

HIV INFECTION AND ACQUIRED IMMUNODEFICIENCY SYNDROME

PATIENTS PRESENT TO ED AT VARIOUS STAGES OF INFECTION WITH A WIDE SPECTRUM OF ILLNESSES INVOLVING VIRTUALLY EVERY ORGAN SYSTEM

RISK FACTORS INCLUDE:

- Homosexuality/bisexuality
- Injecting drug use
- Heterosexual exposure receipt of blood transfusion prior to 1985
- Maternal HIV infection

PATHOPHYSIOLOGY:

- HIV is a cytopathic retrovirus that kills infected cells
- The virus is extremely labile and is neutralized easily
- There are two major subtypes (HIV-1 and HIV-2) → HIV-1 is the predominant subtype worldwide whereas HIV-2 is restricted primarily to Western Africa
- After infection, HIV selectively attacks host cells involved in immune function --. PRIMARILY CD4+ T cells → viral genome becomes permanently integrated into the host's genome
- IMMUNOLOGIC ABNORMALITIES EVENTUALLY OCCURS → LYMPHOPENIA, QUALITATIVE CD4 FUNCTION AND AUTOIMMUNE PHENOMENA
- Profound defects in cellular immunity ultimately result in development of a variety of OPPORTUNISTIC INFECTIONS AND NEOPLASMS
- Transmission occurs through semen, vaginal secretions, blood or blood products or breast milk/transplacental
 - NEVER THROUGH CASUAL CONTACT

NATURAL HISTORY AND CLINICAL STAGES OF INFECTION:

- Symptoms of acute HIV infection occur → ACUTE RETROVIRAL SYNDROME → reported in 50-90% patients, but the diagnosis is missed in up to 75% due to nonspecific presentation. Symptoms usually develop 2-14 days post exposure and manifest as fever (>90%), fatigue, pharyngitis, rash, headache and lymphadenopathy
- Seroconversion reflects detectable antibody response to HIV and usually occurs 3-8 weeks after infection → delays of up to 11 months occur
- Mean incubation time from exposure to the development of AIDS in untreated patients is estimated at ~ 8 years for adults and 2 years for kids <5
- Variables predictive of DISEASE STAGE:
 - VIRAL LOAD AND CD4 are best predictors → steeper decline in CD4 count and higher viral burden associated with rapid decline and poor outcome
 - CD4 count less than 200 and viral load of > 50,000 copies/mm3 is associated with increased risk of AIDS-defining illness

- The total lymphocyte count can be used to approximate CD4 count
→ total lymphocyte count < 1200 combined with symptoms is strongly associated with CD4 <200
- In age of HAART (anti-retroviral treatment) → age and malignancy are more predictive of prognosis
- As CD4 count DROPS BELOW 200 PER MM3, frequency of opportunistic infections increases dramatically
- AIDS is defined by the CDC as APPEARANCE OF ANY INDICATOR CONDITION (BELOW) OR A CD4 COUNT BELOW 200:

Table 149-1 Indicator Conditions for Case Definitions of Acquired Immunodeficiency Syndrome
Esophageal candidiasis
Cryptococcosis
Cryptosporidiosis
Cytomegalovirus retinitis
Herpes simplex virus
Kaposi sarcoma
Brain lymphoma
<i>Mycobacterium avium</i> complex infection
<i>Pneumocystis jirovecii</i> (<i>P. carinii</i>) pneumonia
Progressive multifocal leukoencephalopathy
Brain toxoplasmosis
HIV encephalopathy
HIV wasting syndrome
Disseminated histoplasmosis
Isosporiasis
Disseminated <i>Mycobacterium tuberculosis</i> disease
Recurrent <i>Salmonella</i> septicemia
<i>Added in 1993:</i>
CD4+ T-cell count of <200 cells/mm ³
Pulmonary tuberculosis
Recurrent bacterial pneumonia
Invasive cervical cancer

DIAGNOSIS:

STANDARD DIAGNOSTIC TESTS:

- Number of methods used for diagnosis:
 - Viral specific antigen detection
 - HIV nucleic acid detection
 - Viral culture
 - DETECTION OF ANTIBODIES TO HIV → most common method, used ELISA assay → 99% specific and 98.5% sensitive

