HIV Disease: An Overview

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Conflicts of Interest

• Consultant: Abbott, BMS, Gilead, GSK, Merck, Janssen, ViiV
• Grant Support: BMS, Gilead, Merck, Janssen

HIV Disease: 2012 Update

• Case-based review of information important to all clinicians in practice, including:
  – HIV testing and baseline evaluation
  – Basics of antiretroviral therapy: Who gets treated?
  – Important drug-drug interactions
  – Post-exposure prophylaxis

Case Presentation

• A 35 year old man is seen for a routine office visit, and is offered an HIV test
• He has no known risk factors, and feels entirely well
• He is concerned about the accuracy of the test

Question

• What is the approximate rate of false-positive results in standard HIV testing?

1. 1 in 100
2. 1 in 1,000
3. 1 in 10,000
4. 1 in 100,000
5. 1 in 200,000

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm
HIV Treatment Dramatically Reduces HIV-related Deaths

Data from CDC, HOPS Study.

HIV Epidemiology: USA

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number HIV infected</td>
<td>1,106,400</td>
</tr>
<tr>
<td>Number unaware of their HIV infection</td>
<td>232,700 (21%)</td>
</tr>
<tr>
<td>Estimated new infections/year</td>
<td>56,000</td>
</tr>
</tbody>
</table>


Data from CDC, HOPS Study.

Estimates of Source of HIV Transmission

- ~25% Unaware of Infection
- ~75% Aware of Infection

People Living with HIV/AIDS: ~1,050,000
New Infections Each Year: ~40,000

Knowing HIV+ Status Reduces High Risk Behavior

- After people become aware they are HIV-positive, the prevalence of high-risk sexual behavior declines substantially
- Reduction in unprotected anal or vaginal intercourse with HIV-neg partners: 68% (HIV-pos Aware vs. HIV-pos Unaware)


Revised Testing Guidelines: Key Components

- HIV screening is recommended for patients in all health-care settings
  - Testing should be done after the patient is notified that testing will be performed unless the patient declines (‘opt-out screening’)
- Persons at high risk: repeat annually
- Separate written consent for HIV testing should not be required
- Pre-test counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings


Question

In the United States, are there more patients with undiagnosed HIV infection, or more who are known to be HIV infected but not in care?

1. Undiagnosed
2. HIV positive, but not receiving care
Of all with HIV infection, 850,000 individuals do not have suppressed HIV RNA (72%)
**Question**

- The HIV ELISA is positive, but the Western blot returns negative.
- What is the most likely interpretation?

A. False-positive HIV ELISA due to syphilis
B. False-negative HIV Western blot due to “window period”
C. False-negative HIV Western blot due to prozone phenomenon
D. HIV-2 infection
E. Laboratory error

**Epidemiology of New HIV Infections in the US**

- **Methodology**
  - New non-AIDS HIV cases from 22 states
  - Use of novel immunoassay to identify recent infections (avg 156 days post seroconversion)
- **Revised estimate 2006**
  - 56,300 (95% CI: 48,200 - 64,500)

**Racial Distribution**

- Black: 45%
- White: 35%
- Hispanic: 17%

**Risk Groups**

<table>
<thead>
<tr>
<th>Period</th>
<th>MSM</th>
<th>IDU</th>
<th>MSM/IDU</th>
<th>Heterosexual</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-2002</td>
<td>70,000</td>
<td>70,000</td>
<td>60,000</td>
<td>10,000</td>
</tr>
<tr>
<td>2003-2006</td>
<td>60,000</td>
<td>60,000</td>
<td>50,000</td>
<td>5,000</td>
</tr>
</tbody>
</table>

**HIV Disease: Acute Infection**

- Plasma viral titer by PCR or bDNA assay
- Number of CD4 cells

**Symptoms of Acute HIV Infection**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>500</td>
<td>46</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>124</td>
<td>74</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>146</td>
<td>70</td>
</tr>
<tr>
<td>Rash</td>
<td>146</td>
<td>70</td>
</tr>
<tr>
<td>Mumps/Arthritis</td>
<td>122</td>
<td>64</td>
</tr>
<tr>
<td>Chorea</td>
<td>122</td>
<td>70</td>
</tr>
<tr>
<td>Headache</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>56</td>
<td>27</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

**Diagnostic Tests for Acute HIV Infection**

- **HIV RNA (“viral load”) test of choice**
  - More sensitive than p24 antigen test
  - Turns positive 10-15 days after HIV acquired ("eclipse" period)
  - Result very high (>100,000 copies/mL)
  - False-positives may occur with low-level results (< 5,000 copies/mL)

- **HIV antibody**
  - Window period with current tests averages 2-3 weeks
  - Combined antibody/antigen test reduces window period further
  - Patients may still be symptomatic with AB positive
  - Western blot may be negative or indeterminate

