What the Primary Care Provider Should Know About HIV

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Ten Things Primary Care Providers Should Know About HIV/AIDS

Covered in the First Segment:

- What is the global status of HIV/AIDS and what is the history of this disease?
- What are the common modes of transmission?
- Who should be tested?
- What is the status of HIV in pregnancy?
Ten Things Primary Care Providers Should Know About HIV/AIDS

In this segment we will cover:

- How is HIV infection treated?
- When to initiate antiretroviral therapy?
- What is Primary HIV infection?
- What are the current co-morbidity issues?

In the last two segments we will cover:

- How Do I assess my patients for risk of HIV?
- How Do I get testing for my patient?
HIV Replication Cycle and Sites of Drug Activity

1. Attachment
2. Uncoating
3. Reverse Transcription
4. Integration
5. Transcription
6. Translation
7. Assembly and Release

- **Attachment Inhibitors**
  - HIV Virions
  - CD4 Receptor
  - CCR5 or CXCR4 co-receptor

- **NRTIs**
  - Viral RNA
  - Unintegrated double stranded Viral DNA
  - Integrated viral DNA

- **NNRTIs**
  - Reverse Transcriptase
  - Integrase
  - Nucleus
  - Cellular DNA

- **Protease Inhibitors**
  - Protease
  - gag-pol polyprotein
  - Capsid proteins and viral RNA
  - New HIV particles

- **Reverse Transcriptase**
- **Integrase**
- **Protease**

Increasing Number of Treatment Options

- Retrovir
- Videx
- Zerit
- Hivid
- Epivir
- Viramune
- Rescriptor
- Sustiva
- Ziagen
- Viread
- Trizivir
- Combivir
- Viracept
- Kaletra
- Truvada
- Epzicom
- Lexiva
- Epivir
- Trizivir
- Emtriva
- Fuzeon
- Reyataz
- Sustiva
- Crixivan
- Norvir
- Invirase
- Fortovase
- Agenerase
- Agenerase
- Viracept
- Kaletra
- Truvada
- Epzicom
- Lexiva
- Emtriva
- Fuzeon
Regimens Are Getting Much More Effective

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

- d4T + ddI + EMV (MKC-302)
- AZT + 3TC + APV (PROAB 3301)
- AZT + 3TC + IDV (START II)
- AZT + 3TC + ABC (CNA3005)
- d4T + ddI + IDV (START II)
- AZT + 3TC + IDV (DMP-006)
- AZT + 3TC + IDV (AVANTI 2)
- AZT + ddI + NVP (INCAS)
- AZT + 3TC + NFV (AVANTI 3)
- AZT + 3TC + IDV (CNA3005)
- AZT + 3TC + IDV (START II)
- d4T + 3TC + EMV (MKC-302)
- d4T + ddI + 3TC (Atlantic)
- d4T + 3TC + IDV (START I)
- d4T + ddI + NVP (Atlantic)
- 2 NRTIs + SQV-SGC (NV-15355)
- d4T + 3TC + NFV (M98-863)
- AZT + 3TC + ABC (CNAB3003)
- d4T + ddI + IDV (Atlantic)
- AZT + 3TC + EFV (DMP-006)
- d4T + 3TC + LPV/RTV (M98-863)
- d4T + 3TC + EFV (DMP-043)
- d4T + 3TC + EFV (GS-903)
- TDF + 3TC + EFV (GS-903)

% with HIV RNA <50 copies/mL at 48 Weeks (ITT)

## When to Start Treatment

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4+ Cell Count</th>
<th>Plasma HIV-1 RNA</th>
<th>General Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe symptoms*</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt; 200</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200-350</td>
<td>Any value</td>
<td>Treatment should be offered following full discussion of pros and cons of treatment.</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt; 350</td>
<td>≥ 100,000</td>
<td>Most clinicians recommend deferring therapy, but some clinicians will treat.</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt; 350</td>
<td>&lt; 100,000</td>
<td>Deferring therapy</td>
</tr>
</tbody>
</table>
# Initial Treatment: Preferred Regimens

## NNRTI-Based

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pills/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz* (Sustiva) + (lamivudine or emtricitabine) (Epivir) + (zidovudine or tenofovir) (Retrovir)</td>
<td>2-5</td>
</tr>
</tbody>
</table>