- Diagnosis of acute HIV infection cannot be made with standard serologic tests because seroconversion usually has not yet occurred
→ DNA, RNA and antigens are used in this instance

BENEFITS OF EARLY DIAGNOSIS:

- Initiation of early and aggressive antiretroviral therapy, which can lead to IMMUNE RECONSTITUTION, PREVENTION OF VIRAL MUTATION AND DRUG RESISTANCE
- Can thus slow disease progression and improve long-term outcomes

CLINICAL FEATURES AND TREATMENT:

- Spectrum of disease caused by HIV varies greatly → symptomatic patients may have involvement of any organ system → makes ED evaluation and diagnosis difficult
- HISTORY → past and current medications, previous infections
- EXAMINATION → presence of thrush, evidence of temporal wasting and dementia

CONSTITUTIONAL SYMPTOMS AND FEBRILE ILLNESSES:

- Systemic symptoms such as fever, weight loss and malaise are common and account for majority of HIV-related ED presentations → MUST EXCLUDE SYSTEMIC INFECTION AND ACUTE LIFE-THREATENING MANIFESTATIONS SUCH AS MALIGNANCY
 - Consider LP in those with neurological signs or unexplained fever
- Patients with later stage HIV/AIDS may not manifest typical signs and laboratory findings associated with systemic infection
- Ill-appearing patients should receive fluid resuscitation, empiric antibiotics in the ED and admission for further evaluation

HIV STAGE AND CAUSES OF FEVER:

- In HIV patients without obvious localizing signs or symptoms → source of fever vary by stage of diseases
 - Patients with CD4 >500 have causes of fever similar to those in the non-immunocompromised population
 - Those with CD4 200-500 are most likely to have early bacterial respiratory infections
 - CD4 < 200 → most common causes of fever without obvious localizing findings include → PCP (P jiroveci), central line infection, infection with MAC or TB, CMV, drug fever
 - LESS COMMON CAUSES OF FEVER → endocarditis, lymphoma, Histoplasma capsulatum, Cryptococcus neoformans
- Disseminated MAC infection occurs in CD4 <100 → fever, night sweats, weight loss, ↑ALP → AFB found in stools or other body fluids → treatment reduces bacteraemia and improves symptoms but does not eradicate → clarithromycin plus rifampicin and ethambutol

- CMV is the most common cause of serious opportunistic viral disease in HIV patients → if disseminated it involves GI, pulmonary, CNS, eyes (RETINITIS) → treat with FOSCARNET OR GANCICLOVIR
- **THE MOST COMMON NONINFECTIOUS CAUSE OF FEVER IN HIV PATIENTS IS NEOPLASM AND DRUG FEVER** → NHL is the most frequent neoplasm and is characterised by high grade and rapidly growing lesions

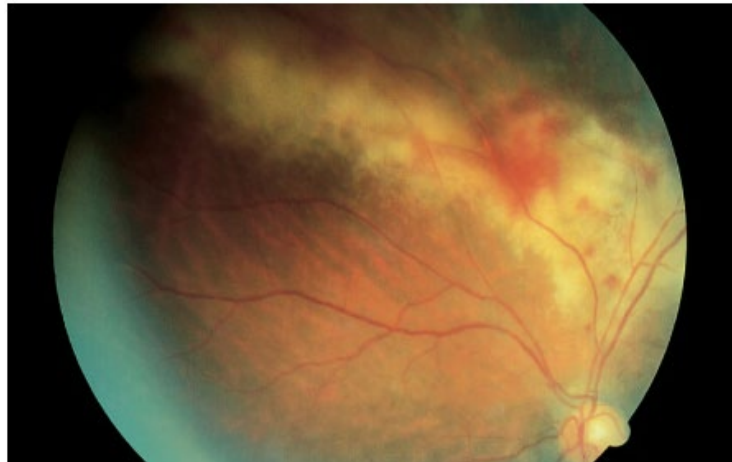
NEUROLOGIC COMPLICATIONS:

- CNS disease occurs in 90% patients with AIDS, and 10-20% of patients with HIV
- CNS disease is caused by variety of opportunistic infections, neoplasms as well as indirect and direct effects of HIV infection
- ED evaluation should include CT and LP → fever, meningismus, altered mental state are independent predictors of space-occupying lesions → for those with CD4 < 200, an aggressive approach is indicated
- CSF studies → opening pressures, cell count, glucose, protein, MCS, INDIA INK, toxoplasmosis and Cryptococcus antigen assays
- Most common causes of neurologic complications:
 - AIDS DEMENTIA
 - TOXOPLASMA GONDII INFECTION
 - CRYPTOCOCCUS NEOFORMANS INFECTION
 - With increased use of HAART, rates of CNS infection have declined significantly, but rates of AIDS dementia are unchanged
- AIDS DEMENTIA:
 - AIDS dementia complex (aka HIV encephalopathy) is a progressive disorder heralded by subtle impairment of recent memory, occurs in 10-15% of HIV patients, but rises to 30% in patients with CD4 < 100
 - Later phases characterised by obvious changes in mental status as well as aphasia and motor abnormalities
 - CT shows cortical atrophy and ventricular enlargement
- TOXOPLASMOSIS:
 - Most common cause of focal encephalitis in AIDS patients → headache, fever, focal neurological deficits common
 - Serologic tests NOT USEFUL because antibodies are prevalent in the general population, although findings of CSF antibodies is more helpful
 - CT findings → multiple subcortical lesions with predilection for basal ganglia. If contrast used → ring-enhancing lesions. DDX → lymphoma, fungal infection and cerebral TB
 - TREATMENT → PYRIMETHAMINE AND SULFADIAZINE WITH FOLINIC ACID. Steroids beneficial if significant oedema or mass effect
- CRYPTOCOCCUS:
 - CNS infection can produce focal cerebral lesions or diffuse meningoencephalitis → FEVER AND HEADACHE most commonly and presentation may be subtle
 - Diagnosis relies on findings of organisms in CSF → antigen testing, INDIA INK (60-80%), culture (95-100%)

- Treatment → IV AMPHOTERICIN B WITH ORAL FLUCYTOSINE FOR 14 DAYS followed by FLUCONAZOLE FOR 8 WEEKS ORALLY
- Other neurologic issues:
 - Bacterial meningitis
 - Histoplasmosis
 - CMV
 - Progressive multifocal leukoencephalopathy
 - HSV
 - Neurosyphilis
 - GB
 - CNS lymphoma

OPHTHALMOLOGIC COMPLICATIONS:

- 75% AIDS patients develop ocular complications → most commonly retinal microvasculopathy
- CMV RETINITIS:
 - CMV retinitis is the most frequent and serious ocular opportunistic infection and is the leading cause of blindness in AIDS patients
 - Intraocular ganciclovir implants or oral ganciclovir without implants
 - Causes changes in visual acuity, visual field cuts, scotoma, eye pain
 - White perivascular lesions characteristic



- HERPES ZOSTER OPHTHALMICUS:
 - Presents with paraesthesiae and discomfort in the distribution of cranial nerve V1 → followed by typical vesicles → complications include conjunctivitis, episcleritis, iritis, glaucoma and retinitis

PULMONARY COMPLICATIONS:

- MOST COMMON COMPLICATIONS ARE:
 - Bacterial CAP
 - PCP
 - TB
 - CMV infection
 - Cryptococcosis

- Histoplasmosis
- Neoplasms
- Most common cause of pneumonia in HIV-infected patients is PNEUMOCOCCUS
- CXR findings are useful in narrowing differential:

Table 149-3 Chest Radiographic Abnormalities: Differential Diagnosis in the Acquired Immunodeficiency Syndrome Patient	
Finding	Causes
Diffuse interstitial infiltration	<i>Pneumocystis jiroveci</i> (<i>P. carinii</i>) infection
	Cytomegalovirus infection
	<i>Mycobacterium tuberculosis</i> infection
	<i>M. avium-intracellulare</i> complex infection
	Histoplasmosis
	Coccidioidomycosis
Focal consolidation	Lymphoid interstitial pneumonitis
	Bacterial pneumonia
	<i>Mycoplasma pneumoniae</i> infection
	<i>P. jiroveci</i> infection
	<i>M. tuberculosis</i> infection
Nodular lesions	<i>M. avium-intracellulare</i> complex infection
	Kaposi sarcoma
	<i>M. tuberculosis</i> infection
	<i>M. avium-intracellulare</i> complex infection
	Fungal lesions
Cavitary lesions	Toxoplasmosis
	<i>P. jiroveci</i> infection
	<i>M. tuberculosis</i> infection
	Bacterial infection
	Fungal infection
Adenopathy	Kaposi sarcoma
	Lymphoma
	<i>M. tuberculosis</i> infection
	Cryptococcosis

