



CRACKCast Episode 132 – HIV/AIDS

Key Points

- HIV/AIDS can affect any organ system, and the nonspecific complaints seen with viral illness are common. Consider acute HIV infection in the evaluation of patients with mononucleosis-like syndromes in the presence of risk factors.
- The presenting illness may originate from acute HIV infection, opportunistic infections, medication side effects, inflammation, and immune reconstitution inflammatory syndrome (IRIS).
- Patients with CD4+ count above 500 cells/ μ L tend to have illnesses similar to those of individuals without HIV infection.
- Opportunistic infections are more frequent as the CD4+ count declines but can occur at any stage of HIV infection.
- Formulation of the differential diagnosis should be guided by the patient's immune status—consider CD4+ count, viral load, current medications, and prior opportunistic infections.
- Patients with HIV infection are at a greater risk of morbidity and mortality from common disease entities than non-infected patients.
- Patients with advanced AIDS suffer unusual diseases and often have multiple co-infecting pathogens.
- The current medications used for treatment of HIV infection (especially ART) can interact with many commonly prescribed drugs.

Signposts

1. Define AIDS
2. List 5 risk factors for AIDS
3. List 10 AIDS defining conditions
4. Describe 3 serum tests for HIV
5. List 6 ddx for respiratory infection in HIV?
6. Describe the presentation and treatment of PCP pneumonia
7. Describe an approach to diagnosis and management of CNS infection in AIDS
8. List 5 causes of odynophagia in HIV
9. List 6 causes of diarrhea in the HIV patient
10. Describe HAART therapy
11. Describe prophylaxis of opportunistic infections

WiseCracks

1. Risk stratify exposure to HIV
 2. What is Coccidiomycosis?
 3. Name common ART agents and their adverse effects
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Rosen's In Perspective

Box 124.2: Dermatologic and Mucocutaneous Manifestations of WHO Stage 4 HIV Disease

1. Chronic herpes simplex virus ulcers
2. Extrapulmonary tuberculosis
3. Kaposi's sarcoma
4. Extrapulmonary cryptococcosis
5. Disseminated mycosis
6. Atypical disseminated leishmaniasis
7. Disseminated nontuberculous mycobacterial infection
8. Extrapulmonary cryptococcosis including meningitis

Box 124.3: Cutaneous Findings Highly Suggestive of HIV Disease

1. Any WHO criteria for stage 4 HIV disease
2. Facial molluscum in an adult
3. Proximal subungual onychomycosis
4. Herpes zoster scarring
5. Oral hairy leukoplakia
6. Bacillary angiomatosis
7. Widespread dermatophytosis
8. Severe seborrheic dermatitis

See Figure 124.4 for a graphic representation of the natural history of untreated HIV.

Core Questions

[1] Define AIDS

CDC definition: "a CD4+ cell count below 200 cells/ μ L or the presence of an AIDS-defining condition."

At this level, immune dysfunction is severe and, without ART, survival is short. Those with a CD4+ cell count below 50 cells/ μ L have advanced AIDS and are at much higher risk for death and development of opportunistic infections. Some infections are so common in patients with AIDS that primary prophylaxis is indicated and is cost-effective. Prophylaxis is started for PCP when CD4+ counts are less than 200 cells/ μ L, for toxoplasmosis, when CD4+ counts are less than 100 cells/ μ L and, for Mycobacterium avium complex (MAC) infection, when CD4+ counts are less than 50 cells/ μ L (Table 124.2).



[2] List 5 risk factors for HIV / AIDS

- Contact with semen, blood, vaginal secretions, and breast milk of viremic individuals
- These fluids must come into contact with damaged tissue / mucous membrane / entry into bloodstream.
- **HIV-positive blood transfusion MOST COMMON**
- exposure to serum with a high viral load
- lack of male circumcision
- presence of an ulcerative, sexually transmitted infection.
- Type of sexual contact:
 - 1% to 30% for receptive anal intercourse
 - 0.1% to 10% for receptive vaginal and insertive anal intercourse
 - 0.1% to 1% for insertive vaginal intercourse.

After transmission, the virus replicates in the mucosal surface or lymphoid tissue at the site of entry in lymphocytes and macrophages. If enough cells are infected, the virus spreads to draining lymph nodes and infection is established, usually within 48 to 72 hours.

