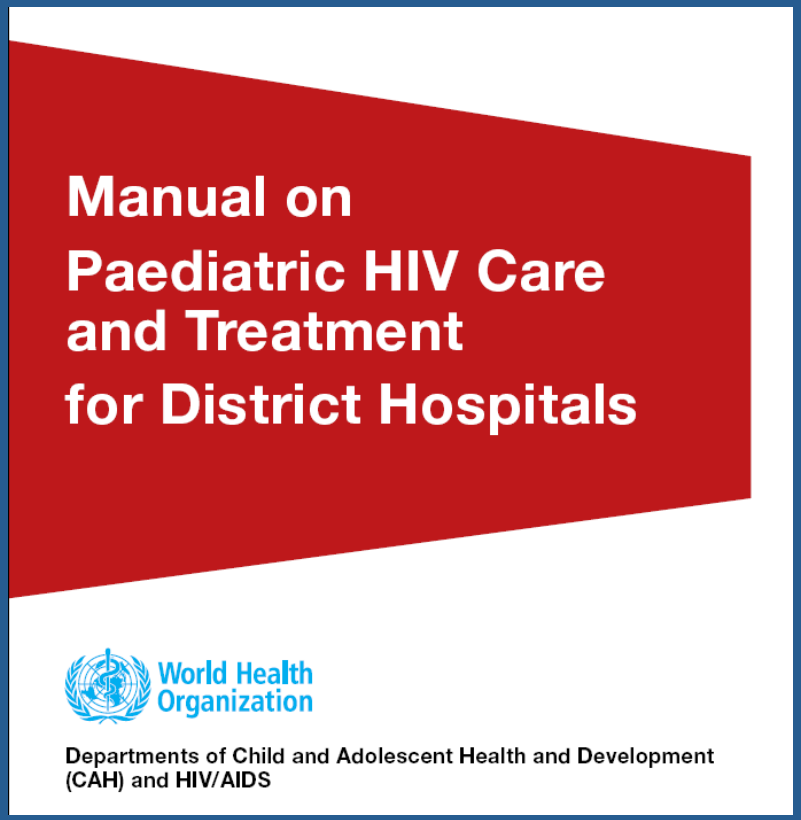
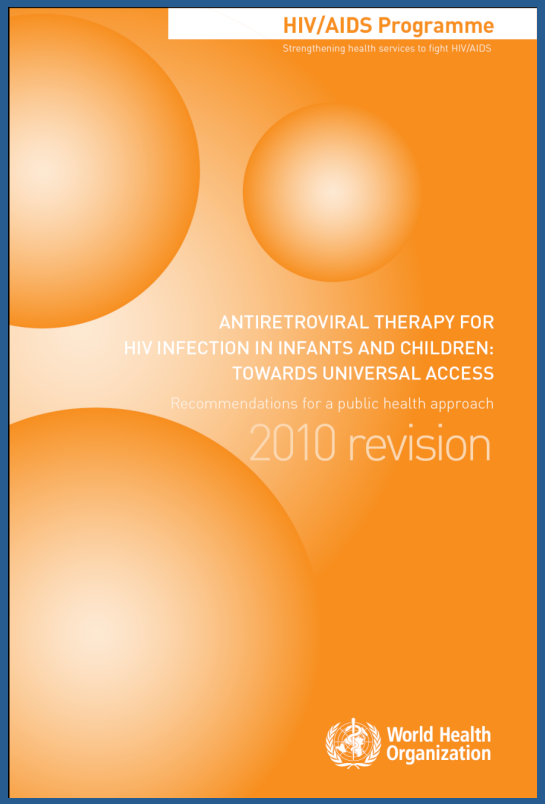




