HIV and the Emergency Department Patient

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Why Physicians Education and patient prevention remains critical

- CDC estimates 950,000 US residents are infected, 1/4 are unaware
- HIV infects 40,000 people each year
- Americans continues to die from AIDS
- Treatment remains difficult, life-long, expensive, and is not a cure
- There is no vaccine
- An ounce of prevention....

Adults and children living with HIV

33.2 (30.6-36.1) million people infected

www.unaids.org
Rising rates of AIDS cases in U.S. women

- Proportion of all AIDS cases in women has more than tripled in 15 years, from 7% in 1985 to 29% today.
- Leading cause of death in black women ages 25-34; 3rd in black and women ages 35-44; 5th overall in women 35-44.

Rise of HIV infection

- Safe sex fatigue: decrease condom use, increased unprotected sex.
Rise of HIV infection

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- Medications (HAART/ART)
Rise of HIV infection

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- Medications (HAART/ART)
- Increased access to sex: internet, circuit parties, public sex venues
- Increased recreational drug use, esp crystal methamphetamines and ecstasy
Rise of HIV infection

- Safe sex fatigue: decrease condom use, increased unprotected sex
- Medications (HAART)
- Increased access to sex: internet, circuit parties, public sex venues
- Increased recreational drug use, esp crystal methamphetamines and ecstasy
- Viagra
- Viagra + Ecstasy = Sextasy

Objectives

- Learn how to recognize subtle complaints in the most common life-threatening AIDS infections.
- Identify what tests may be helpful in the diagnosis of the most common OI in the US.
- Summarize the treatment and management of these OI’s.
- Learn about the adverse effects of HIV-Therapy
- Become aware of drug induced metabolic changes and Immune Reconstitution Syndrome

Case #1

- 28 year old HIV positive man complains of dry cough for 2-4 weeks and fevers. He has no history of Opportunistic Infection (OI’s) and takes no medicines. Normal Vital signs. O₂ saturation 95%. CXR clear.
What is the Stage of HIV infection?

- Defined by CD4 count:
  - Early: CD4 > 500/mm³
  - Intermediate: CD4 200-500/mm³
  - Late: CD4 < 200/mm³
  - Very Late: CD4 < 50/mm³

Viral Load

- Monitors therapy
- It is essential in suggesting the medications are not working either to
  - non-adherence
  - drug interactions
  - malabsorption
  - mutations

Always need CD4 count in your decision making
- < 200 and no PCP prophylaxis, all URI’s need close follow up
- > 200 or on prophylaxis (and compliant), then bronchitis

Returns 10 days later with diffuse pneumonia and goes to the ICU with the diagnosis of PCP.

What could have changed this management?

What was the stage of the HIV infection?

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Pneumocystis jiroveci Pneumonia

- Clinical presentation
  - CD4 cell count ≤ 200 cells/mm³
  - Symptoms: fever, DOE, dry cough, fatigue
  - Duration: >2-4 weeks
  - Signs: Nonspecific
  - Labs: Serum LDH often elevated

PCP Chest Radiographic Presentation

- Bilateral > Unilateral, Symmetric > Asymmetric
- Pattern
  - Interstitial (reticular) or granular
  - Alveolar (consolidation)
  - Cyst(s)
  - Normal
  - Pneumothorax
- Atypical
  - Intrathoracic adenopathy
  - Pleural effusion(s)
Cryptococcal neoformans is the most common fungus responsible for infections in patients with AIDS.

Signs: Focal lung findings
Labs: WBC often (relatively) elevated

Treatment
- Trimethoprim-sulfamethoxazole
- Clindamycin + Primaquine
- Trimethoprim + Dapsone
- Atovaquone
- Pentamidine

Treat for 21 days followed by prophylaxis
- Steroids 40 mg PO BID if PaO2 < 70 mm Hg

Bacterial Pneumonia
- Clinical presentation
  - CD4 cell count: any
  - Symptoms: Fever, SOB, chest pain, productive cough w/ purulent sputum
  - Duration: 3-5 days
  - Signs: Focal lung findings
  - Labs: WBC often (relatively) elevated

Case #2
- 28 year old HIV + man complains of headache. No medications.
- What do you need to know?
- Is his HIV infection early, intermediate, or late?
- CD4 < 100, need LP to rule out cryptococcal meningitis

CNS Emergencies
- Cryptococcal meningitis
- Cryptococcal neoformans is the most common fungus responsible for infections in patients with AIDS.
- Clinical presentation
  - CD4 < 100 cells/mm³
  - Symptoms: fever, headaches
  - Duration: weeks to months
Cryptococcal meningitis

