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, December 2007

Rising rates of AIDS cases in U.S. women

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 (OIs) and takes no medicines. Normal Vital signs. \( O_2 \) saturation 95%. CXR clear.
- 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?

What is the Stage of HIV infection?

- Defined by CD4 count:
  - Early: CD4 > 500/mm\(^3\)
  - Intermediate: CD4 200-500/mm\(^3\)
  - Late: CD4 < 200/mm\(^3\)
  - Very Late: CD4 < 50/mm\(^3\)

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

Pulmonary disease is one of the most common HIV-related emergencies
- PCP is the leading AIDS-defining condition in the United States
- Pneumocystis jiroveci ("yee row vet zee" - formerly carinii) pneumonia

CDC. HIV/AIDS Surveillance Reports Emerging Infectious Diseases 2002;8(9):891-896
**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)

**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

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

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

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, folinic acid
- Expect clinical and radiologic improvement in 2 weeks

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: fever, headaches
- Duration: weeks to months

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

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

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

**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

Prophylaxis for HSV (genital or oral)

- Outbreaks up-regulate HIV viral production and can threaten HIV viral suppression, shed both HSV and HIV

Therapies currently on market

- **NRTI’s:**
  - Zidovudine (AZT) (Retrovir)
  - Lamivudine (3TC) (Epivir)
  - Didanosine (ddI) (Videx)
  - Stavudine, d4T (Zerit)
  - Tenofovir, TFV (Viread)
  - Emtricitabine, FTC (Emtriva)
  - Combivir (AZT/3TC)
  - Trizivir (AZT/3TC/ABC)
  - Truvada (FTC/TFV)
- **NNRTI’s:**
  - Delavirdine (DLV)
  - Nevirapine, NVP (Viramune)
  - Efavirenz, EFV (Sustiva)
  - Etravirine* (Intelence)
- **Fusion inhibitors:**
  - Enfuvirtide, ENF (Fuzeon)
- **Combination**
  - Atripla (EFV/FTC/TFV)

Protease inhibitors:

- Indinavir, IDV (Crixivan)
- Saquinavir, SQV (Invirase, hgc)
- Nelfinavir, NFV (Viracept)
- Amprenavir, APV (Agenerase)
- Atazanavir, AT2 (Reyataz)
- fosamprenavir, FPV (Lexiva)
- Kaletra (lopinavir/ritonavir)
- Tipranavir (Aptivus)
- Darunavir (Prezista)*

HAART/ART

- Highly active antiretroviral therapy/antiretroviral therapy
- Combination of at least 3 drugs
- Standard of care

HAART

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.
Case #3

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

**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
Mitochondrial toxicity

- 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 36% vs 26%.
  - Lipodystrophy combining both thinning and fat accumulation 40% vs 1-2%.

Fat Redistribution ("lipodystrophy")

Fat Wasting (NRTI)

Truncal Obesity (PI’s)

8th Conference on Retroviruses and OI's, 2001 Abstract 538
HIV+ patient with obesity. Subcutaneous fat is thick and fat in the abdomen is scant.

CT Scans of Two HIV+ Patients

Images courtesy of D.A. Wohl.

Buffalo Hump (PI’s)

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

- 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

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

Are HIV patients at increased risk of premature cardiovascular disease?

- Case Series/Reports:
  - Early MI’s
  - CVA’s
  - hypercholesterolemia
  - hypertriglyceridemia
  - decreased HDL
  - increased rates of atherogenic lipids
- 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.
D:A:D Study: Incidence of MI
A Small Increase in Incident CVD Is Associated With Duration of Combination Antiretroviral Therapy


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

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<th>Subgroups</th>
<th>P With Events (n)</th>
<th>Relative Risk</th>
<th>95% CI</th>
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<td>CVD, liver, renal deaths</td>
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<tr>
<td>Nonfatal CVD events (ECG changes included)</td>
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<td>Nonfatal hepatic events</td>
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<tr>
<td>Nonfatal renal events</td>
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Traditional Factors Contribute Most to Coronary Heart Disease in HIV Population

The French hospital cohort
Kaiser Permanente of Northern CA cohort
APRICO 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.

Dyslipidemia
- Lifestyle Modification
  - Increase exercise
  - Weight loss
  - Dietary changes
  - Smoking cessation
- Pharmacotherapy
  - Statins

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

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

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**Rashes by NNRTIs**
- Toxic epidermal necrolysis
- Stevens-Johnson syndrome
  - 8% of pts on nevirapine
  - Admit to burn unit

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

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**Stevens-Johnson syndrome**

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**Atazanavir**
- Protease Inhibitor (PI)
- Elevated indirect bilirubin
- 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.

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

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

Immune Reconstitution Syndrome

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

“Worsening” of miliary TB on HAART

Immune Reconstitution Syndrome

- TB: peripheral lymphadenopathy; onset 1-6 wks
**Immune Reconstitution Syndrome**

- **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.

**Rapid HIV Testing**

**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)
- HIV testing for those at high risk for HIV infection at least qyear
- General consent for medical care implied; separate written consent not required
- Prevention counseling requirement relaxed
- (Some controversy and barriers, state-by-state)² ³


**www.nccc.ucsf.edu/StateLaws**

**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
- Only 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 follow-up 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.jhu.edu
- www.AIDsmeds.com
- www.healthypenis.org
- www.cdcncpguide.org

US Government-sponsor 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

Questions?