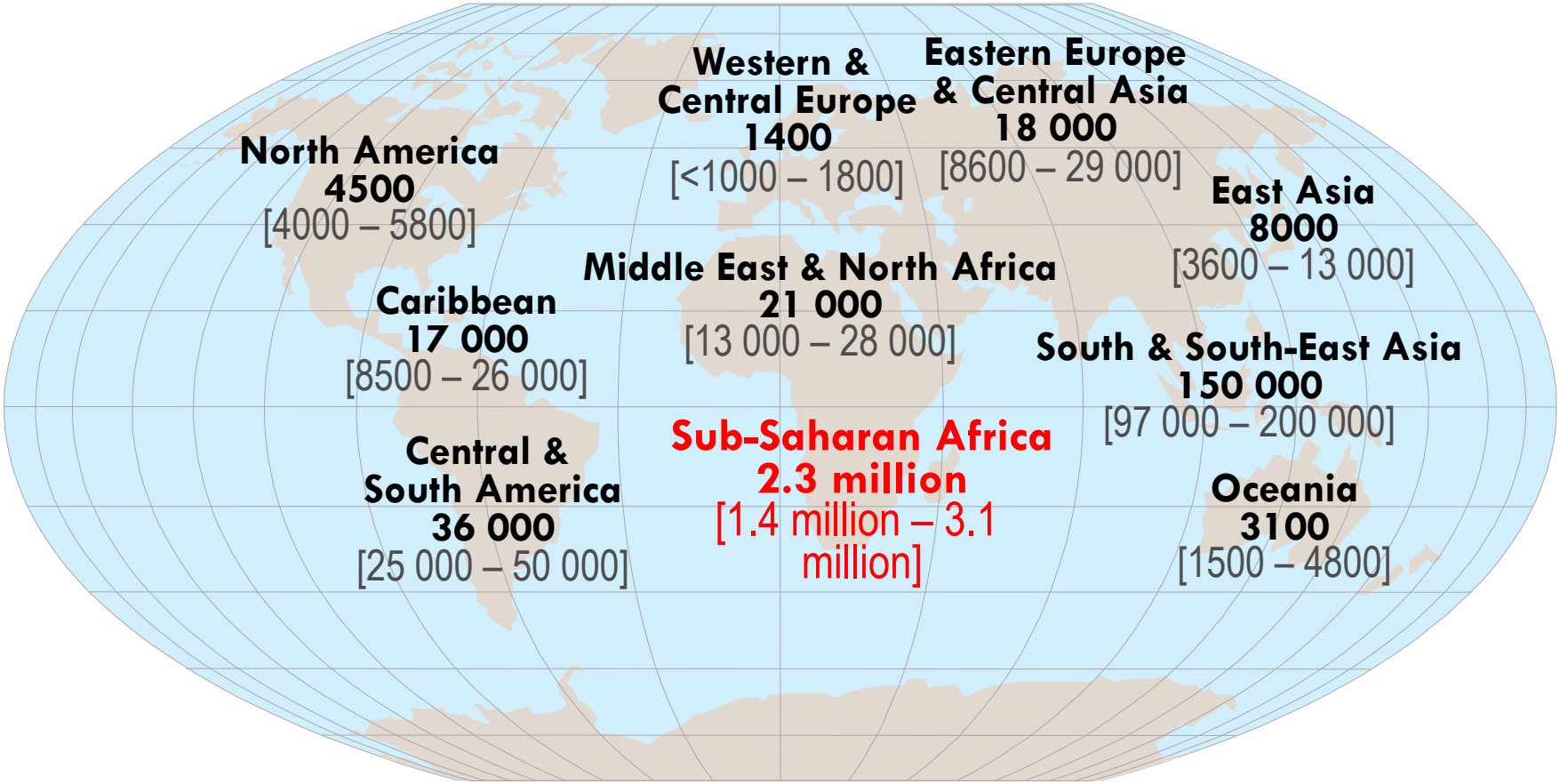
Paediatric HIV/AIDS

MINGHA AFRICA ONLUS

Dr. Gianluca Russo, MD, PhD

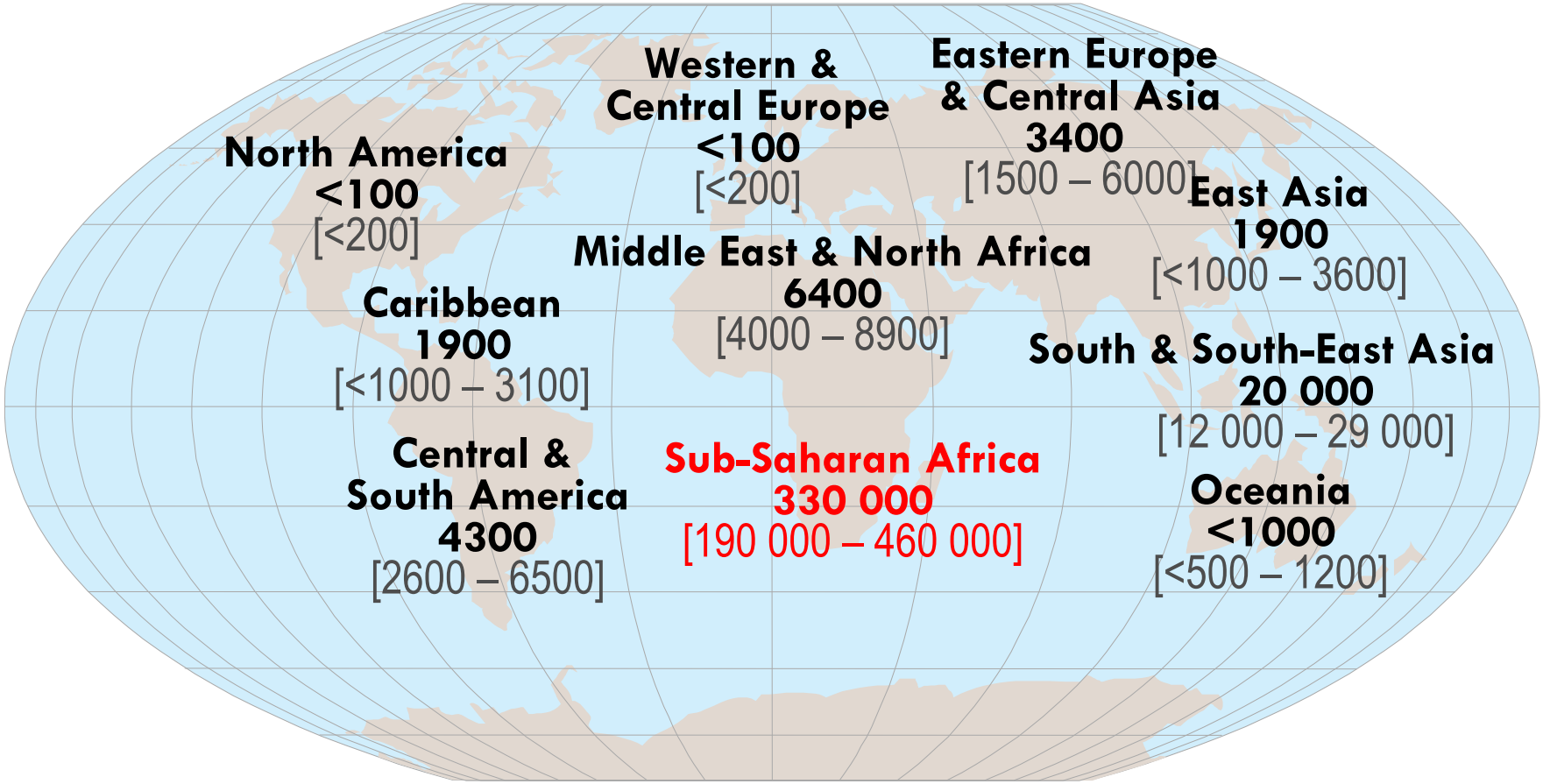
Epidemiology

Children (<15 years) estimated to be living with HIV (2009)



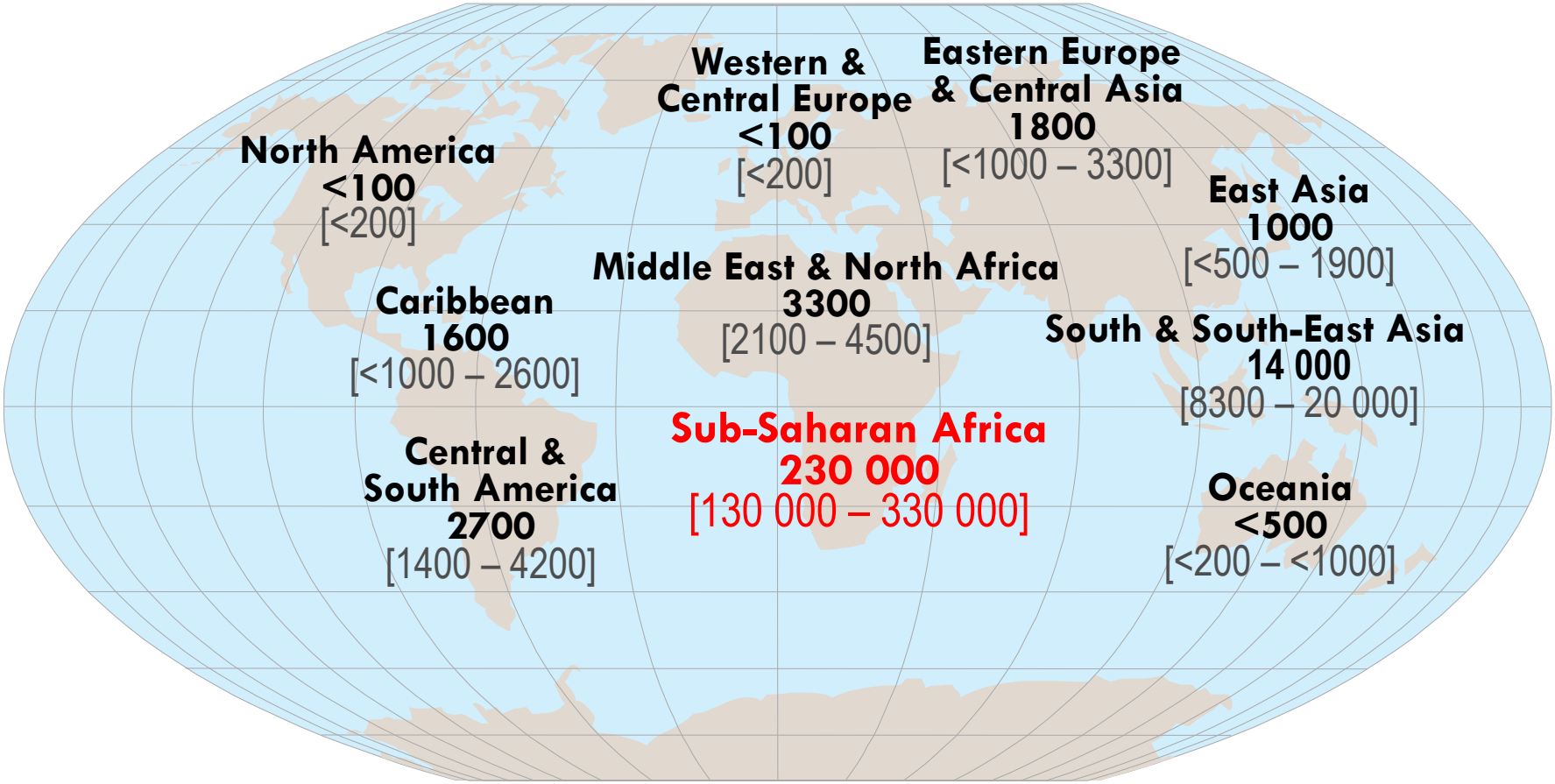
Total: 2.5 million [1.6 million – 3.4 million]