- Clinical presentation
  - Signs: ± meningeal signs
  - Dx:
    - CT/MRI usually negative
    - CSF CrAg+: > 90-95%

- Treatment
  - Amphotericin B +/- Flucytosine for 2 wks
  - Oral fluconazole for chronic suppressive therapy
  - Manage increased ICP, hydrocephalus, seizures

CNS Emergencies

- Cerebral Toxoplasmosis
  - Toxoplasma gondii, a parasite, is the most common cause of focal brain lesions in people with AIDS
  - Clinical presentation
    - CD4 < 200 cells/mm³
    - Symptoms: headache, fever, AMS, focal signs over days to weeks
    - Signs: seizures (25%-50%), focal signs over days to weeks
    - Labs: Toxo titers usually positive

Cerebral Toxoplasmosis

- Diagnosis
  - CT/MRI: multiple ring-enhancing lesions
  - Inferred by response to empiric therapy

- Treatment
  - Pyrimethamine, sulfadiazine, folic acid
  - Expect clinical and radiologic improvement in 2 weeks

Ocular Emergencies

- CMV retinitis is the most common vision-threatening condition in people with AIDS
Ocular Emergencies

Clinical presentation
• CD4 < 50 cells/mm³
• Symptoms: blind spots, peripheral visual field loss, flashing lights, floaters, decreased or blurred vision

Treatment
• Goal is to slow down progression, prevent further spread of the infection in the retina and preserve visual function
• Valganciclovir, foscarnet, and cidofovir
• Prophylaxis

Prophylaxis and Treatment of OI’s- What’s New?
• Cessation of primary prophylaxis for PCP
  • Short-term data CD4 > 200 for 3-6 months, no PCP
• Cessation of prophylaxis for disseminated MAC
  • CD4 > 100-200
• Cessation of treatment of CMV retinitis,
  • CD4 > 200
• Prophylaxis for HSV (genital or oral)
  • Outbreaks up-regulate HIV viral production and can threaten HIV viral suppression, shed both HSV and HIV

HAART/ART
• Highly active antiretroviral therapy/antiretroviral therapy
• Combination of at least 3 drugs
• Standard of care

CDC, MMWR
Case #3

- 40 year old HIV positive woman complains of diffuse RUQ pain, anorexia, nausea, and malaise. No history of gallstones or alcohol. She is on HIV medications. CD4 400/mm³.

Therapies currently on market

- Nucleoside and nucleotide RTIs
  - Zidovudine, AZT (Retrovir)
  - Abacavir, ABC (Ziagen)
  - Lamivudine, 3TC (Epivir)
  - Didanosine, ddI (Videx)
  - Stavudine, d4T (Zerit)
  - Tenoforvir, TFV (Viread)
  - Emtricitabine, FTC (Emtriva)
  - Combivir (AZT/3TC)
  - Trizivir (AZT/3TC/ABC)
  - Epzicom (3TC/ABC)
  - Truvada (FTC/TFV)
- NNRTI’s
  - Delavirdine (DLV)
  - Nevirapine, NVP (Viramune)
  - Efavirenz, EFV (Sustiva)
  - Etravirine* (Intelence)
- Protease inhibitors:
  - Indinavir, IDV (Crixivan)
  - Saquinavir, SQV (Invirase, hgc)
  - Nelfinavir, NFV (Viracept)
  - Amprenavir, APV (Agenerase)
  - Atazanavir, ATZ (Reyataz)
  - Fosamprenavir, FPV (Lexiva)
- Fusion inhibitors:
  - Enfuvirtide, ENF or T20 (Fuzeron)
- Combination
  - Atripla (EFV/FTC/TFV)

*Approved in past year

Orange text – combination agents

Case #3

- Labs
  
<p>| | | | |</p>
<table>
<thead>
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<td>103</td>
<td>3</td>
<td>84</td>
</tr>
<tr>
<td>4.5</td>
<td>12</td>
<td>0.5</td>
<td></td>
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</table>

- SGOT-85, SGPT-63, Alk phos-239
- Lipase 342
- Ultrasound showed no stones
- CT scan showed a fatty liver

Case #3

- She was treated for pancreatitis, floor bed was ordered. One of her medications were stavudine (d4T).
- What was missed was lactic acidosis with hepatic steatosis associated with nucleoside reverse transcriptase (NRTI) medication. Her lactate level was 9.2. Transferred to an ICU bed.
- Bicarb continued to drop to 10 despite IVF with bicarbonate.
Mitochondrial toxicity