[3] List 10 AIDS defining conditions

Box 124.1 AIDS-Defining Conditions

1. Bacterial infections, multiple or recurrent
2. Candidiasis of bronchi, trachea, or lungs
3. Candidiasis of esophagus
4. Cervical cancer, invasive
5. Coccidioidomycosis, disseminated or extrapulmonary
6. Cryptococcosis, extrapulmonary
7. Cryptosporidiosis, chronic intestinal (>1 mo duration)
8. Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
9. Cytomegalovirus retinitis (with loss of vision)
10. Encephalopathy, HIV related
11. Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
12. Histoplasmosis, disseminated or extrapulmonary
13. Isosporiasis, chronic intestinal (>1 mo duration)
14. Lymphoma, Burkitt's (or equivalent term)
15. Kaposi's sarcoma
16. Lymphoma, immunoblastic (or equivalent term)
17. Lymphoma, primary, of brain
18. *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
19. *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary
20. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
21. *Pneumocystis jiroveci* pneumonia



- 22. Pneumonia, recurrent
- 23. Progressive multifocal leukoencephalopathy
- 24. *Salmonella* septicemia, recurrent
- 25. Toxoplasmosis of brain, onset at age >1 mo
- 26. Wasting syndrome attributed to HIV

Think head to toe and start listing conditions.

[4] Describe 3 serum tests for HIV

- A screening CBC and CD4 count are the place to start, but you still need to send for serology!!!
- Absolute lymphocyte count between 1000 and 2000 cells/ μ L appears to correlate with immunosuppression
- CD4 count below 200!
- Routine HIV antibody testing may be negative for several weeks or even months after exposure
- The diagnosis of acute HIV infection is confirmed with:
 - presence of high titers of viral RNA and a negative antibody screen.
 - Assay reactivity is dynamic; a plasma RNA test will detect HIV infection approximately 1 week before the ability to detect the p24 antigen and 12 days before antibodies to HIV develop (Table 124.1).
- A viral load test in the absence of symptoms of acute HIV infection is not recommended; false-positive results occur, and the test is costly.
- Confirmed cases of acute HIV infection should be referred immediately to a specialist for consideration of starting antiretrovirals.

Table 124.1: HIV Testing by Laboratory Stage

STAGE	LABORATORY MARKER				HIV STAGE
	RNA	p24 Antigen	Third-Generation Antibody (EIA)	Western Blot	
1	+	-	-	-	Acute HIV infection
2	+++	+	-	-	Acute HIV infection
3	+++	+/-	+	-	Seroconversion
4	+++	+/-	+	Intermediate	Seroconversion
5	++	+/-	+	+	Seroconversion
6	+ +++	+/-	+	+	Chronic HIV infection (all Western blot bands are positive, older antibody tests react)

EIA, Enzyme immunoassay.



[5] List 6 causes of respiratory infection in HIV?

TABLE 124.3 Differential Diagnosis of Respiratory Infections in HIV-Infected Patients by CD4⁺ Count

CD4 ⁺ COUNT AND STAGE	DIFFERENTIAL DIAGNOSIS
Present at any stage	Acute bronchitis
	Bacterial pneumonia
	Tuberculosis
>500 cells/μL	Bacterial pneumonia ^a
Early HIV infection	PCP ^a
	HHV-8–related Kaposi’s sarcoma
200–500 cells/μL	Bacterial pneumonia ^a
	PCP ^a
<200 cells/μL	Bacterial pneumonia ^a (consider bacteremia)
AIDS	PCP ^a
	<i>Histoplasma capsulatum</i> or <i>Coccidioides immitis</i> pneumonia
	<i>Cryptococcus neoformans</i> pneumonia
	Extrapulmonary or disseminated tuberculosis ^a
≤50 cells/μL	Bacterial pneumonia ^a
Advanced HIV infection	PCP ^a
	<i>Toxoplasma gondii</i> pneumonia
	Pulmonary Kaposi’s sarcoma
	<i>Histoplasma capsulatum</i> or <i>Coccidioides immitis</i> pneumonia
	<i>Mycobacterium avium</i> complex pneumonia
<i>HHV-8</i> , Human herpesvirus 8; <i>PCP</i> , <i>Pneumocystis jirovecii</i> pneumonia.	