Children (<15 years) estimated to be newly infected with HIV (2009)



Total: 370 000 [230 000 – 510 000]

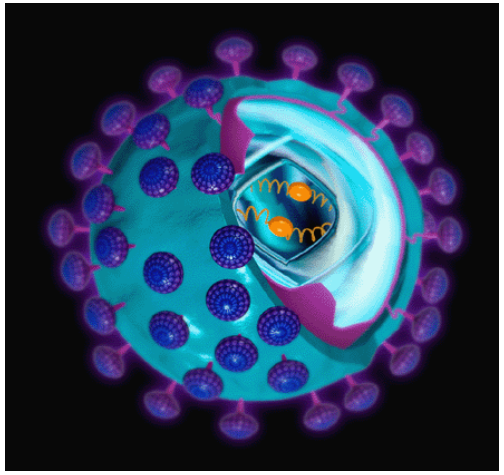
Estimated death in children (<15 years) from AIDS (2009)

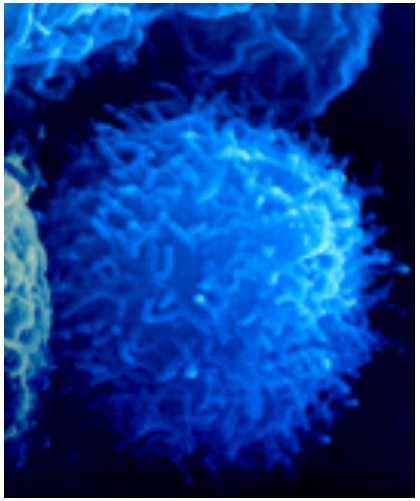


Total: 260 000 [150 000 – 360 000]

The Virus: Pathogenesis

- **The most important target of HIV are the lymphocyte T CD4+**
- The CD4+ cells play a crucial role in the immunitarian response
- The virus has a high mutation rate





Human Cells Susceptible to HIV

Hematopoietic
- T lymphocytes
- B lymphocytes
- Macrophages
- NK cells
- Megakaryocytes
- Dendritic cells
- Promyelocytes
- Stem cells
- Thymic epithelium
- Follicular dendritic cells
- Bone marrow endothelial cells

Skin
- Langerhans cells
- Fibroblasts

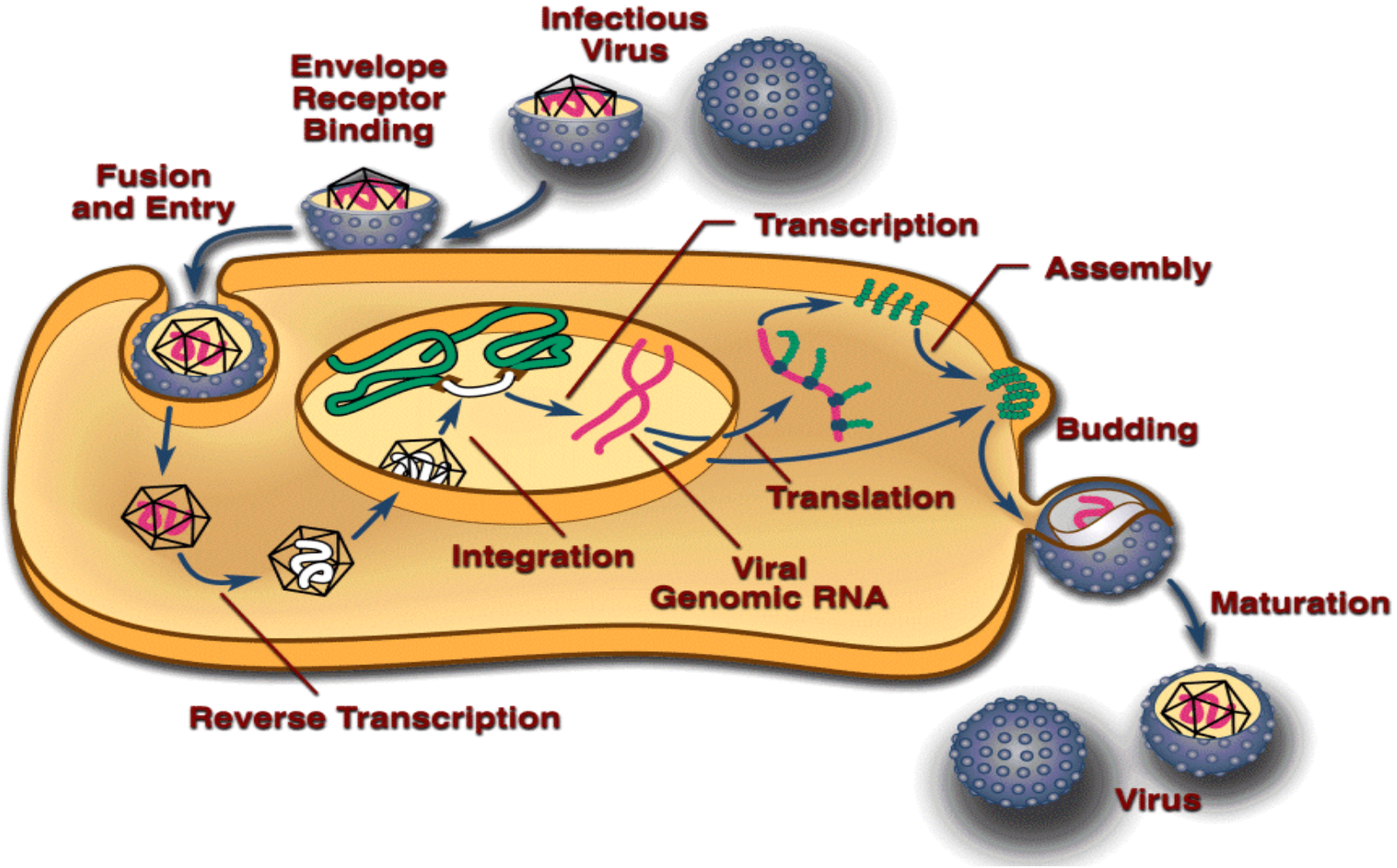
Brain
- Capillary endothelial cells
- Astrocytes
- Macrophages (microglia)
- Oligodendrocytes
- Choroid plexus
- Ganglia cells
- Neuroblastoma cells
- Glioma cell lines
- Neurons (?)