- Lactic acidosis with or without hepatic steatosis
  - May be sudden or gradual onset
  - Signs and sx: nausea, vomiting, abdominal pain, weight loss, malaise, fatigue, SOB, occ. fevers, diarrhea, tachycardia and tachypnea
  - Labs: abnormal LFTs, moderate to severe acidosis (lactate > 5 mmol/L)
  - Mortality 80% in lactate levels > 10 mmol/L

Emergencies Related to HIV Therapy

- Pancreatitis
- Mitochondrial toxicity
  - Lactic Acidosis
- Rash by Non-Nucleoside Reverse Transcriptase Inhibitors
- Drug interactions

www.aidsmeds.com

HIVinsite.com
Nucleoside reverse transcriptase inhibitors (NRTIs)
- Pancreatitis ("d" drugs, ie: ddI, d4T, ddC)
- Neuropathy ("d" drugs)
- Myopathy (AZT)
- Hepatic steatosis and lactic acidosis (all)
- Peripheral lipoatrophy (predominantly d4T)

Mitochondrial toxicity

Lipodystrophy Syndrome
- Definition? Thinning of the face, arms, or legs (lipoatrophy) occurred in 25-35% of HIV-infected subjects vs 2% of HIV-negative men.
- Fat accumulation in the belly was 35% vs 26%.
- Lipodystrophy combining both thinning and fat accumulation 40% vs 1-2%.

Fat Redistribution ("lipodystrophy")
HIV+ patient with truncal obesity. Subcutaneous fat is scant and fat in the abdomen is thick.

CT Scans of Two HIV+ Patients

HIV+ patient with visceral adiposity. Subcutaneous fat is scant and fat in the abdomen is thick.

Images courtesy of D.A. Wohl.
Abstract No 739

11th Conf Retroviruses Opportunistic Infec. 2004 Feb -11;

Hospitalization for Coronary Heart Disease and Myocardial Infarction among CHD and MI were significantly higher among HIV+ aged 35-64 compared to HIV - (CHD: 6.6 vs. 3.0 events/1,000 persons-yrs, p<0.0001 MI: 3.9 vs 2.2, P<0.005

7.5 year observation period
4,726 HIV-infected patients experienced 111 CHD events (66 MI’s)
CHD and MI were significantly higher among HIV+ aged 35-64 compared to HIV - (CHD: 6.6 vs. 3.0 events/1,000 persons-yrs,p<0.0001 MI: 3.9 vs 2.2, P<0.005

Case Series/Reports:
- Early MI’s
- CVA’s
- hypercholesterolemia
- hypertriglyceridemia
- decreased HDL
- increased rates of atherogenic lipids

Are HIV patients at increased risk of premature cardiovascular disease?

- increased levels of insulin resistance and diabetes
- higher rates of smoking
- substance use
- increased visceral abdominal fat
- HTN

All of these are known to increase the risk of CAD. CAD may be the next wave of the epidemic.

Metabolic complications- PI’s

- Glucose metabolism
  - Insulin resistance
  - Impaired glucose tolerance
  - Hyperglycemia
  - Frank diabetes

- Lipid metabolism
  - Increased triglycerides
  - Increased total and LDL cholesterol, low HDL

Hyperlactemia

Kaiser Permanente Northern California HMO group

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Hospitalization for Coronary Heart Disease and Myocardial Infarction among Northern Calif. Men with HIV-1 Infection: Additional follow-up. 11th Conf Retroviruses Opportunistic Infec. 2004 Feb -11;
Abstract No 739
**D:A:D Study: Incidence of MI**
A Small Increase in Incident CVD Is Associated With Duration of Combination Antiretroviral Therapy

![Incidence of MI per 1000 PY](image)


**Smart Study: Uncontrolled HIV Replication Increases the Risk of CVD**

- CD4+ guided drug conservation (DC) strategy associated with significantly greater disease progression or death compared with continuous viral suppression (VS); RR 2.5 (95% CI, 1.8–3.6; P<0.001)
- Includes increased CVD-, liver-, and renal-related deaths and nonfatal CVD events

