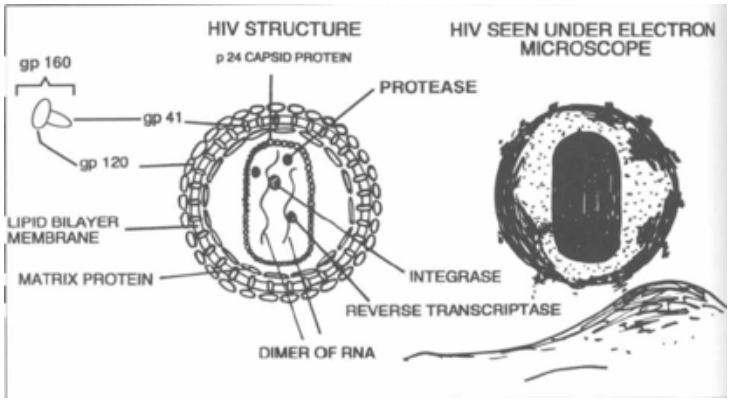
General Introduction to Retroviruses

- found in all vertebrates (can infect both animals and humans)
- transmission may be either: -
  Horizontal or Vertical
  either as free viral particle or through cell-cell contact

Overview

- Enveloped virus with lipid bilayer and viral spike glycoproteins.
- Have outer matrix protein and inner core capsid containing viral genome.



Classification

- There are many types of retroviruses. We will discuss HIV which is an example of the genus Lentivirus

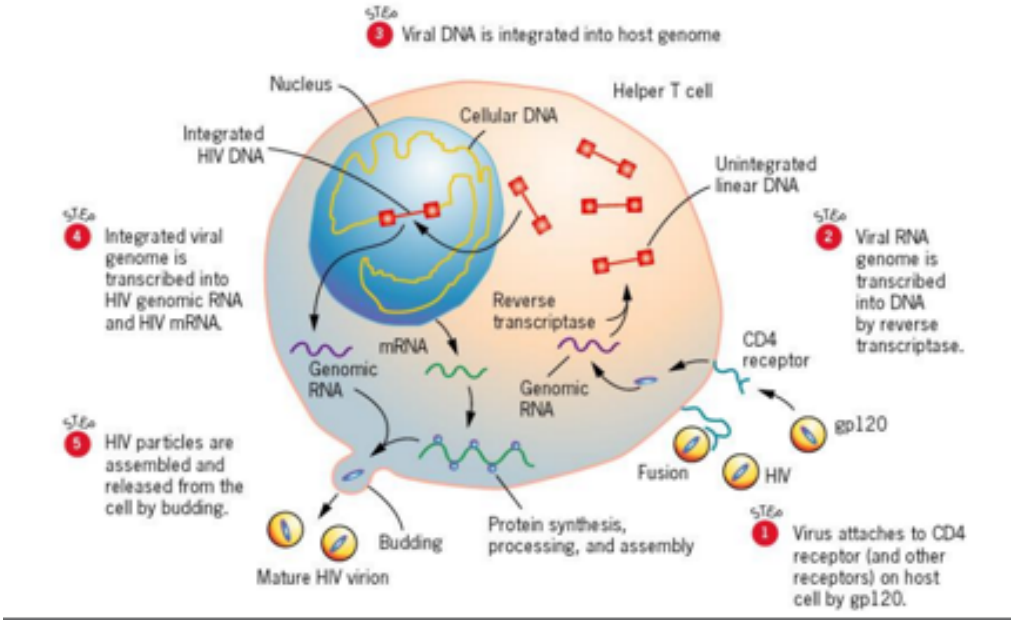
HIV

- Human Immunodeficiency Virus
- HIV-1 may have spread to humans over 100 years ago
- The likely source was primate-to-human transmission through bites or blood exposure, with chimpanzees being the most likely candidate for HIV-1 transmission to humans.
- HIV was identified as the causative organism of AIDS in 1981
- HIV-1 isolated in 1984, and HIV-2 in 1986
- Belong to the lentivirus subfamily of the retroviridae
- Enveloped, +ve ss RNA virus (two copies)
- HIV-2 shares 40% nucleotide homology with HIV-1

