RETROVIRUSES & HIV - *2016*

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RETROVIRUSES
(FAMILY : RETROVIRIDAE)

- Positive sense single stranded RNA.
- Icosohedral nucleocapsid.
- Enveloped.
- Sphericle.
- 100 -120 nm in size.
- Contain RNA dependent DNA polymerase. (Reverse transcriptase)

Transfer genetic information

Viral RNA → **Viral DNA**

enzyme
(Reverse transcriptase)

↓

Integrate into host-cell chromosomal DNA (**Proviral DNA**)

RETROVIRUSES

↙ ↘

Lentiviruses: eg. HIV 1 & 2

Oncoviruses eg. HTLV - 1, HTLV – 2

HIV- 1 & 2 (human immunodeficiency virus) → AIDS.

HTLV -1 (human T-cell lymphotrophic virus)

↙ ↘

T-cell leukaemia, lymphoma

HTLV -2 → Hairy cell leukaemia

HIV INFECTION

1981 - CDC Atlanta/ USA noted,

I. Increase requests for drugs to treat *Pneumocystis. carinii* infection (Pentamidine) in previously well people.

II. Also suffered severe infections with normally harmless organisms.
(*C.albicans, toxoplasma, Cryptosporydiae)*

III. Evidence of immunosuppression = with immunosuppressive drugs.

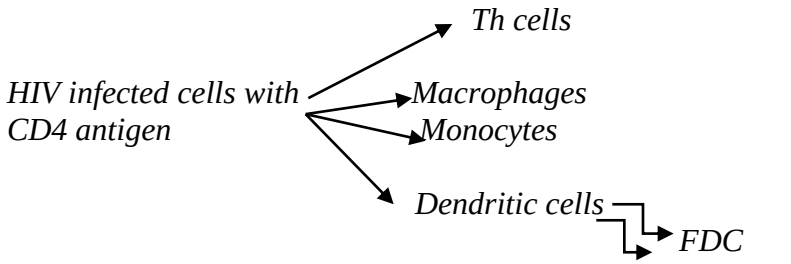
↓

Acquired Immunedeficiency Syndrome (AIDS)

1983 - Causative virus HIV isolated from blood lymphocytes.

1. STRUCTURE OF THE VIRUS: refer

2. PATHOGENESIS



CD4 molecule is the binding site for gp 120 envelope antigen.

1. Attempts to respond HIV antigens

2. Secondary microbial infections

↓

Activation of Th cells → *virus infection leads to productive replication & cell destruction.*

Monocytes & macrophages
Follicular dendritic cells
Langerhan's cells ⇒ *express CD4* ⇨ *infected by virus but not generally destroyed*

Only a proportion of Th cells infected.

It is possible virus triggered autoimmune responses to normal CD4+ cells which have bounded HIV antigens & Loss of Th cells

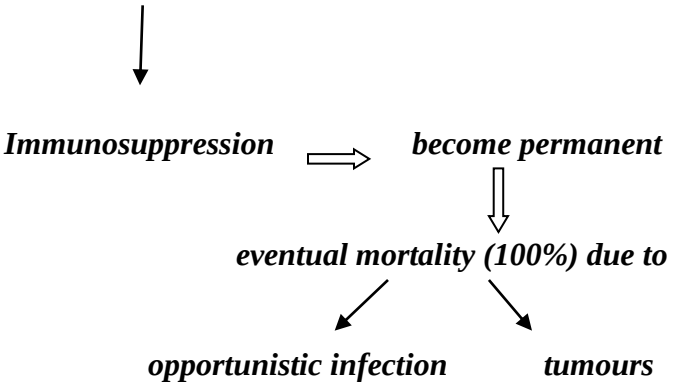
HIV INFECTION

Decrease CD4 + Th cells.
Defects in antigen presentation.
Produce virus coded immuno-suppressive molecules gp 120 & gp 41
Absence of skin test-(dTH) responses.
Decrease NK cell activity.
Other immunological abnormalities, ie. Polyclonal B-cell activity.

Infected cells have gp41 the fusion protein
→ *fuse with other infected or uninfected cells*

→ *help virus to spread* → *form multinucleated giant cells (ie. in brain)*
Only a proportion of Th infected.

It is possible virus triggered autoimmune responses to normal CD4+ cells (with bound HIV antigens) leads to the loss of Th cells



POOR CMI

Neutralizing antibodies ⟶ formed.

Virus specific CD8 cells ⟶ detectable.

