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Retroviruses including Human immunodeficiency viruses (HIV) causing of AIDS  
Classification

### Sub Family

- **Oncovirinae**
  - Include
    - Human T cell leukemia virus 1 (HTLV-1)
    - Human T cell leukemia virus II (HTLV-II)
      - Adult T. cell lemphoma (TCL) in human
      - hairy cell leukemia in human

- **Spumavirinae**
  - Cause
    - inapparent persistant infection
    - natural host
    - Primate + other animals

- **Lentivirinae**
  - Include
    - simian imm. Deffeciency virus (SIV –I)
      - cause
      - semian immunodifficiency
      - No – disease
      - monkey but Aids Rheuses

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Human immuno-defeciciency virus (HIV)-1
cause 2 diseases
- Immunodifficiency encephalopathy
- infect children but no clinical signs in human

Human immuno-defeciciency virus II (HIV –II)
- cause
- Immunodifficiency less pathogenic than HIV –I
  - in
  - human and primate

Simian imm. Deffeciency virus (SIV –I)
cause
- semian immunodifficiency
- No – disease
- monkey but Aids Rheuses
Properties of Lentiviruses

- Non oncogenic
- Cytocidal retroviruses

Virion:
- Spherical in shape
- Size 80-100 nm
- = of influenza virus

Genomes:
- Single + strand RNA (diploid)
- All viruses are haploid except of this family

Envelope:
- Present

Replication
- Reverse transcriptase
- RNA → DNA
  - Which mean proviral DNA is template for viral RNA

Maturation
- Particles bud from plasma membrane
  - Slow progressive disease
  - Chronic disease

Disease
- This sub family include causative agent of Aids
- (acquired immunodeficiency syndrome)

Inactivation of HIV by treatment for 10 minute with any following at room temp

- 10% bleach
- 50% ethanol
- 35% isopropanol
- 1% detergent
- 0.3 H₂O₂
- at low PH (PH=1)
- at high PH (PH=13)
  - i.e acidic and alkaline

Also lyophilized blood product should be heated at 68 °C for 72 hrs. to insure inactivation contaminating virus
HIV have

3 Structural gene (or protein)

(1) gag (group specific antigen) viral protease cleavage

matrix antigen P18 (MA)
Core (CA) P24
Nucleocapsid (NC) P9

(2) pol protease cleavage

Reverse transcriptase (RT) P66
Integrase (IN) P11
Protease (PR) P160

Based on ENV-gene sequence divided

HIV-1 Divide to 3 type

M N O

Further divided to 11 sup type (A-K)

6 sup types found in west Africa

%40 of the frequency of HIV-1, HIV-2 are identical

(3) ENV Cellular protease

surface (SU) gp 120
Trans membrane (TM) gp 41

40% of the frequency of HIV-1, HIV-2 are Identical

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Acquired immunodeficiency syndrome (AIDS)

- Lipid bilayer
- Reverse transcriptase
- Viral envelope
  - Cup 41
  - Cup 120
- Glycoprotein
- Viral integrates
- RNA
- Gag proteins
  - P18 matrix
  - P24 Core protein
  - NC P9

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Regulatory genes for replication and pathogenesis are 6 genes + up to sex additional gene regulate viral expression and important For pathogenesis in vitro

- TAT protein (Trans activation)
  - Transcription
  - Function
  - Which mean viral gene Product is involved
  - In transcriptional activation
  - Of other viral genes
  - So trans activation is highly efficient in Aids
  - So
  - This play Avery important role in Virulent nature of HIV infections

- REV
  - Regulation of expression of viral proteins
  - Function
  - REV Facilitate the export of uncepliced viral Transcribed mRNA from nucleus to ribosome in cytoplasm
  - then
  - uncepliced mRNA
  - translated to
  - Structural proteins during late phase of viral replication

- accessory genes (Nef. ViF1 vpr, vpu)
  - not clearly defined and not absolutely required for replication
Infection with HIV required binding of gp 120 to two receptors on the host cell. And those receptors are:

1. CD4+ receptor
   - Which is a high affinity receptor for HIV

2. Chemokine receptor (core receptor)

These receptors are usually found in CD4+ T-cell, which contains or expresses high levels of CD4 (1) and also expresses (2) core receptor. So it is considered as the main target cell to HIV.

- Other cells like Macrophage, Monocyte, dendritic cell, some rectal lining cells express or contain low levels of CD4+ and also core receptor so infected by HIV.
- Macrophage and Monocyte play a major role in the dissemination and pathogenesis of HIV.