See Table 124.4 for the pulmonary manifestations of disease in HIV patients.

[6] Describe the presentation and treatment of PCP pneumonia

Presentation:

- Gradual onset non productive cough / dyspnea / fever >2weeks
- Typical CD4 < 200



Diagnosis:

- Hypoxia w/ exercise (walk test)
- Elevated LDH
- CXR - bilateral retic / interstitial pattern (aka bat wing)
- CT Chest - ground glass

See figures 124.5 and 124.6 for x-ray and CT images of *Pneumocystis pneumonia*.

TABLE 124.5 Treatment of *Pneumocystis jiroveci* Pneumonia in Patients with HIV Infection

SEVERITY OF ILLNESS	PREFERRED THERAPY	ALTERNATIVE THERAPY
Moderate to severe	TMP-SMZ, IV; switch to oral administration after clinical improvement 21-day therapy	Pentamidine <i>or</i> Primaquine + clindamycin
Mild to moderate	TMP-SMZ	Dapsone + trimethoprim <i>or</i> Primaquine + clindamycin <i>or</i> Atovaquone

[7] Describe an approach to diagnosis and management of CNS infection in AIDS

Any HIV/AIDS patient w/ headaches, abnormal neuro exam, change in mental status needs labs, cultures, imaging and CSF sampling.

Imaging: CT with Contrast

Common problems:

- cryptococcal meningitis
- Toxoplasmosis
- primary central nervous system (CNS) lymphoma
- progressive multifocal leukoencephalopathy
- Neurosyphilis
- Cryptococcal meningitis

See Table 124.6 for an extended list.



Treatment:

- ART is first line!
 - Chemo for lymphoma
 - amphotericin B and flucytosine for Crypto
 - pyrimethamine and sulfadiazine for toxoplasma
 - Careful with steroid use and false negatives for CNS lymphoma
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[8] List 5 causes of odynophagia in HIV

Esophagitis is common in HIV/AIDS, think about it especially in patients with CD4 <100

1. CANDIDA
 2. Herpes simplex virus
 3. CMV
 4. Deep aphthous ulcers
 5. Kaposi Sarcoma
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-

[9] List 6 causes of diarrhea in the HIV patient

Bacteria

- Clostridium difficile
- Salmonella
- Shigella
- Campylobacter
- Yersinia spp

Parasites

- Cryptosporidium
- Isospora
- microsporidia.

Virus

- CMV
-
-

[10] Describe HAART therapy

Taken from uptodate

“OVERVIEW OF HIV REPLICATION — The life cycle of HIV can be broken down into 6 steps: (1) entry (binding and fusion), (2) reverse transcription, (3) integration, (4) replication (transcription and translation), (5) assembly, and (6) budding and maturation. The



identification and understanding of these processes have provided the basis for antiretroviral drug discovery.

- **Entry** – **Entry inhibitors: Maraviroc and enfuvirtide** are antiretroviral agents that inhibit binding and fusion, respectively. However, these agents are not commonly used for the treatment of HIV infection.
- **Reverse transcription** – **Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)** inhibit the process of reverse transcription. There are several agents in each of these classes that are widely used for the treatment of HIV.
- **Integration** – **Integrase strand transfer inhibitors (INSTIs)** inhibit the process of integration. In many countries, INSTIs are considered the preferred third agent (in combination with two nucleoside analogues) for treatment-naïve individuals.
- **Replication** – **There are no antiretroviral agents that inhibit this step of the replication cycle.**
- **Assembly** – **There are no antiretroviral agents that inhibit this step of the replication cycle.**
- **Budding and maturation** – **Protease inhibitors** are antiretroviral agents that inhibit the HIV protease enzyme, and therefore, prevent this final step in the replication cycle.

See figure 124.3 for a visual representation of the HIV replication cycle.

[11] Describe prophylaxis of opportunistic infections

CD4 count	Opportunistic Infection	Treatment
<200	PCP / PJP	Trimethoprim-Sulfamethoxazole DS x 1 tab daily
<100	Toxoplasmosis	Trimethoprim-Sulfamethoxazole DS x 1 tab daily
<50	Mycobacterium Avium Complex	Azithromycin / other macrolides



Wisecracks

[1] Risk stratify exposure to healthcare associated HIV and non-healthcare associated HIV.