Host response ⟶ handicapped by antigenic variation of gp 120

Antigenic variant in an given individual resistant to current cytotoxic T cells**.**
(immune escape = increased pathogenicity)

Peripheral blood mononuclear cells major source of transmitted HIV. (10 000 inf.dose/µl) (low doses much less infectious than Hep.B virus)

Amount of virus reduce with seroconversion.

Increase with development of AIDS & AIDS related complex.(ARS)

Virus present in small amounts in semen , saliva , colustrum (even smaller amounts), human cervix , tears , submucosal CD4 cells in rectum & large bowel.

Sub acute encephalitis with dementia in infected patients.

- *Virus infecting CNS occurs independently of AIDS.*
- *Multiple small inflammatory nodules seen.*
- *Most infected cells are Microglia & Infiltrating MQ (have CD4 antigen)*
- *Infected monocytes carry virus to the brain*
- *Most AIDS patients develop neurological disease.*
- *Picture complicated by persistent infections activated have CNS Pathology of their own.*

  ie. HSV
  VZV
  Toxoplasma gondii
  JC virus
  Cryptococcus neoformans
  Kaposi's sarcoma
  EBV - B cell lymphomas

CLINICAL FEATURES

Initial infection

- *May accompany a mild mononucleosis -*
  Characterised with -- fever
  -------- malaise
  ------- rash
- *Antibodies detect after many months.*
- *Individual remain well.*

(Arrested viral replication)

Later Stage

AID RELATED COMPLEX (ARC)
- *Weight loss*
- *Fever*
- *Persistent Lymphadenopathy*
- *Oral Candidiasis*
- *Diarrhoea*

Further Virus replication ⟶ *Full blown AIDS*

- *Sub acute encephalitis with Dimentia. (Direct CNS effect)*
- *Infant microcephaly*
- *Some patients in Africa → wasting disease*
- *Microbial Diseases → Acquired*
  Reactivated.

CLINICAL SYNDROMES ***(Wide Spectrum)***

1). Acute HIV infection → *most of them are asymptomatic (0-15%)*

⇩

Seroconversion occurs

⇩

resolves spontaneously

⇩

After many years

⇩

AIDS manifestations

resembles infectious mononucleosis,
fever
rash
enlarge LN

2). Asymptomatic infection.

Many infected. No symptoms for months

Later → *progress to* → *PGL or*
ARC or
AIDS

Later → *Arrested ?*

3). Persistent Generalised Lymphadenopathy. (PGL)

LN get enlarged → 2 or more non-contiguous extra intestinal site

Fever, malaise, and + for HIV antibodies.

Progress to → ARC or AIDS.

4). ARC or AID Related Complex

i. Constitutional symptom → *Fever*, *Fatigue*, *Diarrhoea*, *Weight loss*

ii. Opportunistic infections → *Oral candidiasis*, *Herpes zoster*

iii. Generalized lymphadenopathy

iv. Splenomegaly.

HIV +ve & May progress to AIDS in few months.

5) AIDS (end stage)

Irreversible break down of immune defences.
Death in Few months

Etiological basis for Complications seen in AIDS patients:

Complication	*Etiological basis*
Respiratory	*Pneumocystis carinii*, *TB*, *Histoplasmosis*
Central Nervous System	*HSV*, *Toxoplasma*, *Cryptococcus*
Gastro-intestinal Tract	*thrush*, *hairy cell leucoplakia*, *Oesophagial candidiasis*
Chronic colotis	*Amoeba*, *Giardia*
Malignancies	*KS* → *HHV8*; *Lypmphomss(Hodgkin& non Hodgkin)* → *EBV*
Cutaneous	*disseminated zoster* → *VZV*

Laboratory Diagnosis

- Lab Tests depend on demonstration of specific antibodies for HIV.

- **AIDS is** → **Clinical definition** + **Presence of antibodies to HIV**

(A) General Tests

1. Total Leucocyte count decreased (**< 2000/mm3**) (leucopenia)

2. T cell subsets
   Absolute CD4 Th cells decreased (< 200/mm3)

3. Platelet count decreased

4. Skin (dtH) test - Negative or decdreased

(B) **Specific Tests**

1. Serology by ELISA, Particle Agglutination. Measure Abs to 1 or more envelop proteins
ie. Gp 120 by ELISA

Occasionally can give false +ve due to clerical errors.
Therefore positive result is confirmed by further blood sample. By Western blotting, RIA or Immuno fluorescence testing.