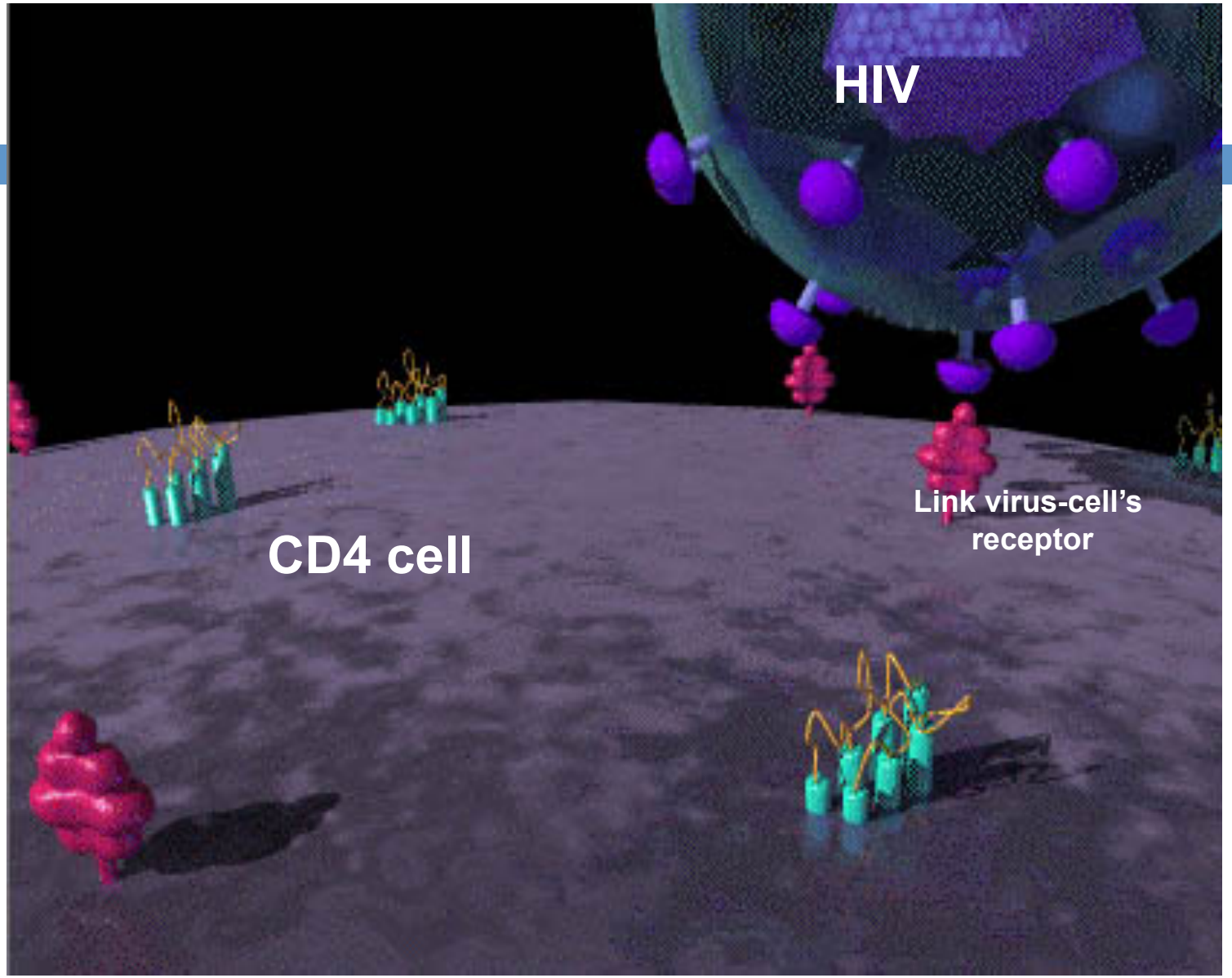
Bowel
- Columnar and goblet cells
- Enterochromaffin cells
- Colon carcinoma cells

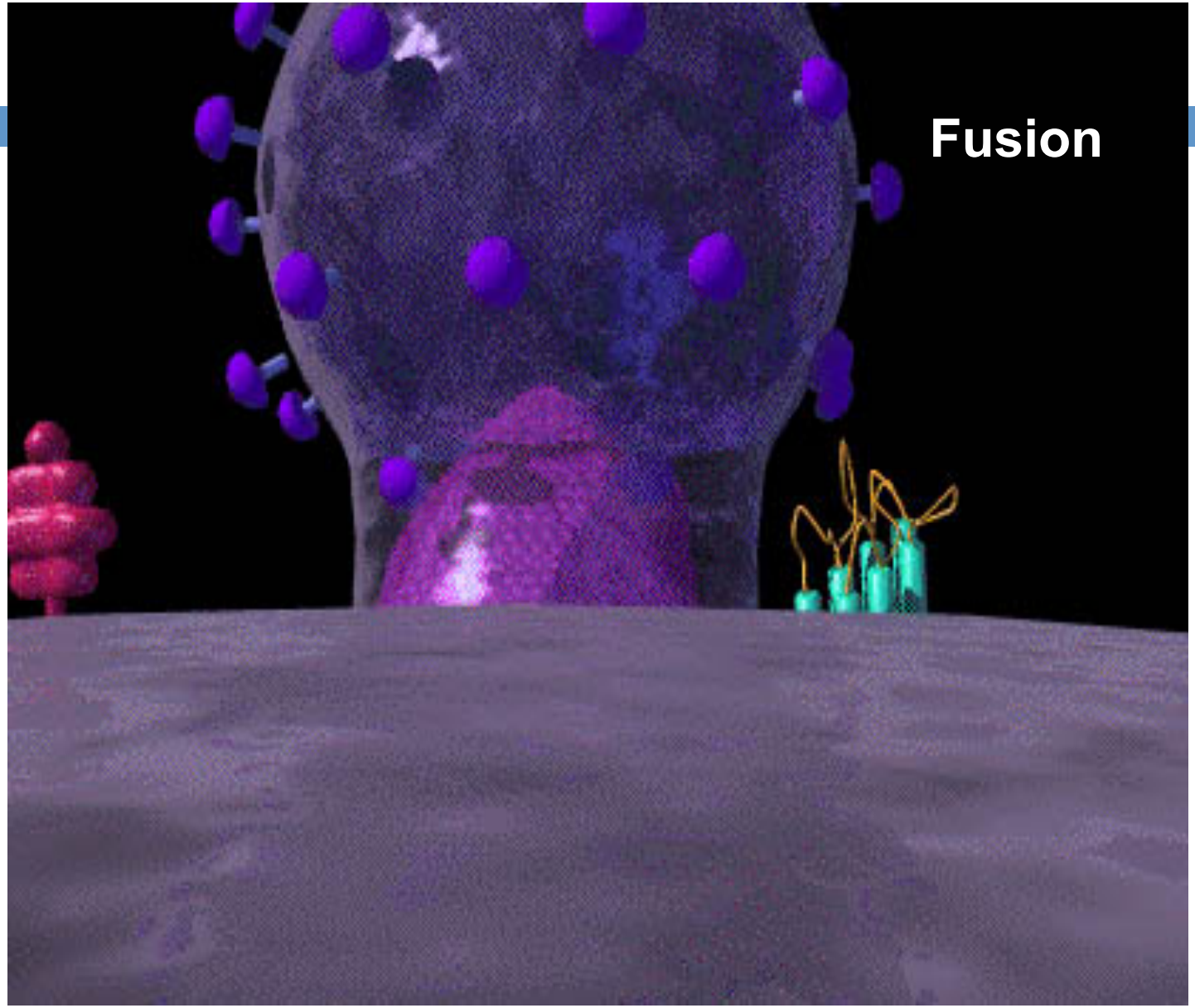
Other
- Myocardium
- Renal tubular cells
- Synovial membrane
- Hepatocytes
- Hepatic sinusoid endothelium
- Hepatic carcinoma cells
- Kupffer cells
- Dental pulp fibroblasts
- Pulmonary fibroblasts
- Fetal adrenal cells
- Adrenal carcinoma cells
- Retinal cells
- Cervix-derived epithelial cells
- Cervix (epithelium?)
- Prostate
- Testes
- Osteosarcoma cells
- Rhabdomyosarcoma cells
- Fetal chorionic villi
- Trophoblast cells