- Genome (like all other retroviruses) consists of 3 main proteins:
  1. gag core proteins - *Matrix* and *Capsid*
  2. pol - *protease*
  3. env – *enevelope*

  plus, other regulatory genes
- Family :- retroviridae
- RNA virus
- Long incubation period (10 -15 years) => patient is labelled as HIV infected (when CD 4 count falls below 200 => AIDS patient thus, prone to all types of opportunistic infections)
- Special characteristic on the level of genome :- 2 copies of single stranded +ve sense RNA
- Envelope :- gp160 (gp120:outer membrane part, gp41: transmembrane part)
- Replication :-
  1. Glycoprotein (gp120) binds its receptor on T cells (CD 4)
  2. Falls off opening the way for gp41 to bind chemokine co-receptors CCR5 & CXCR4 and enters the cell via fusion
  3. When the virus reaches the cytoplasm uncoating starts releasing the 2 copies of +ve sense single stranded RNA
  4. RNA genome is then reverse transcribed via reverse transcriptase forming RNA-DNA intermediate where RNA strand dissociates by RNAse-H (part of the reverse transcriptase enzyme) keeping the DNA strand
  5. The DNA becomes double stranded with sticky ends to integrate with the cell genome via integrase enzyme to become a provirus
  6. The cellular machinery undergoes transcription now giving an mRNA (+ve sense RNA)
  7. This mRNA leaves the nucleus into the cytoplasm
     part of which will go to the ribosomes to make polyproteins which will further be broken down by proteases to give individual proteins and itself becomes assembled into a new virus (which can have 2 copies of viral mRNA or a copy from the virus with a copy for the human – a method of

transformation and one of the reasons why human and retroviral genomes are similar in non-coding sequences)



- Risk factors

  The following factors increase the risk of MTCT (mother to child transmission)

  1. Higher levels of maternal viremia.
  2. Lower maternal CD4 count.
  3. Primary HIV Infection occurring during pregnancy.
  4. Co-existing other sexually transmitted disease.
  5. Invasive intrapartum procedures, eg fetal scalp electrodes, forceps, ventouse.
  6. Rupture of membranes.
  7. Vaginal delivery.
  8. Advanced maternal age.
  9. Preterm birth.

- Modes of transmission :-

  1. Sexual transmission – most common especially among male homosexuals
  2. Blood and blood products
  3. Vertical Transmission

  • perinatal (during pregnancy) in most cases

• transmission rate 15 - 25%
• Caesarean section has a role in reduction of transmission in some cases
• transmission can be decreased by approximately 2/3 by administration of antiretrovirals
– to the mother in pregnancy (orally)
– in labour (iv and orally)
– to the infant for the first 4 weeks (orally) - this is post exposure prophylaxis

4. Other less common modes of transmission include accidental needle stick or sharps injuries in health-care workers and splashes of contaminated material onto mucous membranes or nonintact skin
5. HIV infection from a transfusion is less than one in 1.5 million.

• Casual contact (shaking hands, sneezing, coughing, sharing drinking glasses, sharing a toilet, exposure to saliva from social kissing, etc.) does not pose a threat for HIV infection

- Antenatal testing
• Unlinked testing indicated that only 25-50% of HIV+ women were identified
• Routine anti-HIV testing introduced Rotunda January 1998
• >90% of cases of paediatric HIV are due to vertical transmission
• Prevention is dependent on identification of infected mothers and giving them antiretroviral therapy, with post-exposure prophylaxis to the infant
• caesarean section in selected cases (not always helpful)

- HIV Staging
1. Stage 1 = Acute stage of illness
   Characterized by flu-like symptoms with CD4 count above 500
2. Stage 2 of disease occurs when the CD4 count is between 200-500

but again there are no AIDS-defining conditions present.

3. Stage 3 disease is synonymous with AIDS and is the most severe stage
   CD4 falls below 200 here as we said before
   Vulnerable to opportunistic infections (all latent viruses can be reactivated in this stage)
   The most frequent opportunistic tumor, Kaposi's sarcoma, associated with a human herpes virus 8 (HHV-8)
   Cervical cancer, Pneumocystis jirovecii pneumonia and candidiasis could also affect the patient

- Clinical manifestations
  1. Acute infection: 2-4 weeks up to 3 months after infection with HIV, "the worst flu ever." It is called primary HIV infection (caused by the body's natural response to the HIV infection). Symptoms: fatigue, sore throat, enlarged lymph nodes, and loss of appetite. Orally: thrush or mouth sores(fungal). Fever, neck stiffness, headache, and rash may occur
  2. Clinical latency: (asymptomatic HIV infection or chronic HIV infection) During this phase, HIV reproduces at very low levels. No symptoms (last up to eight years or longer). Pts are contagious to others. Constitutional symptoms such as fatigue and other nonspecific symptoms develop.
  3. AIDS: CD4 cells <200 (Normal CD4 500- 1,600) Vulnerable to opportunistic infections. AIDS pts survive about 3 yrs without treatment. Once someone has a dangerous opportunistic infection, life expectancy falls to about one year.

- Other Manifestations
  • It is now recognized that HIV-infected patients may develop a number of manifestations that are not explained by opportunistic infections or tumors.
  • The most frequent neurological disorder is AIDS encephalopathy which is seen in two thirds of cases.

• Other manifestations include characteristic skin eruptions and persistent diarrhoea.