## PI-Based

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pills/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir (Kaletra) + (lamivudine or emtricitabine) (Epivir) + zidovudine (Retrovir)</td>
<td>8-10</td>
</tr>
</tbody>
</table>

*Avoid in pregnant women and women with high pregnancy potential.*
Main Reasons for Discontinuation of ART

- Virologic Failure: 14%
- Nonadherence: 20%
- Other: 8%
- Toxicity: 58%

N=312 discontinuations.

d'Arminio Monforte A et al. AIDS. 2000;14:499-507
Timeline for New Antiretrovirals

- **Entry inhibitors** (anti-gp120, CCR5)
- **Maturation inhibitors**
- **Integrase inhibitors**

**CCR5 Inhibitors**
- GW695634
- TMC278
- TMC125
- D-d4FC
- TMC114
- GW640385

**CXCR4 Inhibitors**
- PA-457

**Integrase Inhibitors**
- TMC114
- GW640385

**Pls**
- TMC114
- TMC278
- TMC125
- D-d4FC
- GW640385

**NNRTI**
- GW640385

**NRTI**
- D-d4FC
- GW640385

Timeline:
- 2005
- 2006
- 2007
- 2008
- 2009
Sometimes You Find Yourself in a Precarious Situation...
<table>
<thead>
<tr>
<th>Drug Interactions with ARVs: Dose Modification or Cautious Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Oral contraceptives (may require second method)</td>
</tr>
<tr>
<td>● Methadone</td>
</tr>
<tr>
<td>● Erectile dysfunction agents</td>
</tr>
<tr>
<td>● Herbs - St. John’s wort</td>
</tr>
<tr>
<td>● Lipid-lowering agents</td>
</tr>
<tr>
<td>● Anti-mycobacterials, especially rifampin</td>
</tr>
<tr>
<td>● Psychotropics – midazolam, triazolam</td>
</tr>
<tr>
<td>● Ergot Alkaloids</td>
</tr>
<tr>
<td>● Antihistamines – astemizole</td>
</tr>
<tr>
<td>● Anticonvulsants</td>
</tr>
</tbody>
</table>
Now What??

Primary HIV Infection
Factors That Facilitate Transmission

- High HIV titers in plasma reflected in semen, vaginal and rectal secretions- ART reduces titer
- Co-infections with malaria, tuberculosis and especially other STDs increase viral load-activate CD4
- Genital ulcers facilitate submucosal inoculation
Factors that facilitate transmission

- Lack of circumcision facilitates spread to male
- Menses, vaginal mucosal thinning (estrogen deficiency) increase transmission to & from woman
Exposure to HIV at mucosal surface (sex)

Virus collected by dendritic cells, carried to lymph node

HIV replicates in CD4 cells, released into blood

Virus spreads to other organs

Day 0

Day 0-2

Day 4-11

Day 11 on

Acute Course of HIV Infection

Source: http://hivinsite.ucsf.edu
Primary HIV: The Key to HIV spread!

- Highest HIV titers (several million/ml plasma),
  - initial viremia 4-11 days after infection
  - peaks at 4 weeks.
Primary HIV: The Key to HIV spread!

- Symptoms in 50% by 5-14 days
  - Similar to mononucleosis, possibly secondary to a cytokine storm from immune activation.
Primary HIV: The Key to HIV spread!

- Only 7% are diagnosed at 1\textsuperscript{st} visit
  - ELISA usually negative until 4-6 weeks post infection,
  - HIV-RNA/p 24 + by 9-11 days (watch for false + with low HIV viral load).
Signs of Acute Infection

- Fever (> 101°)
- Lymphadenopathy
- Rash (upper body, scattered oval macules)
- Ulcers: oral, pharyngeal, esophageal, genital
- Thrush

Source: http://hivinsite.ucsf.edu
Symptoms

- Flu-like symptoms
- Malaise, fatigue, myalgias, arthralgias
- Sore throat, mouth (no rhinnorhea)
- GI symptoms: abdominal pain, diarrhea
- Meningeal symptoms: head ache, photophobia, stiff neck
- Dehydration symptoms