To:

- Brain (occur by Monocyte and macrophage)
  - Neuro psychiatric Manifestation

- Infect pulmonary alveolar cell
  - interstitial pneumonitis
**Immune dysfunction**

The depletion and functional impairment of CD4+ T cell subst. occurs due to:

- Accumulation of RNA and unintegral DNA in the cytoplasm of CD4+ T cell
- Multinucleated giant cell
  - with mean Syncytial Formation
  - Lead to Depletion in TCD4+ cell

**ADCC**

- (Ab-dependant cell medial cytotoxicity)
- (CD+TC) act as Ag presenting cell
- ADCC
  - NKC
  - So Nkc Destroy ADCC

- HIV induce T cell apoptosis
  - Viral budding
  - Lead to Cell weakening and lysis
  - W mean during budding of HIV when release from CD4+ cell
  - Weakness and lysis of cell → apoptosis

Not only T cell destroyed during HIV infection but also production of new T cell from thymus, bone marrow is inhibited

**All of these lead to depletion of CD4+ T cell and this depletion may cause**

- Decrease in response to Ag and mitogen lead to decrease IL2 production
  - Th CD+4
  - Auto immune disease
  - Auto Ab
  - Polyclonal B activation
- Changes in cytokine production
- Decrease TC lymphocyte
- Increase in CD8+
AIDS

Selective loss of helper/inducer CD4+ cell lead to

(1) Diminished in vivo T. Cell function
- decrease ability to specific Ab
- decrease ability to remove virus infected cells
- decrease ability to remove malignant cell
- decrease ability to respond to chemical Ags decrease T cell

Diminished vitro T. cell function lead to
- decrease ability to remove virus infected cells
- decrease ability to remove malignant cell
- decrease ability to respond to chemical Ags decrease T cell

Deceased CD4/CD8 ratio Lead to
- Polyclonal B cell activation
- Serum level of IgG, IgA
- Spontaneous antibody producing B-lymphocyte
- Auto – antibody formation
- Auto immune disease

Rout of transmission
- sexual contact
  - sexual contact
  - semen

- transfer by
  - cervical fluid

- perinatal Transmission
  - Infected Blood and blood product
  - from mother to neonate by

- Trans placentally

- via breast milk

- at birth (passage of the children Through infected Canal)

Also Some research about saliva at tears transmission
Individual at risk

- Promiscuous Homosexual Men
- Heterosexual (Asia, Africa)
- Intravenous drug abusers
- Hemophilia
- Offspring infected mother
- Heath care person, dentist

Course of HIV infection 3 stages

(1) Primary infection stage 1. p 3-4 week
   - Acute stage
     - Characterized by
       - Mononucleosis
         - Like picture of Fever
       - Sore throat
       - Generalized Lymphoadenopathy
       - Rash
     - Leucopenia in 50-75% of patients
     - Viraemia lasts for 8-12 weeks
     - *Virus is widely disseminated through this time
     - *Lymphocytic organ become seeded
     - *There is significant drop in CD4+ T cell
     - Ab to HIV appear 3-4 weeks after infection
     - Last for 3 months

(2) Clinical latency stage
   - Middle stage
     - Last 10 years
     - Patient is asymptomatic
     - Viraemia is low or absent
     - CD4 rebound
   - HIV infected cell persist in lymph nodes
   - During this stage occur syndrome called AIDS related complex
     - During latent period
     - Charact. by
     - Persistent fatigue
     - Weight loss
     - Lymphoadenopathy
     - Lead to AIDS

(3) Late stage
Late Stage of AIDS

Decline in No. of CD4 cells

high level of virus in plasma (viraemia)

increase in frequency and severity of opportunistic infection and malignancy

* opportunistic infection

protozoal infection

Toxoplasma

Cryptosporidium species

isospora belli

fungal infection

Candida albicans

pneumocystis carrini

Cryptococcus neoformans

Bacterial infection

T.B

listeria

nocardia

salmonella

strep. Spp

Viral infection

cytomegalovirus

herpes simplex V.

hepatitis B virus

adeno.v

Vericella zoster
Cancer

- AIDS patient Exhibit marked
  Predisposition of development
  of cancer like
    - non Hodgkin lymphoma
    - Kaposi Sarcoma

  lymphoma and polyclonal B. cell
  malignancy classified as Burkitt's
    - skin nodules
    - HSV...lymphoma

  *cervical cancer
  *urogenital cancer
  lymphoma

  Neurologic problem
due to
  infection of Brain with HIV or
  many of opportunistic organism like
toxoplasma Cryptococcus, candida
  lead to
  Neuropathy Dementia

Pediatric AIDS

- Acquired from the mother
  In high risk group

  Symptoms
  after 2 year

  death after
  another 2 year

  clinically there is

  lymphoid interstitial
  pneumonitis
  pneumonia
  Sever oral candidiasis
  hepatosplenopathy

