THE NATURAL HISTORY OF HIV INFECTION

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AIDS Research Consortium of Atlanta
Learning Objectives

- Be able to teach your patients how antiretroviral drugs interrupt the viral life cycle to decrease viral load
- Be able to screen for and recognize primary HIV infection
- I do not intend to discuss any non-FDA-approved or investigational uses of any products/devices during this presentation.
The Basics

- Anatomy of HIV
- HIV Replication: Life Cycle Events
- Primary HIV Infection
- Chronic Infection
- AIDS
Anatomy of HIV

- gp120
- gp41
- Matrix protein (p17)
- Capsid protein (p24)
- Protease/reverse transcriptase/integrase proteins
- Lipid bilayer membrane

HIV-1

- env
  - gp 120
  - gp 41
- gag
  - p 17
  - p 24
  - p 7
- pol
  - p 66/51
  - p 32
  - p 11

One spike is made of three gp120 and gp41 subunits
Co-Receptor Tropism and Viral Entry

CCR5 = M tropic = NSI

CXCR4 = T tropic = SI (associated with CD4+ depletion)

R5/X4 (Dual)

Mixed

Weber J, et al. AIDS Reviews 2006; 8:60-77
Natural History of HIV Infection

Pantaleo G, NEJM. 1993;328:327-35
Primary HIV Infection

- May be symptomatic or asymptomatic
  - Symptoms correlate with faster progression
- Commonly missed by medical professionals
- Antibodies usually appear 2-4 wks later
- Viral loads: up to 100 million copies/ml
  - VL predicts disease progression rate
  - VL in source correlates with VL in recipient
  - Extremely infectious
- Virus “seeds” reservoirs very rapidly to establish chronic infection, currently irreversible

3 Hecht F, AIDS 2010:24:DOI:10,1097
Detection of HIV by Diagnostic Tests

- Symptoms
- p24 Antigen
- HIV RNA
- HIV EIA*
- Western blot

*3rd generation, IgM-sensitive EIA
*2nd generation EIA
*viral lysate EIA

After Fiebig et al, AIDS 2003; 17(13):1871-9
Figure 3. Frequency of Newly Diagnosed HIV Infections in North Carolina, November 1, 2002, through October 31, 2003, According to Type of Testing Site and Stage of Disease.

All sites were publicly funded and provided confidential HIV testing. The numbers in parentheses are the population at risk. Data regarding type of site were missing for 705 persons.
Primary Infection: Clinical

- Incubation period: days to weeks after HIV infection
- Usually appears as “flu-like” syndrome with lymphadenopathy, lasting 7-14 days
- Fever/rash followed by pharyngitis/ulcers should raise suspicion

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Fever</td>
<td>80%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>49%</td>
</tr>
<tr>
<td>Malaise</td>
<td>68%</td>
</tr>
<tr>
<td>Fever &amp; rash</td>
<td>46%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>54%</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>37%</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>54%</td>
</tr>
<tr>
<td>Weight loss &gt; 2.5kg</td>
<td>32%</td>
</tr>
<tr>
<td>Rash</td>
<td>51%</td>
</tr>
</tbody>
</table>

Infectivity During Acute Infection: UNC Cohort

- Viral load in semen paralleled that of plasma
- Peak occurred ~ 20 days post infection
- Viral set point occurred at 54 days post infection
- Risk of heterosexual transmission increased 8-10 fold between day 20 and day 54
- During the first 2 months of infection, 7-24% of partners would likely be infected

Blood viral load in acute HIV (n=171)

Average fitted curve, with 95% confidence intervals

Peak: day 23

8-10 fold increase risk from peak to day 54

Cellular Immune Response: CD8+

- Rapid, broad CD8+ T-cell expansion
- HIV-1-specific cytotoxic CD8+ T-cells (CTLs) kill HIV-infected cells
  - Direct cytolysis (MHC class I-restricted)
  - Indirect via cytokines (IFN-γ), chemokines (RANTES), pro-inflammatory proteins (MIP1α & MIP1β)
  - Strength and breadth correlates with viral control and rate of disease progression*
- Rapid selection of virus with CTL epitope mutations = viral escape from CTL control