**Severe Complications Endpoint and Components**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>P With Events (no.)</th>
<th>Relative Risk 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Severe complications</td>
<td>114</td>
<td>1.5</td>
</tr>
<tr>
<td>CVD, liver, renal deaths</td>
<td>31</td>
<td>1.4</td>
</tr>
<tr>
<td>Nonfatal CVD events (ECG changes included)</td>
<td>63</td>
<td>1.5</td>
</tr>
<tr>
<td>Nonfatal hepatic events</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>Nonfatal renal events</td>
<td>7</td>
<td>1.5</td>
</tr>
</tbody>
</table>

![Statistical table](image)


**How about treatment interruptions to reduce time on therapy?**

- Given toxicities, one idea was to reduce total duration on therapy by going off and on
- Strategies for Management of Antiretroviral Therapy (SMART) Study

**Eligibility:** CD4> 350 (N=5472)

- Continuous Treatment
- No Treatment until CD4 <250, then treatment until >350, then stop

*Baseline CD4: 596-599*
*CD4 nadir: 250-252*
*% < 400 copies/mL viral load: 71%*
*Mean follow-up: 14 months (2% LFU)*


**Smarter Study (cont)**

- 1.5-fold greater risk of severe complications not HIV-related (95% CI: 1.0-2.2) among patients undergoing treatment interruption
  - Cardiovascular, liver, or renal disease: 1.4 (95% CI: 0.7-2.8)
  - **Nonfatal cardiovascular events:** 1.5 (95% CI: 1.0-2.5)
  - Nonfatal hepatic events: 1.4 (95% CI: 0.5-3.9)
  - Nonfatal renal events: 2.5 (95% CI: 0.5-13)
- Treatment interruptions basically out as a concept!

Update to data from the published paper?

Edward King, 3/4/2008
- The French hospital cohort
- Kaiser Permanente of Northern CA cohort
- APROCO cohort
- US Veterans Study
- D:A:D study group
- The SMART trial
- INITIO trial

Summary:
- Taken together, these data suggest that HIV-infected patients do have an elevated cardiovascular risk compared to HIV-uninfected patients, which may be due to the HIV infection itself, antiretroviral therapy, or both.

Drug Interactions
- PI + statin = potentially fatal rhabdomyolysis
- PI inhibits cytochrome p450 system
- DO NOT prescribe simvastatin or lovastatin
- Cmax: Simvastatin increased 3,000% (myopathy, rhabdo)
- Pravastatin and fluvastatin not metabolized by p450 and safe

Antiretroviral Drugs May Interact With*
- Other anti-HIV medications
- OI drugs (e.g., voriconazole, clarithromycin)
- Anti-tuberculosis drugs (rifampin, rifabutin)
- Antacids (e.g., omeprazole, cimetidine)
- Cholesterol-lowering statins (e.g., lovastatin, simvastatin)
- Antidepressant drugs (e.g., fluoxetine, sertraline)
- Anticonvulsant drugs (e.g., phenytoin, phenobarbital)
- Benzodiazepines (e.g., alprazolam, midazolam, triazolam)
- Oral contraceptives containing estrogen
- Erectile dysfunction drugs (e.g., sildenafil, vardenafil)
- Recreational, street, or party drugs
- Methadone
- Herbal remedies (e.g., St. John’s wort, garlic)
* not a comprehensive listing
Rashes by NNRTIs

- Non-nucleoside reverse transcriptase inhibitors
  - Delavirdine (Rescriptor)
  - Nevirapine (Viramune)
  - Efavirenz (Sustiva)
- 27-37% in clinical trials developed a rash
- Maculopapular rash within 4-6 wks

Stevens-Johnson syndrome

- Symptoms: diffuse rash with peeling of large skin areas, blistering inside of the mouth, conjunctivitis, bronchitis, fever, myalgia, arthralgia, and malaise

Rashes by NNRTIs

- Toxic epidermal necrolysis
- Stevens-Johnson syndrome
- 8% of pts on nevirapine
- Admit to burn unit
Atazanavir

- Protease Inhibitor (PI)
- Elevated indirect bili
- 8% jaundice
- Not associated with lactic acidosis
- Cosmetic problem, not dangerous
- Treatment: Change medication

Immune Reconstitution Syndrome

HAART has made it possible to control HIV viral load, allowing a partial recovery of the immune system. This recovery is sometimes called “immune reconstitution.”

One benefit of this recovery is an increase in T cells, but this can lead to a strong immune response to opportunistic infections that were previously subclinical.

A number of conditions have been described, some of which may represent medical emergencies in HIV-infected persons.