Source: http://hivinsite.ucsf.edu
Routine Lab Abnormalities

- WBC is LOW
- Lymphocytopenia
- Thrombocytopenia (100K)
- Mild transaminitis

Source: http://hivinsite.ucsf.edu
Diagnosis

- Symptoms: 1 - 4 weeks after exposure
- Antibody seroconversion
  - 1 to 12 weeks after onset of sx
- p 24 antigen
  - 75% positive within 2 weeks of infection
  - Probably positive in most cases of acute HIV
- HIV-1 RNA tests (PCR, bDNA)
  - Positive 1 - 2 weeks before antibody
  - Risk of false positives - only use if high pre-test probability

Source: http://hivinsite.ucsf.edu
Primary HIV Infection

Rash

Trunk and face > limbs
Small pink macules

Mucosal Lesions

Oral ulcers, thrush

(Kahn, NEJM, 1998)
Oral Ulcers in Acute HIV Infection

Genital Ulcer in Acute HIV Infection

Acute HIV Infection: Treatment

Possible benefits:
- Decrease the severity of acute disease
- Alter the viral “set point”
- Reduce the rate of mutation
- Preserve immune function
- Reduce risk of viral transmission

Possible risks:
- Drug-related toxicity
- Earlier emergence of drug resistance
- Limitation of future treatment options
- Potential need for indefinite treatment
- Adverse effects on quality of life
We Would Like the Path to Be Very Clear…

But, unfortunately it is not…
First, The Little Things…
No Clinical Evidence Supports The Need To Alter Treatment Based Solely On HIV Status
Antibiotic Prophylaxis

Indicated when:

- Neutrophils: <500 cells/mm³
- Need for antibiotic prophylaxis is not based on CD4 count
- According to AHA guidelines if patient has heart/valvular problems
Antibiotic Prophylaxis

- Patients with indwelling catheters such as a Hickman catheter may require antibiotic prophylaxis prior to dental care.
  - Medical consultation may be warranted.

- Renal dialysis patients with shunts for hemodialysis require antibiotic prophylaxis prior to invasive dental care.
Considerations in the Use of Antibiotics

- Preferred use of narrow spectrum antibiotics (e.g., Metronidazole) to minimize development of antibiotic resistance
- Possibility of presence of antibiotic resistant strains
  - Culture and antibiotic sensitivity may be indicated
- Use of antibiotics may lead to overgrowth of Candida albicans
  - Antifungal treatment may be indicated in conjunction with systemic antibiotics
- Local delivery antibiotics may be useful but have not been evaluated
hivdent.org

- Treatment information
- Pictorial gallery of Oral manifestations of HIV
- Pediatric health care information
- Public policy and news updates
- CDC updates
- Infection control in the dental health care setting
- Dental patient education
- Research news
Then the Big Things…

**Major Toxicities**

- Metabolic disorders
  - Lipodystrophy
  - Hyperlipidemia
  - Diabetes

- Renal tubular dysfunction

- Anemia

- Kidney stones

- Peripheral neuropathy

- Pancreatitis

- Rashes/Stevens-Johnson syndrome

- Hypersensitivity

- Hepatotoxicity
Metabolic Complications of HIV/Antiretroviral Therapy

- One syndrome or several?
- One etiology or multifactorial?
Lipodystrophy Syndrome: NRTIs vs PIs

NRTIs
- d4T > ZDV

- ↑ Lactic acid
- ↑ SC fat wasting
- ↑ TG

PIs
- ↑ Intra-abdominal fat
- ↑ Cholesterol
- ↑ TG
- ↑ TG
- Insulin resistance

Lipodystrophy and Metabolic Toxicity

**Hyperlipidemia, insulin resistance**
- Modify external factors (e.g., diet, exercise)
- Switch therapy
  - PI to NVP
  - PI to ABC
- Add other therapy (e.g., statins/fibrates, insulin sensitizing agents)

**Visceral fat accumulation**
- Modify external factors (e.g., diet, exercise)

**Subcutaneous fat wasting**
- Switch therapy
  - d4T to ZDV or ABC
  - Sculptra
Multifactorial Etiology of Dyslipidemia

Traditional risk factors
- Familial hypercholesterolemia; obesity

HIV-related factors
- ↑ TGs, ↓ HDL, ↓ total chol, ↓ LDL in untreated advanced HIV

Antiretroviral-related factors
- Most PIs & d4T: ↑ TGs, ↑ total chol, ↑ LDL;
  NNRTIs: ↑ total chol, ↑ HDL; EFV: ↑ LDL
Cardiovascular and cerebrovascular events (CVE) in the D:A:D Study