Cellular Immune Response: CD8+

- High immune activation is associated with earlier mortality
  - Increased expression of T-cell activation markers (such as CD38+ and HLA-DR)\(^1\)
  - Increased Ki-67 (proliferation marker)\(^2\)
  - Increased plasma LPS
- Decreased levels of IL-7 receptor, a T-cell homeostasis marker (CD127)\(^2\)
- Early depletion of naïve CD8+ cells\(^2\)

\(^2\) Ganesan, JID 2010: 201:272-84
Cellular Immune Response: CD4+

- CD4+ T-cell count declines transiently, then rebounds, but usually not to normal levels
- Decline may be dramatic and, rarely, be associated with OIs
- Strong initial CD4+ T-cell proliferative response to Gag but impaired early
- Impaired number and function of central memory (CM) CD4+ cells
  - Accelerated differentiation into effector CD4+ cells
  - T-cell exhaustion
Immune Response: Humoral

- Antibodies are, generally, not primary mechanisms of HIV control
- Neutralizing antibodies (NAb)
  - May be helpful in controlling viremia
  - NAb titers inversely proportional to VL
  - Do not prevent disease progression in absence of strong cellular response
Role of Genetic Factors

- **CCR5 deletion of 32 base pairs (CCR5delt32)**
  - Homozygotes do not express CCR5 and show high levels of resistance to HIV infection
  - Heterozygotes show lower viral setpoints and slower progression of disease

- **HLA Class I alleles**
  - HLA-B57 associated with better viral control and lower frequency of symptomatic acute infection
  - HLA-B27 associated with strong CTL response, lower viral setpoint, slower progression of disease
  - HLA-B35 associates with more rapid progression

The “Elite” Controllers¹

- **Definition:** HIV-1 RNA < 50 copies/ml and ART naive
- **Immune correlates**
  - Strong HIV-1 specific responses
    - CD4+ proliferative responses to p24
    - CD8+ IFN-gamma production
    - Broad Gag- and Pol-specific CTL responses
  - Neutralizing antibodies not strongly protective
- **Genetic correlates**
  - HLA, chemokine receptor deletion, TLR polymorphism
- **Viral correlates**
  - Defective *nef* - long terminal repeat deletions
  - Decreased viral replicative fitness in some cases²

¹Dyer W, Retrovirology 2008:5:112
²Kirchoff F, NEJM 1995;332(4):228-32
Chronic Infection

- Time from infection to AIDS may average 10 years in some settings (SF, 1980’s)\(^1\)
- “Clinical latency” is a virologically and immunologically active period\(^2\)
  - Continuous HIV replication
  - Continuous CD4 depletion
  - Continuous viral evolution

Relationship Between CD4+, HIV-1 RNA & Progression to AIDS

<table>
<thead>
<tr>
<th>CD4 cell count/µL</th>
<th>Viral load copies/mL</th>
<th>% AIDS progression in men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>over 3 years</td>
</tr>
<tr>
<td>&lt;200</td>
<td>&lt;10,000</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>10,000-30,000</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&gt;30,000</td>
<td>86%</td>
</tr>
<tr>
<td>200-350</td>
<td>&lt;10,000</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>10,000-30,000</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>&gt;30,000</td>
<td>64%</td>
</tr>
<tr>
<td>&gt;350</td>
<td>&lt;10,000</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>10,000-30,000</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>&gt;30,000</td>
<td>40%</td>
</tr>
</tbody>
</table>

The Inflammatory Response to HIV: A Silent Killer

- The immune response includes
  - Increased T-cell activation
  - Secretion of pro-inflammatory agents
  - Increases in markers of inflammation (d-dimer, IL-6, hsCRP) – 65-70% higher in HIV-infected