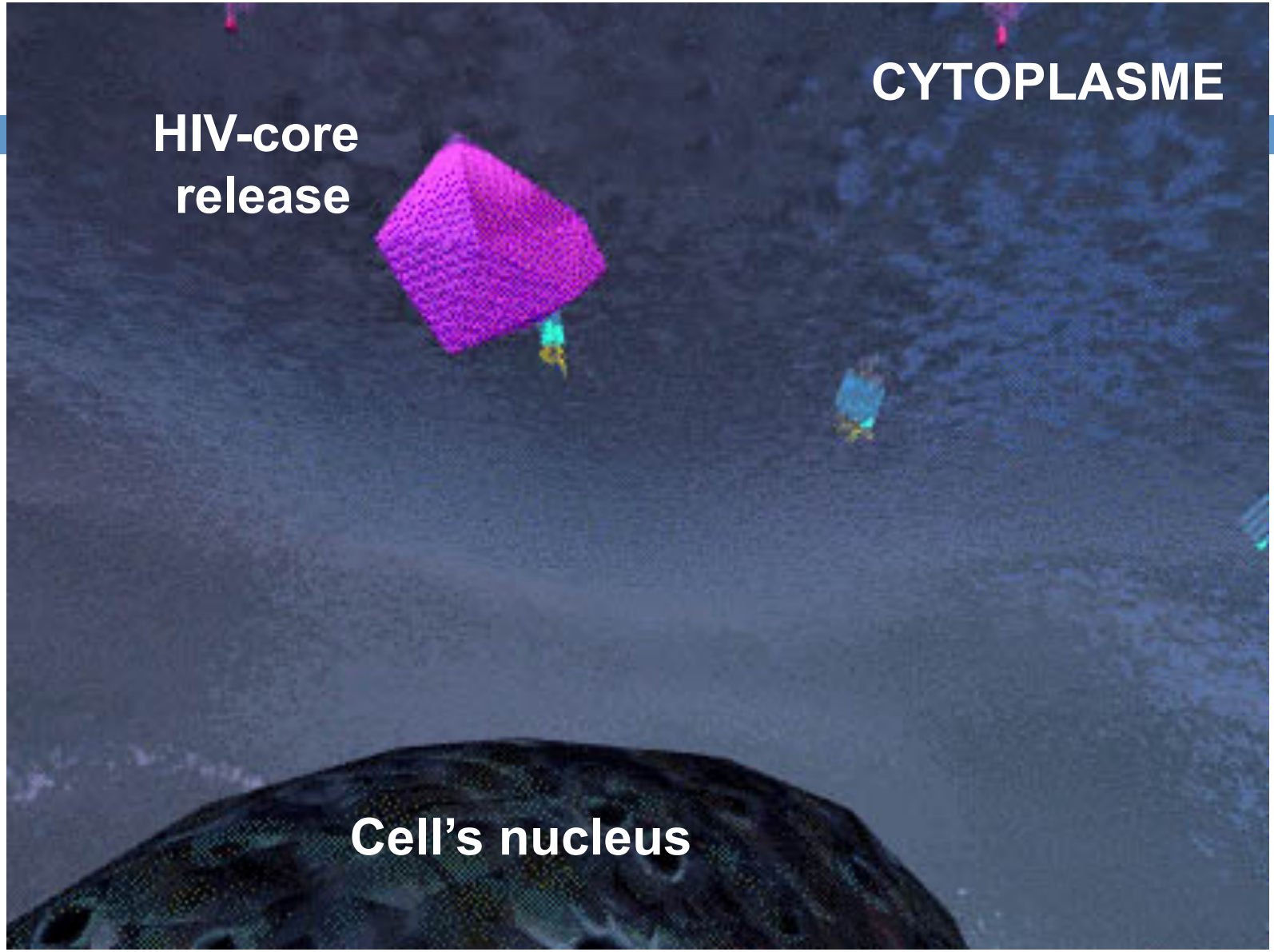
da: *J Levy 2001 (riprodotta con il permesso)*