- Follow-up of ongoing, prospective, multinational cohort study
- 36,151 pt-years follow up
- Endpoints include documented:
  - Myocardial infarction (n=127)
  - CAD on angiography (n=42)
  - Stroke (n=30)
- Estimation of the incidence of MI based upon the Framingham algorithm
  - Observed rate exceeded predicted rate by approximately 25%

Incidence of CVE according to duration of ART exposure

<table>
<thead>
<tr>
<th>ART exposure (yrs)</th>
<th>None</th>
<th>&lt;1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>&gt;4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>7</td>
<td>15</td>
<td>22</td>
<td>30</td>
<td>49</td>
<td>76</td>
<td>199</td>
</tr>
<tr>
<td>PYFU</td>
<td>5711</td>
<td>4139</td>
<td>4795</td>
<td>5841</td>
<td>7210</td>
<td>8456</td>
<td>36151</td>
</tr>
</tbody>
</table>

Test for trend $p<0.00001$

Law MG et al. 11th CROI 2004; abstract 737
Disordered Glucose Metabolism

- Prevalence of diabetes mellitus increased among HIV+ pts on protease inhibitors
  - Prevalence ~2-14%

- Insulin resistance (higher concentrations of insulin required for usual effects) more common

- MACS Study: Risk of new onset DM ~ 4 x higher in HIV+ men vs. HIV- men (adjusted for age, BMI)

Dube M Clin Infect Dis 2000; 31:1467-75
“Lipodystrophy Syndrome”

- No generally accepted case definition of syndrome(s)
- Initial reports suggested clustering of:
  - Central fat accumulation/adiposity
  - Lipoatrophy/fat wasting
  - Dyslipidemia
  - Insulin resistance/type 2 diabetes mellitus
- Recent cross-sectional epidemiological data questions the linkage of lipoatrophy and fat accumulation

Fram J Acquir Immune Defic Syndr 2005;40:121-131
Abdominal MRI Scans

Control subject

Increased Visceral Fat
Potential Etiologies

- HIV infection
- Hormonal influence
- Immune dysregulation
- Antiretroviral therapy
- Host factors
- Mitochondrial dysfunction
- Non-HIV causes
Cardiovascular Risk Factors in Lipodystrophy

Compared with age and BMI matched controls from the Framingham Offspring Study, HIV+ pts with self-reported lipodystrophy had:

- Higher prevalence of impaired glucose tolerance/diabetes
- Higher diastolic blood pressure
- Elevated triglycerides, total cholesterol (not LDL-C)
- Lower HDL-C
- Decreased ability to break down blood clots

Hadigan et al, Clin Infect Dis 2001;32:130
Hadigan et al, JCEM 2001;86:939-43
Some pts with lipodystrophy appear to have a metabolic syndrome that theoretically could predispose to accelerated atherosclerosis and diabetes.
Osteopenia/Osteoporosis

- Decreased bone mineral density (BMD) initially reported in HIV+ on PIs (plus NRTIs)
- Subsequent reports of higher prevalence of decreased BMD in ARV naïve pts and increases in BMD while on PI-containing HAART
- Multifactorial etiology: HIV, cytokines, endocrine factors, liver disease, smoking, ? antiretrovirals

Tebas P et al, AIDS 2000;14:F63-7
Mondy K et al, Clin Infect Dis 2003 ;36:482-90
Osteonecrosis

- Avascular necrosis = aseptic necrosis = osteonecrosis
  - death of cellular constituents of bone & marrow due to ischemia (decreased blood supply)

- Associated with corticosteroid use, possibly duration of antiretroviral therapy & immune recovery

- Most commonly presents as hip pain

- MRI is test of choice if symptoms suggest dx

- Conservative management for early stages of disease

- Surgery
  - total hip replacement vs. core decompression

Allison et al, AIDS 2003;17:1-9
It’s Just One Thing On Top of Another!....
HBV/HIV Co-Infection: ARV considerations

- Unclear if HBV treatment improves the course of HIV infection
- Unclear if HIV treatment alters the course of HBV
- In HBV/HIV patients, liver toxicity from ARVs and flares of HBV may complicate HIV treatment
HBV/HIV Co-Infection: ARV considerations

