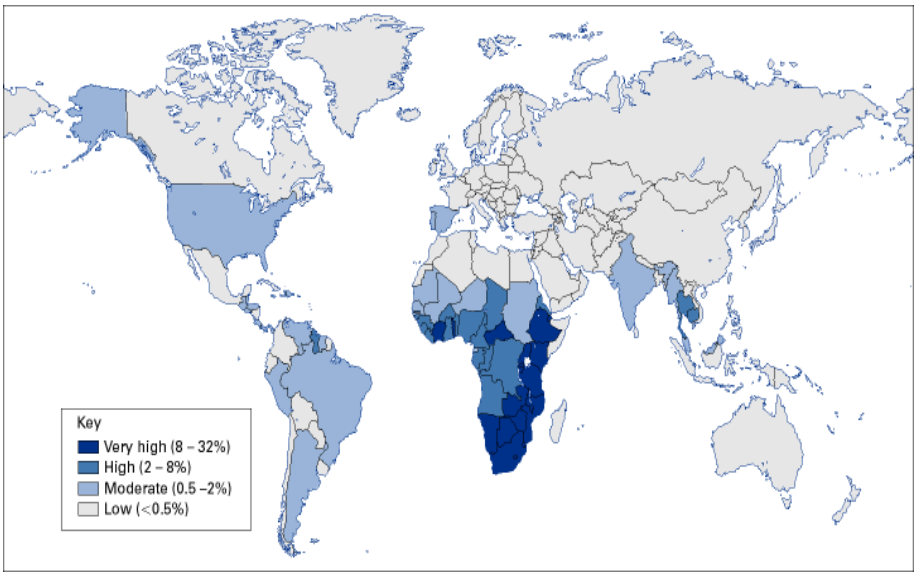
Human Immunodeficiency Virus (HIV)

HIV is a retrovirus that was first identified in 1983:

- Initially named LIV (lymphadenopathy associated virus), then human T-lymphotropic viruses-III (HTLV-III) finally HIV-I and causes AIDS (acquired immune deficiency syndrome) related disease in most parts of the world.
- In 1985 HIV-2 was identified in AIDS patients with West African connections, and is currently still uncommon outside that region.
- HIV binds to CD4 receptors on helper T-lymphocytes, monocytes, macrophages, and neural cells. CD4 cells migrate to the lymphoid tissue where the virus replicates and then infects new CD4+ cells. Depletion or impaired CD4 cells predisposes to immunodeficiency.
- The number of circulating viruses (viral load) predicts progression to AIDS.

Epidemiology



- World prevalence ~40 million.
- 95% cases are in developing countries, mainly Sub-Saharan Africa and South-East Asia.
- 75% sexually transmitted.
- High Risk:
  - Homo-/bi-sexuals,
  - IVDU,
  - Infants of HIV+ mothers,
  - Post-Txf (1980-85),
  - Haemophiliacs,
  - Healthcare workers,
  - W.African patients.

Diagnosis

- Based on detecting anti-HIV antibodies in serum.
- Acute infection: presence of P24 antigen or HIV RNA by PCR and precedes the appearance of IgM and IgG (within 3 months).
- Asymptomatic period: high titres of IgG to core and envelope proteins.
- Increasing immunodeficiency: ↓IgG titre to core protein, and P24 antigenaemia recurs.
- AIDS diagnosis: evidence of HIV infection and presence of indicator disease/s.

Stages of HIV infection

Group 1 – Acute infection, seroconversion illness:

- 1-6wks post-infection. 20-60% present with symptoms at this time.
- Common symptoms are a glandular fever type illness with fever, malaise, myalgia, pharyngitis, headaches, diarrhoea, neuralgia or neuropathy, lymphadenopathy and/or a maculopapular rash. Rarely meningoencephalitis. Acute infection may be asymptomatic.
- Although antibody tests are negative, viral P24 antigen and HIV RNA levels are elevated.
- CD4 count 500-1000.

