RETROVIRUSES

(FAMILY : RETROVIRIDAE)

RETROVIRUSES

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

Transfer genetic information

Viral RNA → Viral DNA

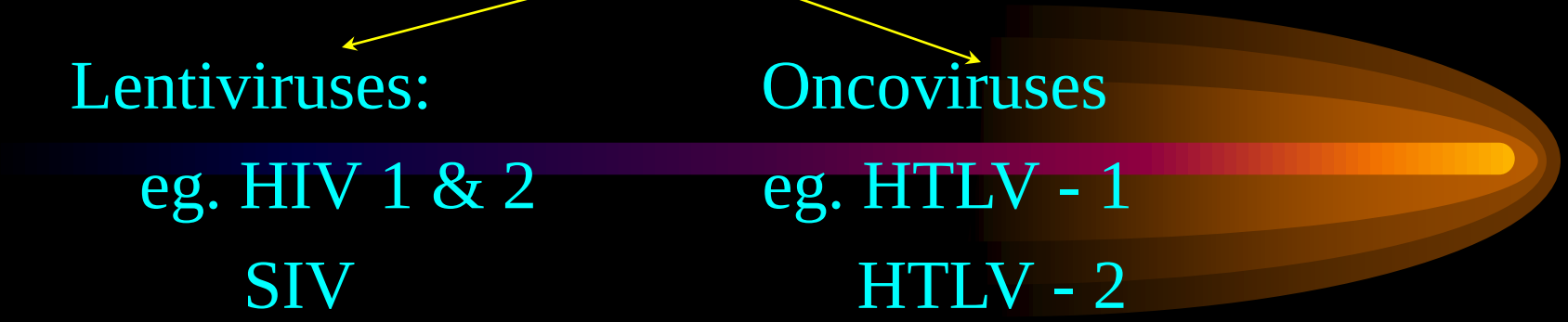
enzyme

(Reverse transcriptase)

integrate into host-cell chromosomal DNA

(Proviral DNA)

RETROVIRUSES



Lentiviruses:
- eg. HIV 1 & 2
- SIV
- FLV

Oncoviruses
- eg. HTLV - 1
- HTLV - 2

- HIV- (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 *P. carinii* infection (Pentamidine) in previously well people.

II. Also suffered severe infections with normally harmless orgamisms.(HIV, KS, *C.albicans, toxoplasma, Cryptosporudiae)*

III. Evidence of immunosuppression = with immunosuppressive drugs.

↓

Acquired Immunedeficiency Syndrome

& **1983 - Causative virus HIV isolated from blood lymphocytes.**

1. **STRUCTURE OF THE VIRUS**
2. **PATHOGENESIS**

HIV infected cells with CD4 antigen

- Th cells
- Macrophages
- Monocytes
- Dendritic cells
  - FDC
  - LH cells

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

Activation of Th cells → Productive replication & cell destruction.

1. Attempts to respond HIV antigens
2. Secondary microbial infections

Monocytes & macrophages
Follicular dendritic cells
Langerhan's cells → infected & express CD4 → not generally destroyed

INFECTION

& Decrease CD4 + Th cells.

& Defects in antigen presentation.

& Produce virus coded immuno-suppressive molecules gp 120

gp 41

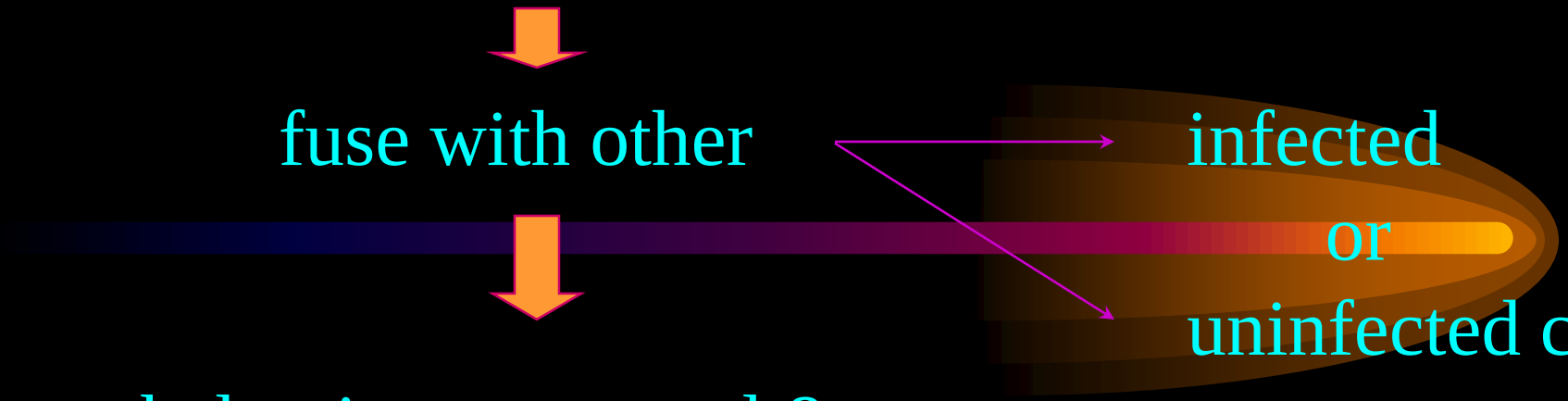
& Absence of skin test-(dth) responses.