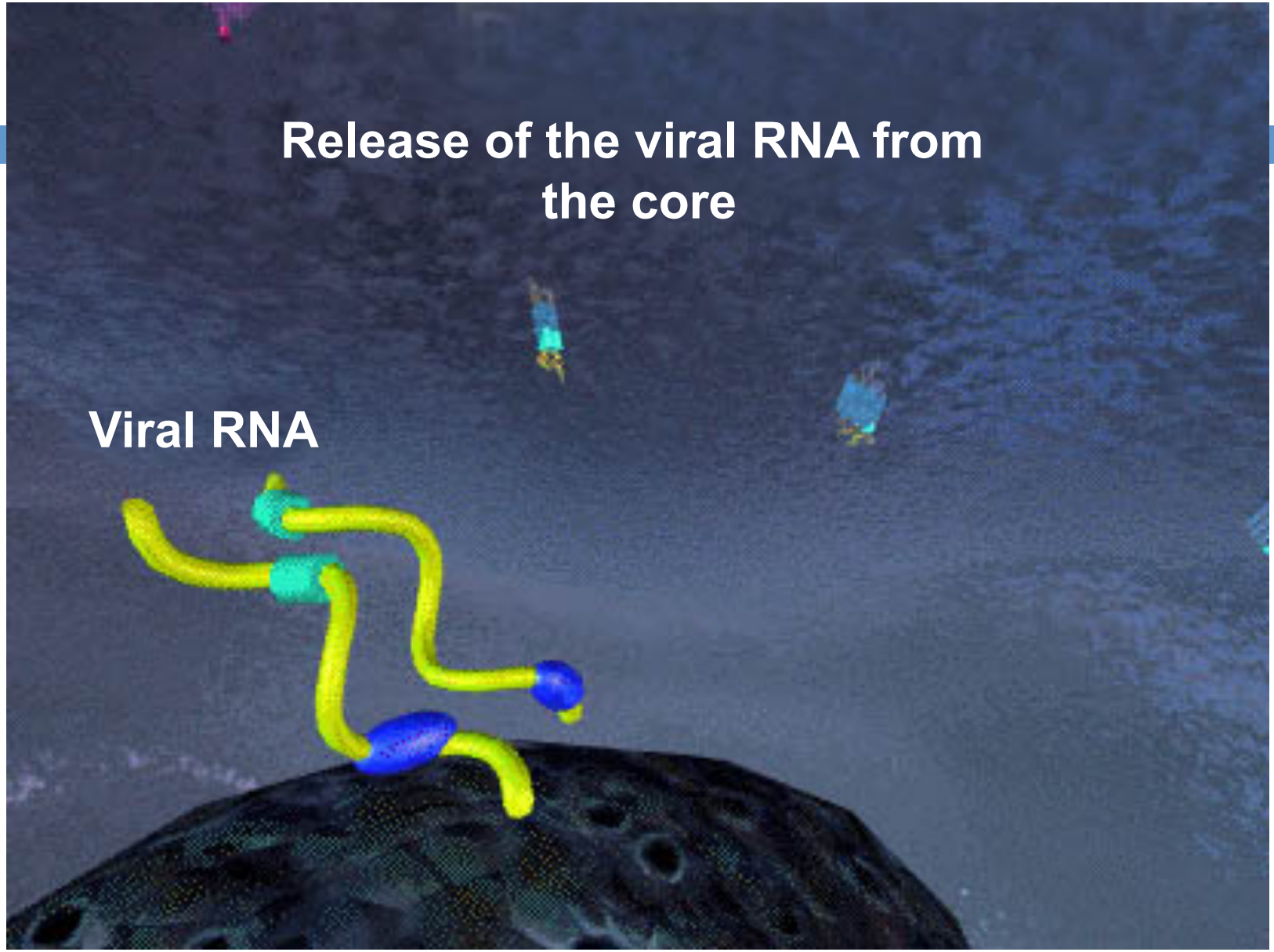
Virus life cycle

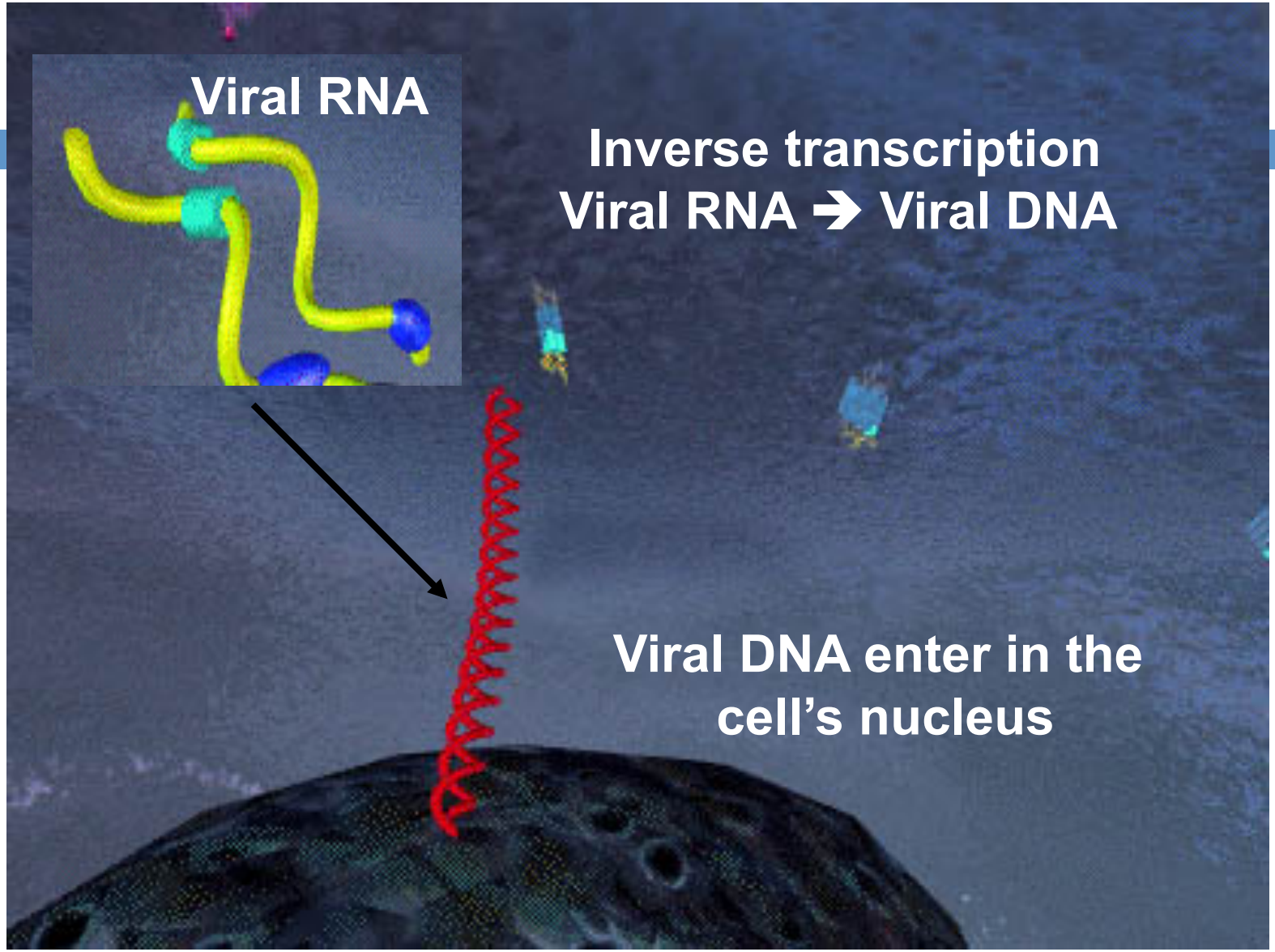


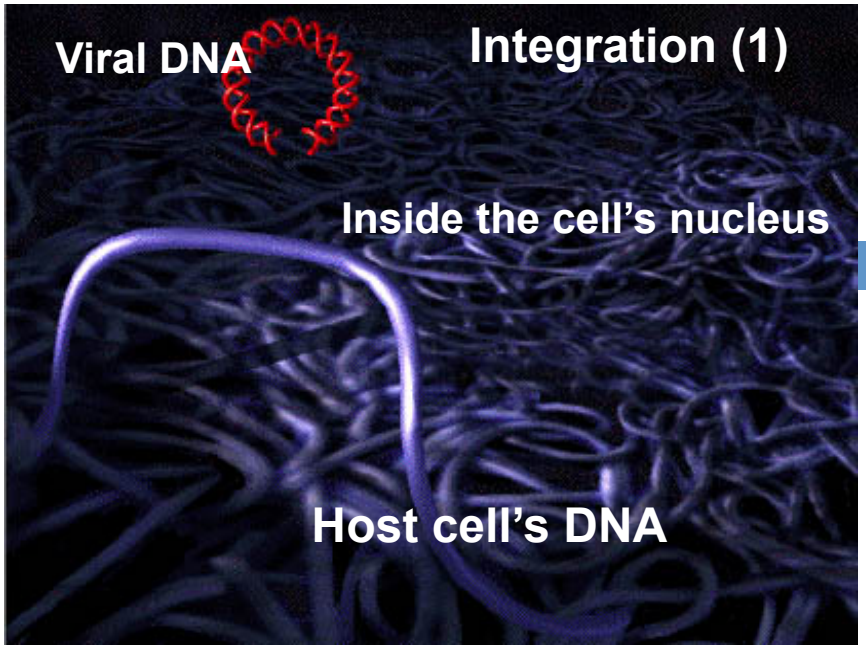

HIV
Link virus-cell's receptor
CD4 cell

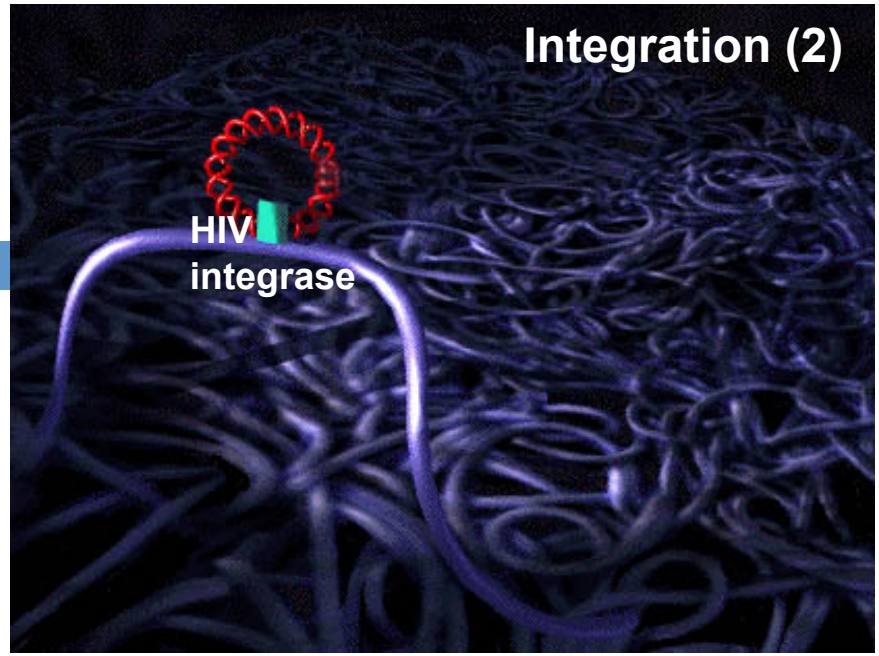

Fusion

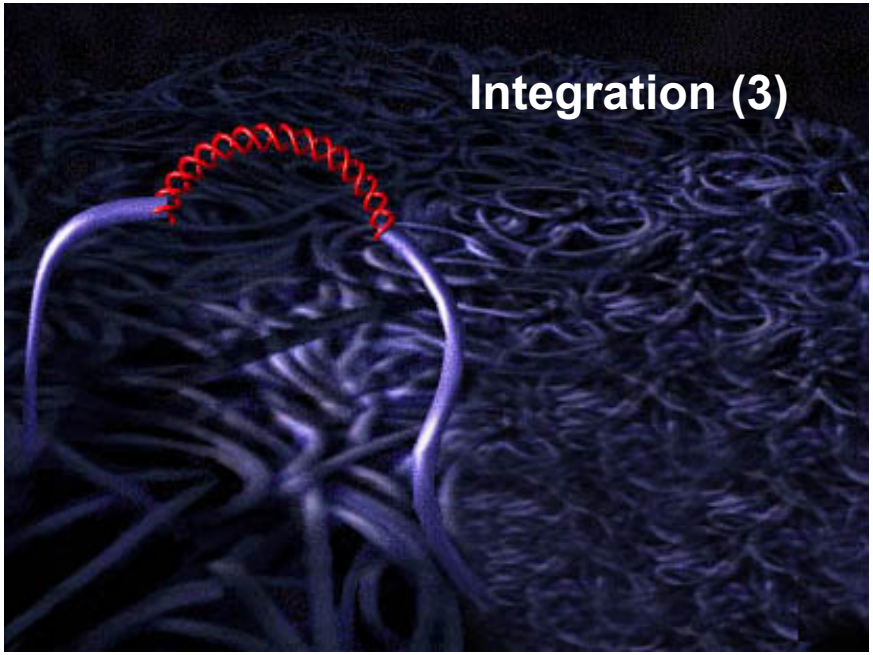

