# HIV: The *Tour de Force* of Virology

**EPIDEMIOLOGY**

Three groups of **HIV-1**

- M: main
  - Divided into clades (a subtype)
- N: (non-M + O)
- O: outlier

In North America: predominant strain is HIV-1 Group M Clade B

**HIV-2:** slower progression than HIV-1 and found in West Africa

**STRUCTURE**

Enveloped RNA retrovirus

- **Pol:** encodes the RT, protease, and integrase
- **Env:** the precursor to GP120
- **Gag:** structural proteins of the viral capsid

**REPLICATION**

Attachment of GP120 to CD4 *and* CCR5 *or* CXCR4 → fusion and release into cytoplasm (requires GP41) → generation of dsDNA via prepackaged RT → integration via **integrase** → host transcription and translation → expression of HIV polyprotein → autoproteolysis and liberation of protease → cleavage of other proteins → viral packaging → budding and release

Within an individual, innumerable quasispecies exist due to small genome, RT error rate (high), and rapid replication.

**PATHOGENESIS**

HIV is transported from site of entry to regional node by dendritic cells → entry into CD4+ cells (mainly R5 tropic → shift to R4 tropic in late infection) → dissemination (primary viremia; 4 – 11 d.): CNS, RES, GALT [this is an asymptomatic period] → depletion of GI CD4+ lymphocytes → lose 80% of CD4+ cells within 2 – 3 wks

→ **massive immune dysfunction (involves all cell types)**

- Loss of lymphoid architecture (cellular depletion)
- CD8+ and NK cell dysfunction
- B cell dysfunction + hypergammaglobulinemia
- Neutrophil dysfunction
- Reservoir in monocytes and macrophages (+microglial cells)

→ **paradoxical immune activation**
AMI: Abs develop once set point of viral load is reached. These are **non-neutralizing!**
CMI: Loss of CD4+ and CD8+ cells, particularly in GI mucosa. Bacterial invasion leads to increased immune activation.

→ **generation of the latent reservoir**
HIV integrates as a provirus in the CD4+ genome

**TRANSMISSION**
Sexual
Intrauterine, delivery, breast-feeding
IV drug use
Transfusion and Transplant
Errors: needle-stick

**PRIMARY HIV : THE ACUTE RETROVIRAL SYNDROME**
This is a self-limited flu-like syndrome
Onset is 2 – 6 wks after infection ; duration is 1 -3 wks with spontaneous resolution
Represents rapid replication and peak plasma viral load

Presentation: fever, fatigue, rash (macular), adenopathy, pharyngitis, myalgia, arthralgia, ngith sweats, thrombocytopenia, leucopenia, diarrhea, **aseptic meningitis**, transaminitis, oral and genital ulcers

Rash: distinguishes primary HIV from influenza and mononucleosis
Aseptic Meningitis: consider HIV when this is seen

The pt. may also have opportunistic infections during this stage!

**Dx**: use RT-PCR for viral RNA! The ELISA will be negative (window period).

**THE STANDARD WORKUP FOR PRIMARY HIV**
CBC
Renal Function
LFTs
CD4+ enumeration, viral load
RPR, Chlamydia, gonococcus
PPD
HCV, HBV, HAV, Toxoplasma serology
Fasting lipids and glucose
Anal PAP

**CHRONIC ASYMPTOMATIC INFECTION**
Progressive drop in CD4+ and immune activation

**CHRONIC SYMPTOMATIC INFECTION**
The onset of opportunistic infection is **preceded** by constitutional symptoms + some 'red flag' infections:
Weight loss + fatigue + generalized adenopathy + night sweats
SOME UNUSUAL INFECTIONS:
Oral candidiasis + herpes zoster + oral hairy leukoplakia (EBV) + seborrheic dermatitis + psoriasis + eczema herpeticum
Look on the skin and oral mucosa!

**AIDS**
CD4+ < 200 cells per mL OR presence of indicator conditions + positive HIV serology
Characterized by progressive opportunistic infections and wasting

Pulmonary: PCP pneumonia, *M. tb*, Hc, recurrent bacterial pneumonia
GI: esophagitis (candida, HSV, CMV), enterocolitis, procitis, anal carcinoma (HPV)
Renal: HIV nephropathy
CNS: toxoplasmosis, lymphoma, PML, meningitis (cryptococcal, TB, CMV, HSV), HIV dementia, neurosyphilis
PNS: polyneuropathy
Dermatologic: generalized HSV, recurrent zoster, Molluscum contagiosum, KS, SCC
Eye: CMV retinitis, HIV retinopathy
CV: HIV cardiomyopathy
Heme: thrombocytopenia, lymphoma, myelosuppression
GU: HPV, HSV, syphilis, *Chlamydia*, Gonorrhea, cervical carcinoma

Oppotunistic infections may be unmasked by immune reconstitution

**PROPHYLAXIS of OPPORTUNISTIC INFECTIONS and CANCER**

CD4+ < 200 : PCP
< 100 : toxoplasmosis, cryptococcal meningitis, cryptosporidium
< 50 : disseminated atypical Mycobacterial disease, CMV, CNS lymphoma

*Prophylactic ABx*
PCP: TMP-SMX
Toxoplasmosis: TMP-SMX
Atypical mycobacteria: Azithromycin (weekly)

**Vaccinations**: Pneumovax, HepA, HepB, Influenza, DTaP
**Screening:** PAP (cervical and anal), PPD

**DIAGNOSIS**

**The Standard Test**

STEP 1: High sensitivity screening ELISA

If non-reactive: HIV –ve

If reactive: repeat 2x (three total tests)

If at least one reactive: proceed to STEP 2

STEP 2: High specificity confirmatory Western Blot

Requires two bands from: p24, GP41, GP120/160

No bands: require additional testing for HIV –ve diagnosis

**The Rapid Test**: STEP 1 of standard test

Window period (false negatives): 22 d. – 6 mos.

Thus, serologic testing is done at exposure, 12 wks, and 6 mos.

**RNA Viral Load:** detects circulating viral titre

**CD4+ Count**: flow cytometry

**Drug Resistance**

**Tropism Assay**: determine efficacy of the Maraviroc (CCR5 receptor antagonist)

**GUIDELINES for INITIATION OF ANTIRETROVIRAL THERAPY**

AIDS-defining illness : e.g. recurrent zoster, thrush, KS, PCP

CD4+ count < 350 cells/mL

Pregnant females

HIV Nephropathy

HBV co-infection

Post-Exposure Prophylaxis (PEP) : 3-drug regimen to 4 wks.

Neonate with HIV exposure