows for a higher number of viral particles to be transmitted, leading to a higher risk of infection.

HIV-1 Transmission, by Stage of Infection

Table 2. Calculation of the basic reproduction number (R0) according to the contribution from each stage of HIV-1 infection, under 2 extremes of sexual behavior.

T. Stéphane Heyderman, Roy M. Anderson, and Christopher Fraser

Fig. B: Amplified transmission of HIV-1. The Aedes aegypti mosquito is highly infectious and can transmit HIV to humans. The amplification of HIV-1 in the mosquito allows for a higher number of viral particles to be transmitted, leading to a higher risk of infection.

Ramp-up virus is highly infectious

Ma et al. Journal of Virology 83; 3288-3297, 2009
target CD4+ T cells and macrophages are likely to be in an activated state in this environment, enhancing their ability to support viral replication.

Anderson et al; PLoS 2010

Potential impact of STI co-infection on detection of AHI

PCR Testing of Pooled Sera to Identify Acute HIV Infection (seronegative, PCR positive)
Pooling and HIV RNA testing

- **Advantages**
  - Seamless (almost) incorporation into HIV testing
  - Reduced cost
  - No real change in specificity
  - Universal application

- **Disadvantages**
  - Requires large testing volume
  - Small loss in sensitivity
  - Logistics
  - Time to Dx and locating patient

NAT Specimen pooling

Advantages of p24 Ag and 4th generation EIAs

- Current 4th generation EIAs can detect both p24 Ag and antibody on a single assay
- Could be used as the initial HIV screening test
- p24 Ag EIAs nearly as sensitive as HIV RNA testing for acute HIV infection
- Sensitivity of 4th generation EIAs is now equivalent to heat p24 assays
4th gen HIV Ag/Ab Combo
considerations / conclusions

- Can detect infection in antibody-negative individuals
- Viral load cutoff may be about 14,000 – 31,000 RNA copies / ml
- Can be used as a replacement for RNA testing, would detect ~90% of Ab+/RNA+ detected by RNA pooling
- Shorter time to Dx, potential for better PPV, and lower cost than RNA pooling

How does a 4th Generation IA (HIV Ag/Ab Combo) perform on the recent / acute infection panel?

- Detects 57 / 64 positively (89%)
  - (3rd gen detected 42%)
- Of the 29 "recently infected" specimens: 29/29 (100%)
  - (3rd gen detected 93%)
  - (Uni-gold Rapid: 76%)
- Of the 35 "acute" specimens (RNA pos, completely Ab negative: 28/35 (80%)
Confirmatory Testing

- Confirmatory test is essential (not just a single EIA)
- For Western blot:
  - Venipuncture for whole blood
  - Oral fluid specimen
- Follow-up testing of persons with negative or indeterminate Western blot results after 4 weeks
- HIV RNA or 4th gen test for suspected acute HIV
- A single positive EIA test is not reportable but confirmation is covered under Ryan White for billing

Rapid HIV Antibody Tests

- Advantages
  - Results in 10 – 20 minutes
  - “Preliminary positive”
  - Better linkage to care
  - Less labor ?, no instrument maintenance
- Disadvantages
  - False positives – especially pregnant women
  - Through put
  - Setting for Confidentiality
  - Cost?

Rapid HIV Antibody Tests

- Other important issues
  - Specimen type – oral fluid, serum, plasma, whole blood, dried blood spot
  - Who will perform rapid test? POCT by nursing staff? Physicians?
  - Waived testing?
  - Laboratory-based testing
  - How meet licensing and accrediting agency requirements?
  - ED “fix what is broken”

Cost Rapid HIV tests

The mean per-test cost of rapid HIV testing and counseling:
- $48.07 for an HIV-neg. test
- $64.17 for a preliminary-positive test
- Pre- and posttest counseling costs accounted for 38.4% of the total cost

Pinkerton et al. AIDS and Patient Care and STDS 2010
Rapid HIV Antibody Tests

- Ability to detect acute infection (n=42)
- 3rd generation EIA detected 34% of RNA positive specimens
- Unigold 26%
- Multispot 17%
- OraQuick 2.3%
- Clearview 2.3%
- Western Blot 0%
- Combo assay 80% (n=35)

Detection of Acute HIV Infection

- Important public health issue
- Identifying AHI may decrease HIV transmission
- Earlier treatment with HAART
- Earlier linkage to care
- Most useful in high risk setting i.e. STD clinic, EDs and MSM populations

What to consider

- AHI important at individual and population level
- Consider panels for acute viral illness that would include testing for AHI
- 4th generation assays provide faster alternative for Dx AHI
- Important to screen for AHI in STD clinics and with MSM populations

Common Symptoms of Acute HIV:
- High Fever
- Rashes
- Fatigue
- Swollen Glands
- Sore Throat
- Nausea/Vomiting
- Night Sweats
- Symptoms usually appear about 2 weeks after exposure

What Puts You At Risk?
- Unprotected Sex
- Sharing Needles

The Acute HIV Program 919-966-8533

If you have an STD, Get Tested for HIV. Learn to Recognize it. Tell a Friend.

Common Symptoms of Acute HIV:
- High Fever
- Rashes
- Fatigue
- Swollen Glands
- Sore Throat
- Nausea/Vomiting
- Night Sweats

If you think you may have Acute HIV, get tested at your Local Health Department or at your doctor’s office.

*Screening for acute HIV can be done at your doctor’s office, but for an HIV RNA test in addition to the standard HIV antibody test.

Spread the Word – Not HIV