Healthcare Associated Exposures

Needle stick injuries less than 1/300 get HIV. No recorded cases from intact skin.

Look at [MDCalc Needle Stick](#)

Factors increasing risk for needlestick injuries:

- depth of injury
- injury from a device visibly contaminated with the patient's blood
- needle stick into a vein or artery

Bodily fluids of concern include -

- Semen / vaginal secretion / any fluid contaminated with visible blood
- Potentially infectious body fluids include CSF / synovial / pleural / peritoneal / pericardial / amniotic
- NO CONCERN: vomitus, feces, nasal secretions, saliva, sputum, sweat, tears, and urine

Low-risk injuries:

- solid needles (eg, suture needles)
- Superficial injuries
- low-risk source patient or body fluid
- mucocutaneous exposures

High-risk injuries: include those involving

- hollow bore needles with visible blood
- percutaneous injury from a needle that was in an artery or vein of the source patient
- Mucocutaneous exposure involves large volumes of blood from a source patient with a plasma HIV viral load more than **1500 copies/ μ L**. Transmission is estimated to be as low as 0.09% (1/1000) for a splash of infectious body fluid to mucous membranes or broken skin.

“Preferred regimens for PEP mirror the treatment of HIV—three-drug combination therapy with a dual NRTI backbone plus an integrase strand transfer inhibitor. Common regimen is tenofovir-emtricitabine (Truvada), along with the INSTI raltegravir

If the exposed person is to receive PEP, the goal is to initiate therapy within 1 to 2 hours after exposure; the efficacy of PEP greatly decreases after 24 to 36 hours.

Follow-up HIV testing should occur at 6 weeks, 3 months, and 6 months.



If fourth-generation HIV antigen-antibody assays are used, HIV testing is performed at baseline, 6 weeks, and 4 months after exposure. Testing can be concluded 4 months after exposure as opposed to 6 months with other HIV antibody assays. An additional test at 12 months can be considered for those exposed to source patients co-infected with HIV and HCV.

Reevaluation of the patient within 72 hours of exposure is recommended. PEP should be continued for 28 days or until the source patient tests negative for HIV.”

Non-Healthcare Associated Exposures

Possible exposure include

1. sexual contact
2. injection drug use,
3. body fluids contact through broken skin or mucous membranes.

High risk exposures:

1. receptive anal intercourse
2. presence of genital ulcerative disease
3. receptive vaginal intercourse and insertive vaginal intercourse
4. IVDU w/ contaminated needle

“The CDC recommends PEP for persons presenting within 72 hours after an exposure to a source known to be HIV-positive if contact of body fluid contaminated with blood (including semen, vaginal secretions, rectal secretions, and breast milk) was made with the vagina, rectum, eye, mouth or other mucous membrane, or nonintact skin or by percutaneous injection.”

Most seroconversions will occur in the first 3 months after the exposure, these patients should be checked for HIV at 6 weeks, 12 weeks, and 6 months.

Check your local PEP guidelines

Call these professionals: <http://www.cfenet.ubc.ca/post-exposure-prophylaxis>

[2] What is Coccidiomycosis?

- Valley Fever!!! Fungal infection usually causing respiratory illness, possible extrapulmonary disease as well
- Think about in HIV/AIDS snowbirds (traveling patients) that visit the southwestern USA



[3] Name common ART agents and their adverse effects

Source: UpToDate

ART Drug Class	Adverse effects
ENTRY INHIBITORS Eg enfuvirtide	local cutaneous reactions
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS) Eg Tenofovir disoproxil fumarate	Mitochondrial toxicity: manifest as peripheral neuropathy, pancreatitis, lipoatrophy, and/or hepatic steatosis [5-7]. "black box" warnings for lactic acidosis
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)	(efavirenz and rilpivirine) can result in neurologic and psychiatric side effects.
INTEGRASE STRAND TRANSFER INHIBITORS (INSTIS) Eg Raltegravir	insomnia and dizziness / depression / suicide
PROTEASE INHIBITORS (PIS) Eg Darunavir	insulin resistance, hyperglycemia, diabetes, hyperlipidemia, lipodystrophy, hepatotoxicity, bleeding in patients with hemophilia, and PR interval prolongation