**The Problem of False Negative Western Blot Tests**

## Importance of Diagnosing Acute HIV

- Public health implications
- Benefits of treatment
  - improved immunologic function, in particular HIV-specific CD4 response
  - slow progression to AIDS
  - target less diverse viral population
- Treatment recommended for symptomatic HIV in several clinical trials and endorsed in some guidelines


### Case Presentation

- A 34 year old woman was informed by a life insurance company that her application HIV test returned positive.
- Her current boyfriend's HIV status is unknown. She is originally from sub-Saharan Africa, having moved to the USA 5 years ago.
- An HIV antibody test done at that time was negative

### Case Presentation

**Which of the following, if elicited on history or PE, would be most suggestive of severe HIV-related immunodeficiency?**

1. Prior history of herpes zoster
2. Presence of adenopathy
3. Weight loss (>5% baseline body weight)
4. Illness in the past compatible with acute HIV infection
5. > 50 lifetime sexual partners

### Initial Laboratory Evaluation

- CBC w/diff
- Creatinine, glucose, LFT's, lipids
- Serologies: toxo, CMV, varicella IgG; hep A, B, C; RPR
- PPD
- PAP smear: cervical and/or anal
- (G6PD, HLA-B*5701)

- CD4 count
- HIV RNA (*“viral load” assay*)
- HIV resistance genotype


### Vaccines for HIV+ Patients

- **Indicated:**
  - Annual influenza
  - Hepatitis A and B if susceptible
  - Pneumococcal (if CD4 > 200)
  - Other non-HIV related vaccines, if indicated
- Some live virus vaccines (zoster, Yellow Fever, MMR) contraindicated with low CD4
- Any vaccine: higher CD4 = better response
- Defer vaccinations until after antiretroviral therapy

### Case Presentation

She is asymptomatic. The PE is normal. Her CD4 cell count returns at 590 cells/mm³, HIV RNA 21,000 cop/ML.

Should antiretroviral therapy be started?

1. No – clinical benefits not proven at this CD4
2. Yes – all patients with HIV should be treated
DHHS Guidelines 2012

“Antiretroviral therapy is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count.”

—DHHS Guidelines, March 27, 2012; available at aidsinfo.nih.gov

Nadir CD4 Increases Risk for Both HIV and non-HIV Complications

- Evaluation of endothelial function by brachial artery flow-mediated dilation in 74 virologically-suppressed patients
- Nadir CD4 cell count < 350 independently associated with worsening endothelial function – stronger predictor than current CD4

Increased Cumulative Viral Replication Associated with Reduced Survival


Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Treatment Prevents HIV Transmission

- 1,736 serodiscordant, sexually active couples randomized
- HIV-positive partner CD4 cell count between 350 and 500 cells/mm³

Immediate ART
CD4 350-550

Delayed ART
CD4 ≤ 250

Primary Transmission Endpoint
Virologically-linked transmission events

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

Randomization

DHHS Guidelines 2012:
The “Out Clauses”

- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence
- Patients may choose to postpone ART
- Providers may elect to defer ART, based on an individual patient’s clinical or psychosocial factors


Combination Therapy for HIV:
1997 vs. 2012

For Patients in Care,
Virologic Failure is Disappearing

Among patients on treatment in 2010, 87% had viral loads <500 copies/mL.


Who Should Start Antiretroviral Therapy?

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4</th>
<th>My View</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe symptoms</td>
<td>Any value</td>
<td>Treat!!!</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;200 µL</td>
<td>Treat!</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200-500 µL</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt; 500 µL</td>
<td>Treat When Patient is Ready!</td>
</tr>
</tbody>
</table>


Case Presentation

- A 55 year old man with stable HIV is admitted with chest pain, and is found to have 3 vessel coronary artery disease
- He undergoes PTCA with stenting, and is D/C’d home
- Current meds: tenofovir, emtricitabine, atazanavir, ritonavir
- Fasting lipids: Total cholesterol 288, HDL 36, CLDL 192, TG 321
**Question**

- Which of the following drug-drug interactions is of concern when prescribing statins to patients with HIV?
  1. Tenofovir, which accelerates metabolism of statins
  2. Tenofovir, which slows metabolism of statins
  3. Atazanavir and ritonavir, which accelerate metabolism of statins
  4. Atazanavir and ritonavir, which slow metabolism of statins
  5. Statins lower effective concentrations of HIV medications, which could lead to HIV treatment failure

**Lipid-Lowering Drugs and HIV Therapy**

- **Fibrates**
  - Low interaction potential
- **Fluvastatin**
- **Pravastatin**
- **Ezetimibe**
- **Fish oil**
  - Use cautiously
- **Statin + fibrate**
  - **Atorvastatin**
  - **Rosuvastatin**
- **Niacin**
- **Fish oil**
  - Contraindicated