Group 2 - Asymptomatic infection:

- Virus levels are low, although replication continues slowly.
- CD4 count 200-1000
- This situation may persist many years.

Group 3 - Persistent generalised lymphadenopathy (PGL):

- LN >1cm at 2 extra-inguinal sites, persisting for ≥3mo, not due to other cause.
- CD4 count 200-500

Group 4 - Symptomatic infection:

- A: Non-specific constitutional symptoms develop: fever, night sweats, diarrhoea, wt loss.
- B: Neurological disease
- C: Secondary opportunistic infections
- D: Secondary cancers
- E: Other conditions
- There may also be,.
- ARC (AIDS related complex) – prodrome to AIDS – 'A' symptoms ± minor opportunistic infections e.g. oral candida, oral hairy leukoplakia, herpes zoster, recurrent herpes simplex, seborrhoeic dermatitis, tinea infections

AIDS:

- Severe immunodeficiency, i.e. HIV+ & having Group 4B-4D conditions.

1993 CDC Classification system

Based on clinical category and CD4 count:

Clinical categories

- A: Documented HIV+, asymptomatic, PGL; or acute HIV infection (Grps 1-3 above)
- B: Symptomatic disease, conditions not listed in clinical category C, including those:
    - attributed to HIV infection or indicative of a defect in cell-mediated immunity; or,
    - considered to have a clinical course or Mx that is complicated by HIV infection.
    - For example: bacillary angiomatosis; persistent or recurrent oral or vaginal candidiasis; moderate to severe cervical dysplasia; constitutional symptoms such as fever (38.5°C) or diarrhoea > one month; oral hairy leukoplakia; herpes zoster (> 1 episode or > one dermatome); ITP; listeriosis; PID; and peripheral neuropathy
- C: AIDS indicator condition (see below).
    - Candidiasis: trachea, LRT, oesophagus
    - Cervical carcinoma: invasive
    - Coccidioidomycosis: disseminated or extrapulmonary
    - Cryptococcosis: extrapulmonary
    - Cryptosporidiosis: intestinal >1mo
    - CMV (other than liver, spleen or LN)
    - CMV retinitis (with loss of vision)
    - Encephalopathy: HIV-related
    - HSV: ulcers >1mo; or bronchitis, pneumonitis or oesophagitis
    - Histoplasmosis: disseminated or extrapulmonary
    - Isosporiasis: intestinal >1 mo
    - Kaposi's sarcoma
    - Lymphoma: Burkitt's, immunoblastic, 1° brain
    - MAC, M. kansasii or other mycobacterium: disseminated or extrapulmonary
    - TB: any site
    - Pneumocystis carinii pneumonia
    - Pneumonia, recurrent
    - Progressive multifocal leucoencephalopathy
    - Salmonella septicemia, recurrent
    - Toxoplasmosis of brain
    - Wasting syndrome due to HIV

CD4 counts

1. CD4 count ≥500 cells/mm3 or ≥29%
2. CD4 count 200-499 cells/mm3 or 14%-28%
3. CD4 count <200 cells/mm3 or <14%

Thus any individual with stage A3, B3, C1, C2, or C3 infection has AIDS by the CDC definitions.

Investigations

- Detection of HIV antibody: ELISA, Western blot to p24, Gp41 or Gp120/160.
- Assessment of viral load: detection of virus or viral antigen: HIV RNA or bDNA assay
- FBC: anaemia, thrombocytopenia, lymphocytopenia with reduced CD4 cell count
- Raised ESR
- Assessment of other infections: e.g. TB, hepatitis B, CMV, toxoplasma, syphilis, varicella
- Screening for co-existing STDs
- Baseline chest x-ray, CT brain and cervical smear
- Consider LP, ABG, bronchoscopy, G6PD (antivirals may cause haemolysis if deficient)

Monitoring HIV infection

- Clinical assessment.
- Monitoring the CD4 count.
- Plasma HIV RNA levels (viral load) strongly predict progression to AIDS and death, whatever the CD4 count.
- Clinical benefit from anti-HIV agents depends on improving the CD4 count AND decreasing viral load by at least 70%. This is now possible with combination therapy.