- Inflammatory cascade correlates with increased morbidity and mortality
  - Association with cardiovascular disease, non-AIDS mortality, even at high CD4+ counts
  - Mitigated by antiretroviral therapy

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²SMART, NEJM 2006: 355; 2283-96
“Non-AIDS” Morbidity and Mortality

- “Non-AIDS” events are an increasing cause of morbidity & mortality
  - Cardiovascular, renal, hepatic disease
  - Malignancies: anal, vaginal, liver, lung, Hodgkin’s lymphoma, melanoma, oropharyngeal, leukemia, colorectal, renal

- All-cause mortality is higher for Non-AIDS than AIDS events (6-month mortality)
  - AIDS event = 4.7%
  - Non-AIDS event = 13.4%

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1 SMART, NEJM 2006: 355; 2283-96
Hypothesis: HIV and Non-AIDS Disease Risk

HIV+ → ↑ inflammation → ↑ coagulation activation

No ART → ↑ risk
ART ↓ risk

Magnitude of absolute risk ↑ depends on other factors

Neaton J, IAS 2007: MOSY202
Adjusted Odds Ratios Associated with a 0.15 μg/mL Increase in D-dimer

<table>
<thead>
<tr>
<th>Event</th>
<th>No. Events</th>
<th>Adj. OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Deaths</td>
<td>74</td>
<td>1.23</td>
<td>1.07-1.42</td>
<td>0.004</td>
</tr>
<tr>
<td>Major CVD</td>
<td>59</td>
<td>1.12</td>
<td>1.01-1.24</td>
<td>0.04</td>
</tr>
<tr>
<td>AIDS</td>
<td>75</td>
<td>1.40</td>
<td>1.19-1.66</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Neaton J, IAS 2007: MOSY202
AIDS: 1993 Case Definition

- CD4⁺ cell count <200 cells/µL, or
- CD4⁺ cells account for <14% of all lymphocytes, or
- Has been diagnosed with one or more specified AIDS-defining illnesses

## AIDS: 1993 Case Definition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis of bronchi, trachea, or lungs</td>
<td>HSV: chronic ulcer(s) (&gt;1-month) or bronchitis, pneumonitis, or esophagitis</td>
<td>Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)</td>
</tr>
<tr>
<td>Candidiasis, esophageal</td>
<td>Histoplasmosis, disseminated</td>
<td>Mycobacterium, other species, or unidentified species, disseminated</td>
</tr>
<tr>
<td>Cervical cancer, invasive</td>
<td>Isosporiasis, chronic intestinal (&gt;1-month duration)</td>
<td>Pneumocystis jiroveci (formerly carinii) pneumonia</td>
</tr>
<tr>
<td>Coccidioidomycosis, disseminated</td>
<td>Kaposi sarcoma</td>
<td>Pneumonia, recurrent</td>
</tr>
<tr>
<td>Cryptococcosis, extrapulmonary</td>
<td>Lymphoma, Burkitt</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Cryptosporidiosis, chronic intestinal (&gt;1-month)</td>
<td>Lymphoma, immunoblastic</td>
<td>Salmonella septicemia, recurrent</td>
</tr>
<tr>
<td>CMV disease (other than liver, spleen, or lymph nodes); CMV retinitis</td>
<td>Lymphoma, primary, of brain (primary central nervous system lymphoma)</td>
<td>Toxoplasmosis of brain (encephalitis)</td>
</tr>
<tr>
<td>Encephalopathy, HIV related</td>
<td>Mycobacterium avium complex or disease caused by M kansasii, disseminated</td>
<td>Wasting syndrome caused by HIV infection</td>
</tr>
</tbody>
</table>

GOOD NEWS...
AND BAD NEWS!
The median CD4+ count at entry to care = 327 cells/µL in the NA-ACCORD cohort (2007) is below the level at which all current guidelines recommend beginning antiretroviral treatment!

Althoff K, CID 2010:50:1512-20
Therefore…

TEST, LINK TO CARE, TREAT!