- PNEUMOCYSTIS PNEUMONIA:
 - PCP is the most common opportunistic infection among AIDS patients
 - Causal agent is *P. jiroveci* (formerly *P. carinii*)
 - Approximately 70% acquire PCP at some time and it is often the initial opportunistic infection that defines AIDS
 - It is also the most common identifiable cause of death of AIDS patients
 - Classic presenting symptoms → fever, cough (nonproductive) and SOB → often insidious in onset
 - CXR shows diffuse interstitial infiltrates (negative radiographs in 15-20%)
 - Further diagnostic testing in those with suggestive symptoms and negative x-rays:
 - LDH (often ↑d)
 - ABG → hypoxaemia and ↑A-a gradient
 - PRESUMPTIVE DIAGNOSIS IN THOSE WITH HYPOXIA WITHOUT OTHER EXPLANATION
 - TREATMENT → BACTRIM (2 double strength tablets tds for three weeks)
 - PENTAMIDINE IS THE ALTERNATIVE
- TUBERCULOSIS:

- Incidence of TB in AIDS population is 200-500x general population
- Clinical manifestations of TB in HIV infected patients vary significantly according to severity of immunosuppression → with worsening immunosuppression typical and extrapulmonary manifestations are more common and classic upper lobe involvement and cavitary lesions are less common, particularly among patients with late-stage AIDS
- MAINTAIN HIGH INDEX OF SUSPICION FOR TB AMONG HIV-INFECTED PATIENTS WITH PULMONARY SYMPTOMS
- Treat with FOUR-DRUG REGIMEN as multi-drug resistance is an emerging concern
- BACTERIAL PNEUMONIA:
 - The most common pulmonary infection in HIV-infected patients
 - Common pathogens → pneumococcus, S aureus, Haemophilus influenzae
 - Classic findings in those with earlier-stage disease
 - Response to empiric treatment tends to be good
- FUNGAL PNEUMONIA AND OTHER LUNG DISORDERS:
 - Severely immunosuppressed are predisposed to DISSEMINATED FUNGAL INFECTIONS → C. neoformans and ASPERGILLUS FUMIGATUS
 - Kaposi sarcoma can occur
 - CMV/MAC unlikely unless CD4 <50

CARDIOVASCULAR COMPLICATIONS:

- Common in late stage disease but difficult to diagnose → CARDIOMYOPATHY, INFECTIOUS ENDOCARDITIS, PERICARDIAL EFFUSION, CHF

GASTROINTESTINAL COMPLICATIONS:

- Complications are common
- Therapy should include volume and electrolyte replacement and initiation of antibiotic treatment when appropriate
- ORAL CANDIDIASIS (THRUSH):
 - Common and frequently contribute to malnutrition
 - Potential clinical marker for viral load and degree of immunodeficiency → poor prognostic sign and is predictive of progression to AIDS
 - Managed symptomatically with NYSTATIN SUSPENSION
 - Amphotericin B reserved for severe cases



- **OESOPHAGEAL LESIONS:**
 - Can occur with Candida, HSV, CMV
 - Complaints of odynophagia or dysphagia indicative of oesophagitis
 - Develops with CD4 <100
 - Treatment is presumptive with ORAL FLUCONAZOLE
 - IV caspofungin or IV amphotericin when oral treatment fails
 - Treatment failure mandates gastroscopy
- **DIARRHOEA:**
 - Most frequent GI complaint with wide range of causes → bacteria, viral, parasitic, fungal (many cases a cause is never found)
 - IT IS A KNOWN COMPLICATION OF PROTEASE INHIBITORS
 - Send stool for ova, cysts, parasites and AFB as well as MCS
 - Bacterial infections generally follow a more acute and fulminant course whereas parasitic infections are more frequently indolent → CIPROFLOXACIN EMPIRICALLY
 - In those with end-stage diseases → consider disseminated MAC infection and CMV
 - About 1-15% of patients with late-stage AIDS experience severe, high-volume watery diarrhoea → AIDS ENTEROPATHY → treat electrolyte imbalances and administer OCTREOTIDE
- **OTHER GI COMPLAINTS:**
 - Hepatomegaly common
 - Coinfection with HBV
 - Anorectal disease is common → proctitis characterised by painful defecation, rectal discharge and tenesmus → caused by gonorrhoea, Chlamydia, HSV, treponema pallidum