CYTOPLASME
HIV-core
release
Cell’s nucleus

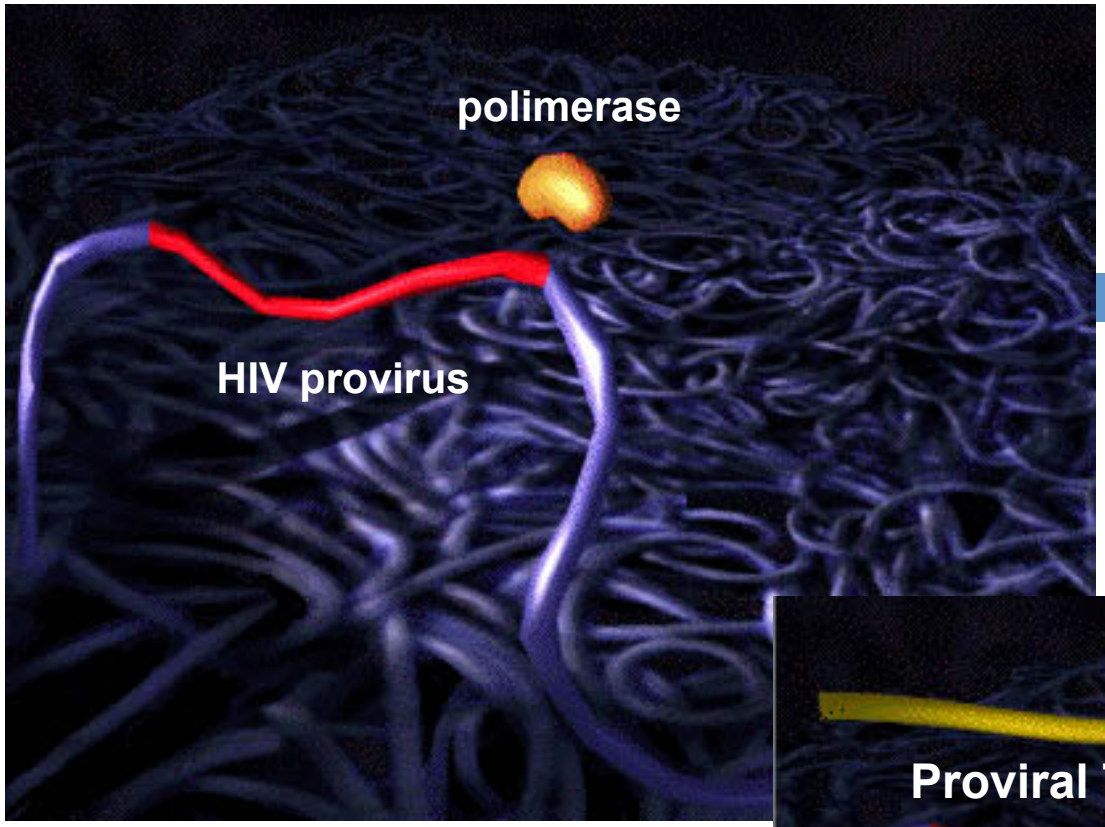

Release of the viral RNA from the core
Viral RNA

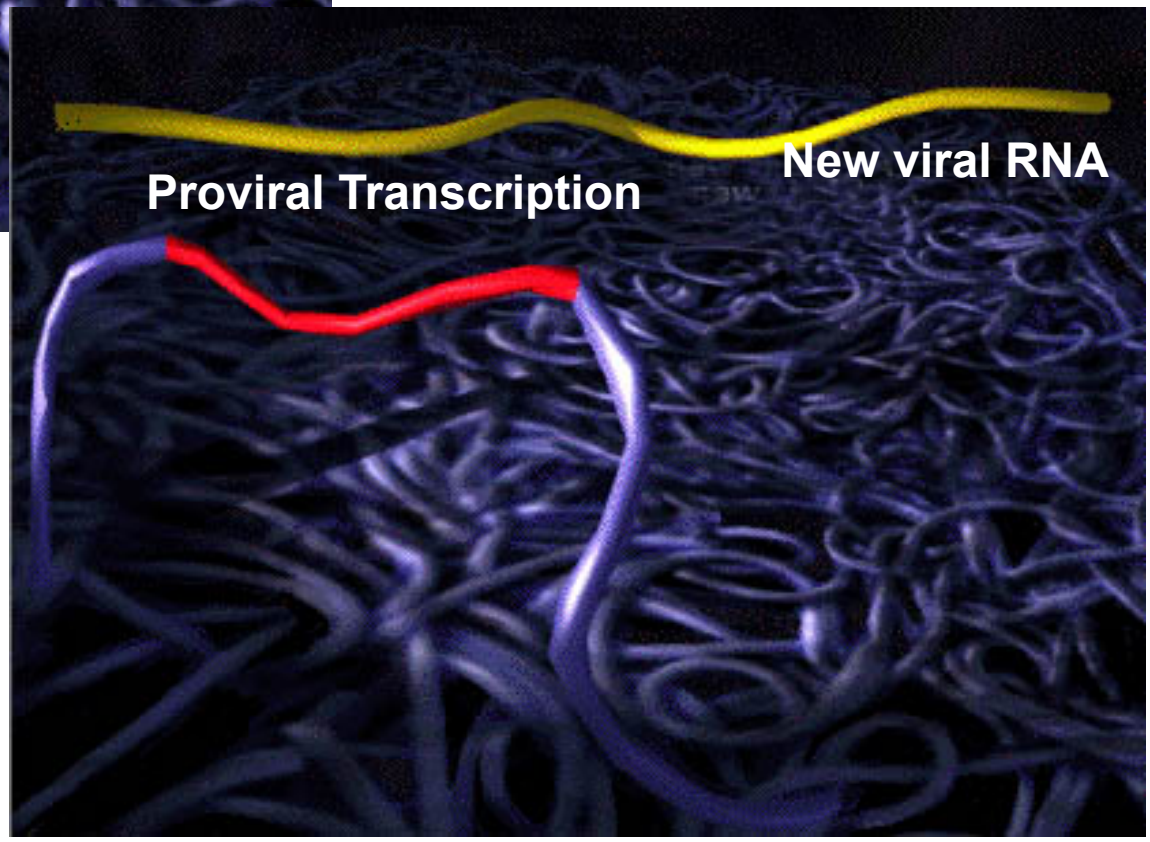

Viral RNA
Inverse transcription
Viral RNA ➔ Viral DNA
Viral DNA enter in the
cell's nucleus