Management

Prevention of spread

- Universal precautions
- Safe sex, prevention of other STDs
- Not sharing needles/Needle exchange
- HIV testing of pregnant women & LSCS for delivery
- Reduce unnecessary blood transfusions
- Education

Antiviral Therapy

- Prevention
  - Post-exposure prophylaxis (PEP) from significant body fluid exposure from known HIV+ source *(see Needlestick/Body Fluid Exposure topic for occupational exposure)*
    - High-risk source patient: Known HIV+,gay/bisex men, sex workers, IVDU, incarceration, country with high HIV, partners of such groups
    - Receptive anal intercourse: 1-30% risk
    - Insertive anal or receptive vaginal intercourse: 0.1-10% risk
    - Oral intercourse: "very low risk" but not zero risk
    - Needle sharing with IVDU: 0.67% per needle-sharing contact
  - Treat HIV+ mother pre-partum & neonate post-partum & avoid BF
- Primary treatment (Highly Active Anti-Retroviral Therapy – HAART)
  - The best time to start treatment is debated. May be started if:
    - Seroconversion illness (no proven benefit)
    - Symptomatic
    - Asymptomatic but CD4 count<500

- Triple therapy is recommended. 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a protease inhibitor or a non-NRTI.
  - **NRTIs:** **zidovudine**, **abacavir**, **didanosine**, **emtricitabine**, **lamivudine**, **stavudine**, **tenofovir** and **zalcitabine**. **Rel CI:** liver/renal disease, pregnancy. **SE:** GIT upset, headaches and ↓Hb, ↓neut, ↓plt.
  - **Protease inhibitors:** **indinavir**, **lopinavir**, **nelfinavir**, **ritonavir**, **saquinavir**. Met. by CytP450 enzymes. **Rel CI:** DM, liver/renal impairment, haemophilia, pregnancy. **SE:** ↑BSL, GIT upset, headaches, lipodystrophy syndrome (fat redistribution, insulin resistance and dyslipidaemia)
  - **Non-NRTI:** **efavirenz**, **nevirapine**. SE: rash (incl SJS), occ. hepatitis, ↑chol.
  - **Fusion or entry inhibitors:** enfuvirtide

Treat Complications – see below

Prophylaxis against infective complications

- HBV, pneumococcal, Hib (± influenza and HAV) immunisation
- Avoid BCG vaccination, varicella, yellow fever, oral typhoid or live oral polio vaccines.
- Primary and secondary prophylaxis – see individual conditions below.

Complications of HIV Infection

Pulmonary complications – PCP, TB, KS, NHL

Pneumocystis carinii pneumonia

- Hallmark disease (60% AIDS) though ↓ since antiretrovirals & primary prophylaxis
- Most have CD4<200 and mainly at <100/mm3.
- Presentation: Insidious SOB, dry cough, fever, malaise, weight loss and chest pain. N.B. **not** haemoptysis. Exam: few signs in the chest - few crepitations, occ pneumothorax.
- Invs: CXR (bilateral perihilar interstitial shadowing), SaO_2<95% at rest or ↓ on exercise, ↓pO_2, sputum (rarely shows orgs), bronchial washing culture better.
- Rx: Initially: O_2, high dose **cotrimoxazole** IV/PO q6-8h x 21d. Other options: IV pentamidine or PO **dapsone**/**trimethoprim**.
- Maint/2° prophylaxis: low dose **cotrimoxazole** OD or IV/INH **pentamidine** q2-4wkly
- 1° prophylaxis: As for Maint/2° prophylaxis when CD4<200.

Bacterial pneumonia

- Commonest pneumococcus, H. influenzae and Moraxella catarrhalis. If advanced: Staph. aureus, Klebsiella spp and other gram-negative rods.