- Immune reconstitution may result in LFT deterioration
  - Patients with immune reconstitution may have loss of e antigen (HBeAg), associated with HBV flare
- All PIs and NNRTIs may increase transaminase levels; ARV toxicity may be difficult to distinguish from HBV flare (and possible precursor to HBeAg seroconversion)
HBV/HIV Co-Infection: Treatment Recommendations

For all HBV/HIV co-infected patients:

- Counsel avoidance of alcohol
- Vaccinate against hepatitis A (if not immune)
- Advise on methods to prevent HBV transmission
- Evaluated extent of HBV infection
HCV/HIV Co-Infection

- Higher rates of progressive liver disease in HIV/Hepatitis C (HCV co-infection)
- Unclear if HCV increases HIV progression
- Poor prognosis; unclear if HIV treatment improves morbidity and mortality for untreated HCV
- Higher rates of ARV-associated hepatotoxicity
HCV/HIV Co-Infection

Treatment indicated:

- Detectable plasma HCV RNA and/or bridging or portal fibrosis on liver biopsy
- Consider other factors such as:
  - stage and stability of HIV disease
  - other co-morbidities
  - probability of adherence
  - possible contraindications to HCV medications
HCV/HIV Co-Infection: Treatment

Pegylated interferon + ribavirin for 48 weeks

- Low rates of sustained virologic response in genotype 1
- Limited data on patients with CD4 <200 cells/mm³
HCV/HIV Co-Infection: Treatment

Potential for drug-drug interactions and additional toxicity in HIV/HCV:

- Avoid use of Videx with ribavirin (neuropathy, pancreatitis, lactic acidosis)
- Avoid use of AZT with ribavirin, if possible (anemia)
- Monitor closely for hepatotoxicity due to ARV
- Monitor closely for neutropenia (due to interferon) and anemia (due to ribavirin); hematopoietic growth factors
TB/HIV Co-Infection

- Increased risk of progression from latent to active TB
- Increased risk of HIV progression
The treatment of TB in patients with HIV infection should follow the same principles for persons without HIV infection.

- For active TB, initiate treatment immediately.
- Directly observed therapy is strongly recommended.
TB/HIV Co-Infection: Treatment Considerations

- In patients on ARV therapy, evaluate ARV regimen for interactions with TB drugs.
- In ARV-naive patients, avoid simultaneous initiation of treatment for TB and HIV.
  - Consider delay of ARVs for 4-8 weeks after initiation of TB treatment to avoid overlapping of adverse reactions and paradoxical reactions.
TB/HIV Co-Infection: Treatment Considerations

- Rifampin/rifabutin-based regimens should be given at least three times weekly in patients with CD4+ T cell count <100 cells/mm³
- Once weekly rifapentine is not recommended in HIV-infected patients
TB/HIV Co-Infection: Treatment Considerations

- Rifamycin should be included in TB regimens
  - Potential drug-drug interactions with PIs and NNRTIs
  - Rifampin may be used only with efavirenz or full-dose ritonavir
  - Rifampin may not be used with ritonavir-boosted PIs
  - Rifabutin recommended with nevirapine, other PIs
    - Dosage adjustment may be necessary
TB/HIV Co-Infection: Treatment Considerations

- Paradoxical reactions more common with immune reconstitution due to ARV
  - Continue treatment for tuberculosis and HIV, use non-steroidal anti-inflammatory agents
  - In severe cases consider use of high-dose prednisone
Things are not always what they seem…
Case Study

- 40 y.o., Heterosexual, Native American female
- h/o exposure to IV drug using male (sex only, no needles)
- 3 years ago, LN bx cervical and axilla = nonspecific inflammation
- 2 years ago rash – eczema
- 1 year ago – worsened – more eczema
- Lost job – went to plasma center = HIV+
- CD4 – 346, VL – 76,000
- Hep C negative
Case Study

- 42 y.o., Native American, heterosexual male with h/o remote IV drug use
- + nasopharyngeal CA 1 year ago
- Basically healthy
- Female sex partner – intermittent x 18 yrs.
  - found HIV+ @ plasma center
- CD4 - 196
- Viral Load - 250,000
- Hep C+
  - 17,700,000
  - Genotype 2b
STRESS CLINIC

Today is the first day of the rest of your life -- but relax! So is tomorrow!