Immune Reconstitution Syndrome

- Cases of
  - Mycobacterium Avium Complex (MAC) lymphadenitis
  - CMV retinitis/vitritis
  - worsening pulmonary tuberculosis
  - and worsening cryptococcal meningitis have been reported in patients who recently initiated HAART with very low baseline CD4
- Pathogenesis may involve enhanced antigen-specific immunity

Immune Reconstitution Syndrome

- MAC: Lymphadenitis, high fever, CXR infiltrates
- Onset 1-12 wks
**Immune Reconstitution Syndrome**

- CMV: Retinitis and vitritis;
  - Onset 1-2 mos.
- Uveitis with macular edema, epiretinal membrane formation, cataracts, papillitis;
  - Onset 2 mos-2 yrs

- TB: Fever, worsening CXR infiltrates/effusions, mediastinal and peripheral lymphadenopathy; onset 1-6 wks

  ![Image](image1.png)

- Zoster: Always localized and responsive to acyclovir therapy; Onset 4-16 wks
- Cryptococcal meningitis: New meningeal signs & symptoms, increased WBC’s in CSF, lymphadenopathy, pulmonary cavities; onset 1 wk-8 mos.

![Image](image2.png)
Rapid HIV Testing

www.nccc.ucsf.edu/StateLaws

CDC guidelines (routine, not risk-based) 9/21/06

- HIV screening in all health-care settings ages 13-64 after patient notified (opt-out screening – assent inferred unless patient declines) 1
- HIV testing for those at high risk for HIV infection at least yearly
- General consent for medical care implied; separate written consent not required
- Prevention counseling requirement relaxed
- (Some controversy and barriers, state-by-state) 2,3


AB682 signed by Gov. Schwarzenegger in CA 10/12/07

- AB 682 (California HIV Routine Screening bill)
  - Repeals written consent for HIV testing
  - Part of unwritten consent for routine medical care

Rapid HIV testing tools for primary care and other settings

- 4 FDA approved rapid HIV tests: Oraquick, Multispot, Reveal G2, Unigold
- Results in ~20 minutes
- Oraquick and Uni-Gold suitable for primary care clinics
  - CLIA-waived for fingerstick whole blood test (easy)
  - Only test for HIV-1, not 2
  - Eliminates loss of f/u for results

Oraquick test on whole blood

1. Obtain blood from fingerstick
2. Insert loop into vial and stir
3. Insert device; test develops in 20-30 min.

Uni-Gold test on fingerstick blood

1. Add 1 drop blood to well
2. Add 4 drops of wash solution
3. Read results in 10-12 minutes

Summary

No doubt that these advanced retroviral drugs (ARD) are saving and prolonging lives. These patients are living longer and fuller lives but are having manifestations of other diseases. Such as life-threatening reactions to medications, immune reconstitution, and perhaps MI’s, CVA’s relating to the development of DM, HTN, increased cholesterol and triglycerides, and decreased HDL.
http://hivinsite.ucsf.edu

Non-Government websites
- HIV InSite
- Johns Hopkins AIDS Service
- Check AIDS meds
- Website for patients STDs
- Practical implementation guide for EDs
  - www.hivinsite.ucsf.edu
  - www.hopkins-aids.edu
  - www.AIDSmeds.com
  - www.healthypenis.org
  - www.edhivtestguide.org

US Government-sponsored websites
- CDC National Prevention Information Network (NPIN)
- AIDS Info
- CDC’s website on testing
  - www.cdcnpin.org
  - www.aidsinfo.nih.gov
  - www.cdc.gov/hiv

Summary
- CD4 count - early, intermediate, or late HIV
- HIV patients susceptible to encapsulated bacteria, such as *Streptococcus pneumoniae*
- PCP most common AIDS defining dx - Dry cough, DOE, serum LDH level
- Low CD4 with Headache - cryptococcus meningitis, serum crypt antigen
- HIV seizure - head CT with and without contrast - toxo, lymphoma
- Low CD4 with Ocular complaints - think CMV retinitis
Summary

- HAART side effects
- Lactic acidosis with or without hepatic steatosis and Pancreatitis with the NRTI's
- Drug interactions
- Rash by NNRTI's
- Premature CAD? CVA?
- Immune Reconstitution Syndrome

National HIV Telephone Consultation Service
(Warmline)  800 / 933 - 3413

National Clinicians' Post-Exposure Prophylaxis Hotline
(PEPline)  888 / HIV - 4911

National Perinatal HIV Consultation and Referral Service
(Perinatal Hotline)  888 / 448 - 8765

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and Centers for Disease Control and Prevention (CDC)

www.healthypenis.org
Questions?
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