& Decrease NK cell activity.

& Other immunological abnomalities,

ie. Polyclonal B-cell activity.

& **Infected cells have gp41 the fusion protein**



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 which have bounded HIV antigens.

→ Loss of Th cells

Immunosuppression → Permanent

↓

eventual mortality due to

opportunistic infection (100%)

tumours

& Neutralizing antibodies formed. Virus specific CD8 Cells detectable → But CMI is poor

& Host response → handicapped by antigenic variation of gp 120.

& Gp 41 = Fusion Protein → Spread of virus

→ Giant cell format

Loss of Th cells → only a proportion infecte

→ others autoimmune respons

& Immune suppression → Permanent eventual mortality (100%)

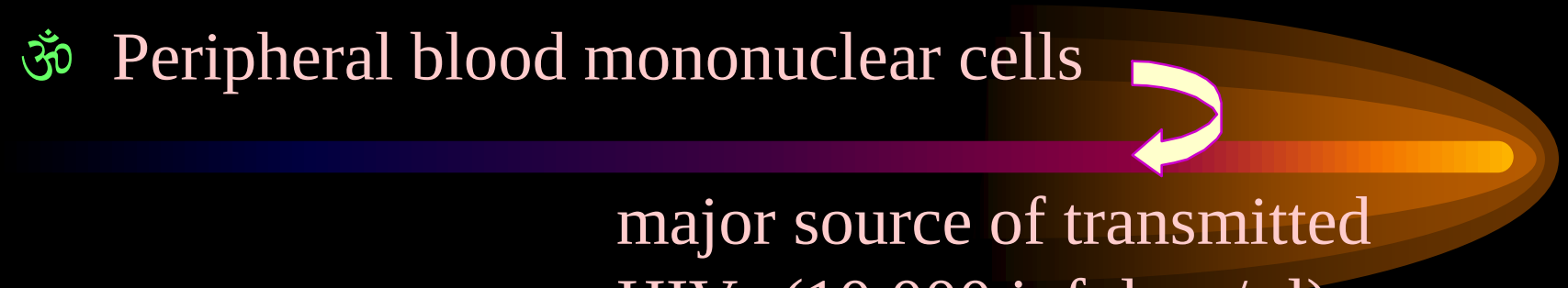
POOR CMI

- Neutralizing antibodies → formed.
- Virus specific CD8 cells → detectable.
- Host response → handicapped by antigenic variation of gp 120

Antigenic varient in an given individual → resistant to current Tcs.

(immune escape = increase 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.

- <u>CNS Pathology of their own.</u>

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 - type 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)
- Infants → microcephaly
- Some patients in Africa → wasting disease
- Microbial Diseases → Acquired
  Reactivated

CLINICAL SYNDROMES

(Wide Spectrum)

1/ Acute HIV infection → most → 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 syptoms for months

Later → progress to → PGL or ARC or AIDS

→ Arrested ?

3/ Persistent Generalised Lymphadenopathy. (PGL)