- HIV Pathogenesis

  • The profound immunosuppression seen in AIDS is due to the depletion of T4 helper lymphocytes. (500-1600/mm3)

  • Acute infection: – In the immediate period following exposure, HIV is present at a high level in the blood (as detected by HIV Antigen and HIV-RNA assays). – Rapid fall in the CD4 count→ viral set point (low level)→ CD4 count begins to increase (CD4 cells killed by HIV are replaced efficiently), but not to pre-infection levels. Virus suppression but not elimination.

  • Clinical latency: – Undetectable viral load and a healthy CD4 cell count without the use of medication for a time – Toward the middle and end of this period, the viral load begins to rise and the CD4 cell count begins to drop

  • Eventually, the immune system succumbs and AIDS develop when killed CD4 cells can no longer be replaced.

- Diagnosis

  1. Screening assay - ELISA are the most frequently used screening assays
  2. Confirmatory assay - Western blot is regarded as the gold standard for serological diagnosis
     - p24 antibody is usually present but may be absent in the later stages of HIV infection
     - The most important antibodies are those against the envelope glycoproteins gp120, gp160, and gp41

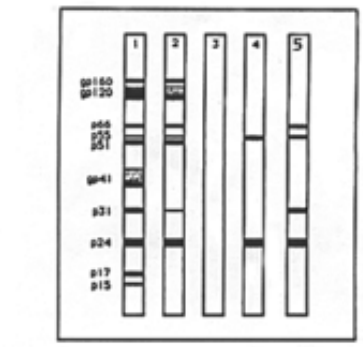


Figure:

Examples of reactions by an HIV-1 Western blot:

1. Positive control (strong)
2. Positive control (weak)
3. Negative control
4. Indeterminate profile
5. Indeterminate profile (highly suggestive)

  3. Viral load and PCR – used for both diagnosis and monitoring effectivity of treatment

4. New fourth-generation tests combine viral detection and antibody detection. Viral detection is done by testing for a component of the virus known as p24 antigen measured by testing the amount of viral RNA in the blood
5. Other diagnostic tests
   - Rapid HIV tests (such as Clearview) were developed that could provide results during the initial visit
   - Self-test or home-test, the person buys a kit (for example, OraQuick), swabs the inside of their cheek, places the swab in the supplied fluid, and reads the results in a test window

- Prognostic tests
  Once a diagnosis of HIV infection had been made, it is important to monitor the patient regularly for signs of disease progression (HIV viral load and HIV Antigen test) and response to antiviral chemotherapy.

- Treatment
  • Zidovudine (AZT) was the first anti-viral agent shown to have beneficial effect against HIV infection.
  • Combination therapy has now been shown to be effective, especially for trials involving multiple agents including protease inhibitors. (HAART - highly active anti-retroviral therapy)
  • The rationale for this approach is that by combining drugs that are synergistic, non-cross-resistant and no overlapping toxicity, it may be possible to reduce toxicity, improve efficacy and prevent resistance from arising.
  •once patient started treatment, it is also important to monitor liver and kidney function

- Anti-Retroviral Agents
  • Nucleoside analogue reverse transcriptase inhibitors e.g. AZT, ddI, lamivudine
  • Non-nucleoside analogue reverse transcriptase, inhibitors e.g. Nevirapine

• Protease Inhibitors e.g. Indinavir, Ritonavir • Fusion inhibitors e.g. Fuzeon (IM only)
• Integrase inhibitors impair the ability of the transcribed viral DNA to insert into the human genome
• HAART (highly active anti-retroviral therapy) regimens normally comprise 2 nucleoside reverse transcriptase inhibitors and a protease inhibitor. e.g. AZT, lamivudine and indinavir. Since the use of HAART, mortality from HIV has declined dramatically in the developed world.

- Prognosis of an HIV infection
  • Without treatment, HIV infection progresses to AIDS in approximately 10 years, with death following within three years after onset of AIDS.
  • With appropriate treatment, a 20-year-old with HIV infection can expect to live to reach 71 years of age.
  • This dramatic increase in life expectancy emphasizes the need for early diagnosis and treatment.
  • There are some factors that decrease life expectancy, including use of illicit drugs and the coexistence of other conditions like chronic hepatitis

- Prevention
  • The risk of contracting HIV increases with the number of sexual partners. A change in the lifestyle would obviously reduce the risk. Using condoms with every sexual encounter reduces the risk of infection.
  • The spread of HIV through blood transfusion and blood products had virtually been eliminated since the introduction of blood donor screening in many countries. • AZT had been shown to be effective in preventing transmission of HIV from the mother to the fetus. The incidence of HIV infection in the baby was reduced by two-thirds.
  • The management of health care workers exposed to HIV through inoculation accidents is controversial. Anti-viral prophylaxis had

been shown to be of some benefit but it is uncertain what is the optimal regimen.

• Items that may be contaminated with blood, such as razors or toothbrushes, should not be shared

• Vaccines are being developed at present but progress is hampered by the high variability of HIV.

Best wishes ☺
Hadil Ahmed Alia