- Statins
- Erectile dysfunction drugs
- Benzodiazepines
- Inhaled steroids
- Rifampin/rifamycin (TB drugs)
- Anticonvulsants
- Methadone
- Oral contraceptives
- Proton-pump inhibitors

**Common Drug-Drug Interactions in HIV Patients**

- **Statins**
- **Erectile dysfunction drugs**
- **Benzodiazepines**
- **Inhaled steroids**
- **Rifampin/rifamycin (TB drugs)**
- **Anticonvulsants**
- **Methadone**
- **Oral contraceptives**
- **Proton-pump inhibitors**

**Key concept for most – protease inhibitors powerfully inhibit cytochrome p450 cyp3A4**

**CLINICAL CASE SEMINAR**

**Iatrogenic Cushing's Syndrome with Osteoporosis and Secondary Adrenal Failure in Human Immunodeficiency Virus-Infected Patients Receiving Inhaled Corticosteroids and Ritonavir-Boosted Protease Inhibitors: Six Cases**

**Aging of HIV Population**

- Population-based HIV registry from 2006-2010
- Registry increased from 9,001 to 9,673 mostly due to decline in deaths
- Those older than 50 now 53% of population, up from 41% in 2006 – fastest growing subset of patients

**Aging of HIV Population: Importance to Non-ID Doctors**

- Most HIV patients in care are stable from HIV perspective
- Risk of AIDS is lower than the risk of non-AIDS complications
- Co-management with ID is the ideal model, especially if there are many comorbid medical conditions
Case Presentation

- A 47 year old hospital worker accidentally sustains a needlestick with a hollow-bore needle while cleaning an empty room.
- The syringe is empty, with no visible blood; the needlestick did penetrate her skin and cause some visible bleeding.
- She washed the wound, then sought medical attention.

**Nature of Exposures in Occupationally-Infected HCWs**

<table>
<thead>
<tr>
<th>Nature of Exposure</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>Percutaneous (puncture/cut injury)</td>
<td>48</td>
</tr>
<tr>
<td>Mucocutaneous (mucous membrane and/or skin)</td>
<td>5</td>
</tr>
<tr>
<td>Percutaneous and mucocutaneous</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>HIV-infected blood</td>
<td>49</td>
</tr>
<tr>
<td>Concentrated virus in a laboratory</td>
<td>3</td>
</tr>
<tr>
<td>Visibly bloody fluid</td>
<td>1</td>
</tr>
<tr>
<td>Unspecified fluid</td>
<td>4</td>
</tr>
</tbody>
</table>

**Relative Risk of Transmission after Percutaneous Exposure**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Transmission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>2-40% (30%)</td>
</tr>
<tr>
<td>HCV</td>
<td>0-7% (3%)</td>
</tr>
<tr>
<td>HIV</td>
<td>0.2-0.5% (0.3%)</td>
</tr>
</tbody>
</table>

**Factors Predicting HIV Transmission**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep (IM) injury</td>
<td>16.1</td>
</tr>
<tr>
<td>Source pt with advanced AIDS</td>
<td>6.4</td>
</tr>
<tr>
<td>Visible blood on device</td>
<td>5.2</td>
</tr>
<tr>
<td>Needle used to enter blood vessel</td>
<td>5.1</td>
</tr>
<tr>
<td>AZT PEP used</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Management of Possible HIV Exposure**

- Step 1: Determine the exposure type: needlestick, needle type, splash, intact vs non-intact skin
- Step 2: Determine the HIV class: ?HIV+; if positive-- symptoms, viral load, resistance status
- Initiate therapy as soon as possible based on published guidelines
- Consultation with person familiar with management of HIV exposures highly recommended!
Recommended Approach to HIV PEP

**PEP Recommended Regimens**

- **Basic Regimen:** for less severe or low volume exposures
  - Tenofovir/emtricitabine (Truvada)
- **Expanded Regimen:** for higher risk exposures
  - basic plus Lopinavir/r (Kaletra) or raltegravir (Isentress) or tailored to resistance profile of source
- **Length of therapy:** Four weeks
- **Tolerability often poor:** nausea, fatigue, diarrhea, anxiety

Adapted from MMWR 2005;54:RR-09;1-17

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**HIV: Where to Get More Information**

- HIV/AIDS Treatment Information Service: aidsinfo.nih.gov
- Infectious Diseases Society of America: www.idsociety.org
- National clinicians’ PEP hotline (PEPline): 888-448-4911, www.ucsf.edu/hivcntr
- Referrals to BWH HIV Program: psax@partners.org

Thank you!