2. Tests for infectious virus, viral Ags (ELISA for P25) and Viral nucleic acids (PCR) are not yet available routinely.

3. Tests to distinguish HIV-1 and HIV-2 available in specialized centers.

4. DIAGNOSIS of HIV in Newborn infants is a problem.
If IgG ab present presumably maternal origin. Tests for virus specific IgM Abs in utero infection. (not yet available)

MCQ:
In AIDS patients

A. Virus antigen Gp 120 can be detected in blood
B. Manteaux test is strongly positive
C. Mycobacterium tuberculosis infection is common
D. CD4 positive T cells count in blood is below $200/mm^3$
E. Polyclonal B cell lymphomas are common

Transmission

HIV can be isolated from

- *blood*
- *lymphocytes*
- *cell free plasma*
- *semen*
- *cervical secretions*
- *tears*
- *saliva*
- *urine*
- *breast-milk*

Primarily transmitted between male to male and male to female
In Africa, transmission from female to male common
Greater heterosexual spread from Africa.
Developed countries heterosexual not common and now becoming important
HIV can be transmitted vertically.
Paediatric AIDS will be a major cause of paediatric deaths

Mother → *offspring (20% cases)* → *50% develop AIDS*

Arthropod transmission ------- probably not occur

Modes of Transmission

- sexual intercourse - Homosexual & Heterosexual
- Contaminated blood products (Blood transfusions and Factors VIII)
- Contaminated needles (IV drug users, Needle stick injuries, Infections)
- Organs & tissue donation (semen, kidneys, skin, corneas, bone marrow)
- Mother to child → In utero
  → at birth
  → ? Breast milk

Epidemiology:

- Global problem.
- Majority detected were infected with HIV1.
- Few HIV 2 infected persons also detected.
- **Refer to recent STI report of** Epidemiology Unit of the Ministry of Health

Data from HIV infected individual in Sri Lanka shows

Age affected 22-44 yrs gp.

69% affected by heterosexual contact

20% affected had no foreign contact (transmitted in Sri Lanka).

Methods of destroying virus.

Virus is highly susceptible

Destroyed by Heat → 560c/30 mins
→ 100°C/seconds
→ Room Temperature/ 7 days
→ Pasteurization

Chemicals → Hypochlorite upto 1:10 000 ppm
→ 2.5% glutaraldehyde
→ alcohol. (70%)

Prevention

1. Preventing sexual transmission.
2. Preventing transmission through drug injections.
3. Preventing transmission from blood, blood products and organ donations
4. Preventing vertical transmission.
5. Mass public education programs.
6. Protection of Health care staff.

A. Preventing Sexual Transmission

1. Prevent sexual contact from high risk groups.
   - Homosexuals
   - Bisexuals
   - Injecting drug users
   - Haemophiliacs
   - Sexual partners of above groups

2. Reducing number of sexual partners.

3. Knowing about partners previous sexual behaviour & drug use history
4. Using a condom.
5. Practicing safer sex.

B. Preventing Transmission through drug injections

1. Stop drug use and ask for help. If not,

→ Sniffing

2. Switch to → Smoking
↘ Swallowing

3. Stop sharing equipments.

C. Preventing Transmission from blood, blood products & organ donated

1. All blood donors should be tested for Ab to HIV.
2. All donors of blood products (fact VIII & other products should be screened for Ab to HIV.
3. Heat treatment for Factor VIII.

4. Instructions to potential donors not to give blood if they have a risk factor.

1. *HIV infected /AIDS men & women*
2. *Homosexual men*
3. *Drug addicts*
4. *had sex with above or partners of haemophiliacs.*
5. *Prostitute men & women.*

D. Preventing Vertical Transmission

1. Counseling sero + women on the risk of pregnancy.
2. Contraception services for sero + women.
3. Antenatal Ab testing with counseling to high risk groups.
4. Termination of pregnancy for sero + women.

TREATMENT for AIDS

a) Opportunistic infections treated in appropriate way.
ie. P. carinii ¬ Pentamidine
CMV ¬ Gancyclovir

b) For HIV ¬ Azidothymidine (AZT) (a nucleoside analogue)

***Refer** to New drug regimes for AIDS patients*

Frequency of opportunistic infections reduced by CD4 Th cells.

Whether drug prevent ARC or AIDS not answered.

Search continues effective cheaper drugs
ie. Soluble CD4 molecules to block binding toTh with gp 120.

Trials with combination of Drug + INF a + human soluble CD4 is in progress.