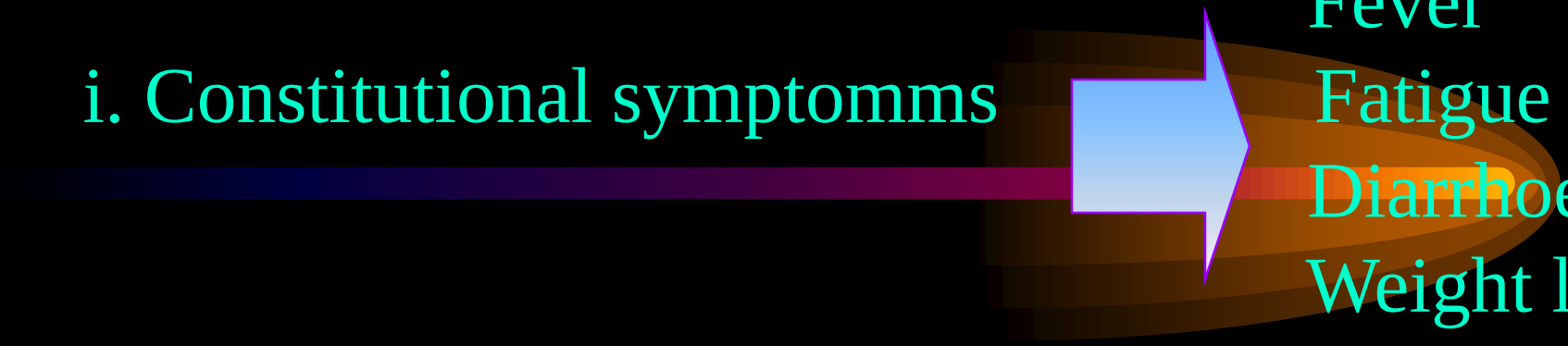
LN enlarge ⇒ 2 or more
Non contigious
Extra intestinal site

Fever, malaise, + for HIV antibodies.

Progress to → ARC or AIDS.

4/ ARC or AID Related Complex

i. Constitutional symptomms



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

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, LH/NH

Cutaneous

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 < 2000/mm^3
   (leucopenia)
2. T cell subsets
   Absolute CD4 Th cells ↓ 200/mm^3

3. Platelet count ↓

4. Skin (dtH) test - Negative or ↓

(B) Specific Tests

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

- Can give false +ve → by ELISA occasionally
  → clerical errors.
- Therefore positive result is confirmed by further blood sample. By, → Western blotting
  → RIA or
  → Immunofluorascence testing.

2. TESTS FOR → Infectious virus
For viral Ags (ELISA for P25)
Viral nucleic acids (PCR)
(not yet routinely available)

Tests to distinguish → HIV-1, HIV-2 — available in specialized centers.

3. 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)

Transmission

- HIV isolated from
  - blood
  - lymphocytes
  - cell free plasma
  - semen
  - cervical secretions
  - tears
  - saliva
  - urine
  - breast-milk
- Primarily transmitted
  - male → male & male → female

- In Africa, transmission from female to male common
- Greater heterosexual spread from Africa.
- Developed countries → heterosexual not common.

Now becoming important

- HIV can be transmitted vertically.
- Paediatric AIDS → will be a major cause → of paediatric deaths
- Mother → offspring (20% cases)

Modes of Transmission

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

Epidemiology

- Global problem.
- In Srilanka ➲ 155 cases ➲ 30 are foreigners (HIV-1)

2 cases of HIV-2 detected

- Age affected 22-44 yrs gp.
- 69% affected by heterosexual contact
- 20% affected had no foreign contact. (ॐ transmitted in SriLanka)

Prevention

1. Preventing sexual transmission.
2. Preventing transmission through drug injections.
3. Preventing transmission from
   - blood
   - blood products
   - organ donations
4. Preventing vertical transmission.

- Mass public education programs.
- Protection of Health care staff.
- Methods of destroying virus.

(highly susceptible)

Heat
- 56^0c/30 mins
- 100^0c/seconds
- RT. / 7 days
- Pasteurization

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

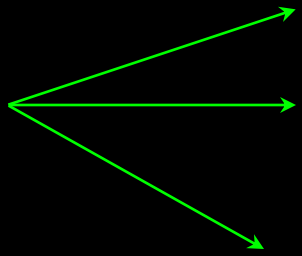
A. Preventing Sexual Transmission

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 behavior
   previous → 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,

2. Switch to  sniffing, smoking, swallowing

   if not,

3. Stop sharing equipments.

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

1. All blood donors tested for Ab to HIV.
2. All donors of blood products (fact VIII & other 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.

- HIV infected /AIDS men & women
- Homosexual men
- Drug addicts
- had sex with above or partners of haemophiliacs.
- 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 OF AIDS

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

b) For HIV ← Azidothymidine (AZT)

(Only anti HIV drug licensed for AIDS)

- Frequency of opportunistic infections reduced by CD4 Th cells.
- Whether drug → prevent → ARC or AIDS

not answered.

- Search → continues → effective
  cheaper

ie. Soluble CD4 molecules to block binding to Th with gp 120.

- Trials with combination of → Drug + INF α human soluble CD4 in progress.