  Bacterial sepsis
  diarrhea
  Failure to thrive
Neurological disease

%90-40 of AIDS patients appear neurological abnormally which include

HIV encephalopathy  Peripheral neuropathy  AIDS dementia complex

Neuro psychiatric manifestation of HIV infection either due to

Direct infection with HIV
  - Macrophage, Monocyte predominant cell type in the Brain that are infected with HIV
  - Virus enter the Brain through infected monocyte and release Cytokines which are toxic to neurons as well as chomotactic Factors
  - Infiltration of the Brain with inflammatory cells
  - HIV found in limited no in neurons and also present of oligodentrocyte and astrocyte

indirect due to
  - Opportunistic pathogen which cause neurological disease associated with HIV
  - Include Toxoplasmosis, Cryptococcus, CMV

Brain spiral cord
- Its not know yet the chieve immune respone that protect from infection With HIV because this virus highly mutant lead to highly antigenic variation

- Most infected individual produce neutralizing antibodies against HIV envelope gps W appear to be the major targets for antibody neutral Bation

These neutral bind Ab can measure in vitro by inhibiting HIV infection of susceptible T. lymphocyte cell line (tissue culture)

**Virus infection is quantified by**

Directly by measuring of reverse Transcriptase W produce from the Virus particles

indirect immuno fluorcent assay

W measure the percentage of infected cell

reverse transcriptase polymerase chain reaction (RT.PCR)

Or branched chain DNA Amplification W measure HIV nucleic acid
Lab.dx.

1. Virus isolation
   - Take lymphocyte from peripheral blood of infected person + mixed with uninfected radioimmuno-mitogen stimulated peripheral blood mononucleus precipitation cells (stimulate with PHA for 1-2 days)

2. Detection of antigen
   - Amount of free HIV-1 protein (p24 Ag) in the plasma by Elisa

3. Serology
   - Elisa as screening blood
   - Confirmed with indirect IF donors
   - But Western blot technique is most widely used which include use of at least 2 bands: P24, gp 41, gp 120, gp 160
   - Abs suspected to be found in serum of patient against these Ags

4. Detection of viral nucleic acid
   - AIDS
     - Fluorescent Ab
       - If AIDS present: band if AIDS not present: no band

Detect viral reverse transcriptase or detect viral specific Ag (P24) (core Ag)

- Multi-nuclear giant cell
- Viral growth is detected by testing of supernatant fluid for HIV reverse Transcriptase Activity
- HIV - P24 Ag production
Detection of the viral nucleic acid by

1. Polymerase chain reaction mean detection of HIV DNA in infected cell (pro viral DNA)
2. Viral RNA in plasma (viral load)
3. A branched chain DNA amplification test
4. Use for detection low level of HIV in donor blood (RNA level) because RNA levels are important predictive for disease Progress – and valuable tools to monitor the Effectiveness of antiviral therapy

Plasma viral lead

The amount of HIV – the blood (viraemia) in of a significant prognosis value because there is continuous correlation of the viral replication and cell killing in each patient.

So

Measurement of plasma viral load of the patient after 6 month after infection – give idea to predict the subsequent risk of development of AIDS for several years later.

plasma HIV RNA level can be determined by using variety commercially available test

know of plasma viral load give idea about

risk of development of disease

important to know the effectiveness of antiviral therapy

measurement of CD4+ lymphocyte give idea about short term risk of Development of opport. infection.

notice
Prevention (vaccines)

Whole virus vaccine
- live attenuated
- killed
- defective HIV virus

subunit vaccine
- Envelope protein

Recombinant DNA technology by using
- bacteria
- vaccinia virus

synthetic peptide of envelope protein

Target cell
- gene therapy
- Protection by

Genetically inserted cell receptor protein
antiidiotype Ab against CD4+ receptor
Antiviral drugs

Nucleoside analogs
- Zidovudine (AZT) (Retrovir) 1987

Didanosin (1991)
- inhibit RT
- block synthesis of proviral DNA

Zaicilabine 19
- Stavudine 1994
- Lamivudine 1995 e.g.

mononucleosid RT inhibitor
- Nevirapine 1996 binding to RT
- without phosphorylation
- disruption enzyme catalytic site

Didanosin ((1991)
- inhibit RT

Nevirapine 1996 binding to RT
- disruption enzyme catalytic site

sequinavir 1995
- Terminal chain

In pregnancy women
- Is effect

indinavir 1998 inhibit protease of HIV-1 + HIV-2
- act as protease inhibition late stay of replication to cleave viral structural protein and activation of RT

No infection

mechanisms zidovudine
- zidovudine triphosphat

inhibition of viral reverse transcriptase because act as competitive substrate of incorporation into proviral DNA

protease inhibitor

Infection

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