Fungal infections

- E.g. Cryptococcus spp. Rx: IV **amphotericin B**.

Tuberculosis

- CD4 200-400. Usually reactivation. CXR like PCP. Highly infectious & drug-resistant.
- Tuberculosis - **isoniazid** considered if low CD4s (<300) or a positive skin test.

Karposi's sarcoma

- Usually with skin lesions. Commonest cause of pleural effusion.

Mycobacterium avium complex

- Usually CD4<50 (1° prophylaxis of clarithromycin can be offered below this)
- Presentation: fever, night sweats, wt loss, diarrhoea, abdo pain, anaemia or liver dysfn.
- Inv: blood, bone marrow culture. Rx: e.g. **clarithromycin**, **ethambutol**, **rifampicin**, and **streptomycin** ± **amikacin**.

CNS complications

Cerebral toxoplasmosis

- Common when CD4<200 usually reactivation → multiple cerebral lesions.
- Presentation: focal neurological disturbances, headache, confusion, fever, and seizures.
- Invs: CT (mass + ring of contrast enhancement and associated oedema), MRI.
- Rx: **sulfadiazine** and **pyrimethamine** + **folinic acid** for 6/52, then at half dose for 2° prophylaxis. Steroids for cerebral oedema. Offer 1° prophylaxis to Tox+ pts if CD4<100.

Cryptococcal meningitis

- Presentation: headache, vomiting and slight fever. Neurological signs are not prominent. Occasionally psychiatric symptoms, convulsions, cranial nerve palsies or truncal ataxia.
- Invs: LP (India ink).
- Rx: **Amphotericin B** ± **5-flucytosine** or **fluconazole** if mild case for 2-4wks.
- 2° prophylaxis with oral **fluconazole**.

HIV encephalopathy/AIDS Dementia Complex

- Presentation: depression, slowed mentation, lethargy, demetia. ↑motor problems →↓ADLs. Parkinsonian. Exam: may have incoordination, weakness, hyperreflexia and ↑plantars.
- Invs: MRI (↓grey matter in cortex and basal ganglia).
- Rx: early HAART

Progressive multifocal leucoencephalopathy

- Progressive demyelinating condition 2° to JC virus → focal neurological signs, changes in personality and ataxia. The diagnosis is by MRI. No specific Rx. Fatal <6mo.

Peripheral neuropathy and myelopathy

- Distal symmetrical neuropathy affecting both sensory and motor systems. May cause postural hypotension, diarrhoea, impotence, impaired sweating and bladder dysfunction.

Ocular disease

CMV retinitis

- Commonly reactivates if CD4<50 unless on prophylaxis (ganciclovir) → blinding retinitis.
- Presentation: blurred vision, partial unilateral visual loss, floaters or flashing lights. Typically irregular retinal pallor + haemorrhages (perivascular starting peripherally)
- Rx IV **ganciclovir** **SE:** severe neutropenia and thrombocytopenia.

Tumours

Kaposi's sarcoma

- Presentation: typically multiple ecchymotic skin nodules, macules or papules, esp on face early, also mucosal surfaces e.g. hard palate. Visceral disease often of lungs and GIT.
- Rx: Radiotherapy, cryotherapy or intralesional vinblastine or pegylated liposomal doxorubicin or liposomal daunorubicin.

Non-Hodgkin's lymphoma

- Most tumours are extranodal. 50% associated with EBV & are more aggressive. CNS sites are common and have high mortality, presenting with symptoms and signs of SOL.

Primary CNS lymphoma

GIT Disease

Oesophageal candidiasis

- Presentation: AIDS-defining condition. Retrosternal pain on swallowing. Rx: **fluconazole**.

Other infective

- E.g. Non-viral GE (e.g. salmonella, giardia, campylobacter, shigella), oral hairy leukoplakia, cryptosporidium, clostridium difficile, etc .