RENAL COMPLICATIONS:

- Renal insufficiency may be secondary to pre-renal failure, drug nephrotoxicity or HIV-associated nephropathy
- RTA is common → hyperchloraemic metabolic acidosis
- INDINAVIR IS COMMON CAUSES OF NEPHROLITHIASIS

CUTANEOUS COMPLICATIONS:

- Generalized conditions are common → XEROSIS (dry skin), seborrhoeic dermatitis, pruritus → treat with emollients
- KAPOSI SARCOMA:
 - Appears more often in gay men than other risk groups
 - Consists of painless, raised, brown-black or purple papules that do not blanch
 - Therapy is indicated only for extensive, painful or cosmetically disfiguring lesions
- HERPES SIMPLEX:
 - Common and may be localised or systemic
 - Diagnosis and treatment are the same → IV acyclovir for extensive disease
- VARICELLA-ZOSTER:
 - Reactivation is more common, the clinical course is prolonged and complications are more frequent
 - Oral acyclovir, famciclovir or valaciclovir are usually sufficient
- SCABIES → occurs in ~20% of HIV infected individuals and is treated with permethrin cream
- HPV → cryotherapy, topical therapy or surgery for widespread problems

PSYCHIATRIC DISORDERS:

- Mood disorders are common prior to and after contracting HIV
- In ED, an aggressive search for organic causes of acute presentations should be sought
- Late-stage mania is closely associated with dementia and carries a poor prognosis

SEXUALLY TRANSMITTED DISEASES:

- STD are epidemiologically associated with HIV infection
- Ulcers provide vascular portals of entry for HIV → 3-5x increased incidence of HIV in those with ulcers
- Also increased in those with gonorrhoea and Chlamydia

IMMUNISATION OF THOSE WITH HIV:

- HIV-infected patients should NOT RECEIVE LIVE VIRUS OR LIVE BACTERIA → one exception is MMR, which does not have adverse effects
- KILLED VACCINES POSE NO DANGER TO IMMUNOSUPPRESSED PATIENTS
- Pneumococcal vaccine is recommended for all patients >2, because risk of invasive infection is 50-100 x greater

Table 149-4 Immunization Recommendations for Adult Human Immunodeficiency Virus–Infected Patients

Vaccine	Adult Recommendation
Tetanus-diphtheria toxoid	Every 10 y or, if injured, after 5 y
Measles-mumps-rubella	Not if immunocompromised (low CD4+ count*)
Meningococcal	One or more doses
Pneumococcal	One dose
Influenza (inactivated)	One dose annually
Hepatitis A	Two doses
Hepatitis B	Three doses
Varicella	Not if immunocompromised (low CD4+ count*)

ANTIRETROVIRAL THERAPY:

- Initial regimen → two nucleoside reverse transcriptase inhibitors plus one or two protease inhibitors or one non-nucleoside reverse transcriptase inhibitors
- Current consensus recommends mandatory treatment for HIV-infected patients with CD4 counts below 350 or with a history of AIDS-defining illness

PRECAUTIONS FOR HEALTH CARE WORKERS:

UNIVERSAL PRECAUTIONS → consider all contacts with blood or body fluids to be potentially infectious. The risk of acquiring HIV through occupational exposure is low. The likelihood of contracting AIDS after a parenteral exposure has been estimated at 0.32%, for mucocutaneous exposure → 0.09%.

POST-EXPOSURE PROPHYLAXIS:

- AZT prophylaxis was associated with a 79% reduction in disease transmission
- Risks for seroconversion include:
 - Deep injury
 - Visible blood on the injuring device
 - Needle placement in a vein or an artery of the source patient
 - A source patient with late-stage HIV infection
- Expanded regimen is recommended for high risk cases
- PEP treatment duration is 4 weeks → GI and constitutional side effects are common