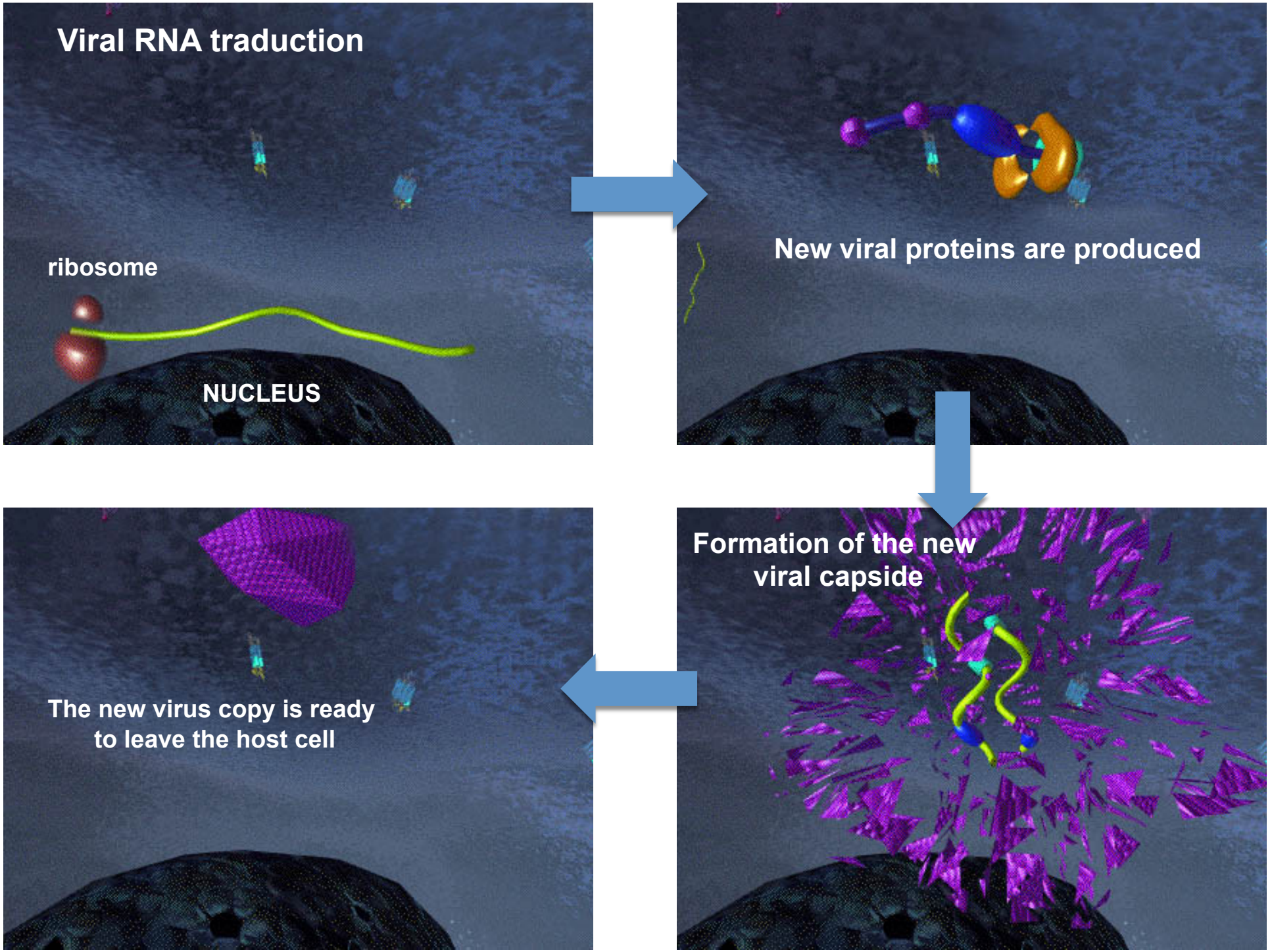

Viral DNA
Integration (1)
Inside the cell's nucleus
Host cell's DNA

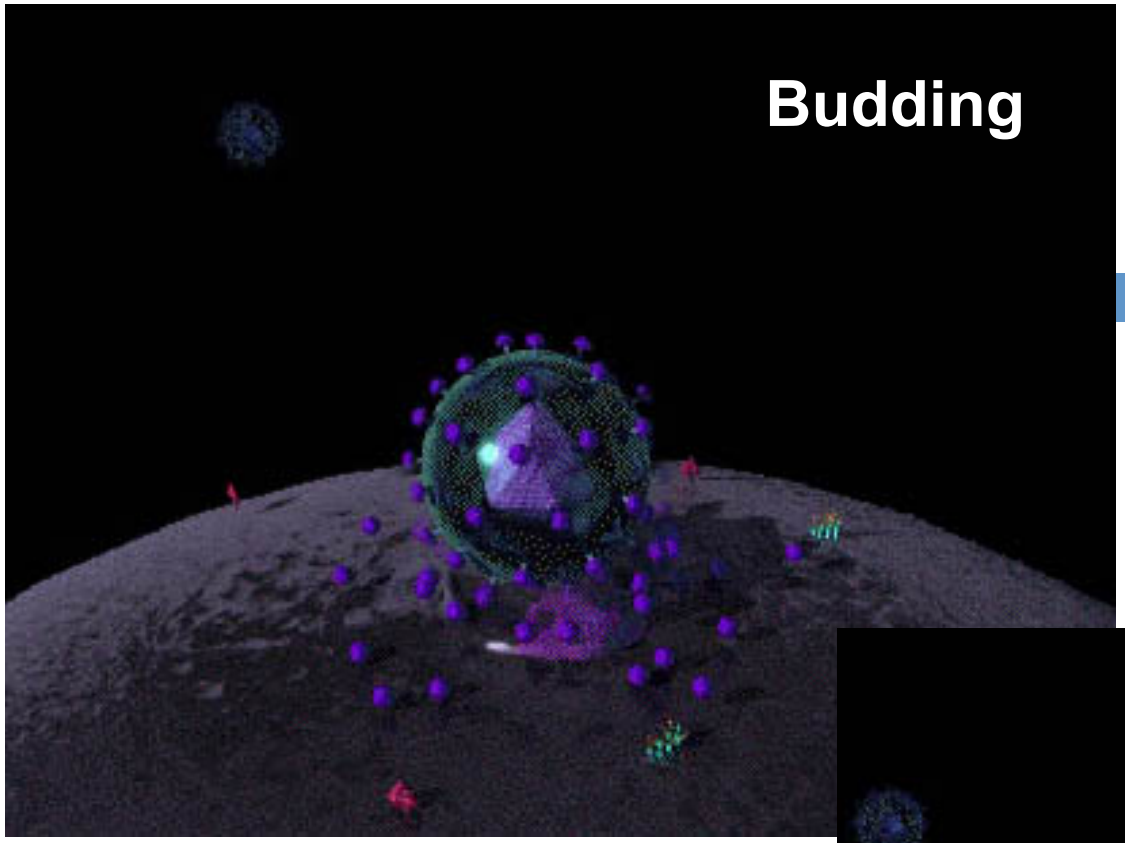

Integration (2)
HIV
integrase


Integration (3)


polimerase
HIV provirus

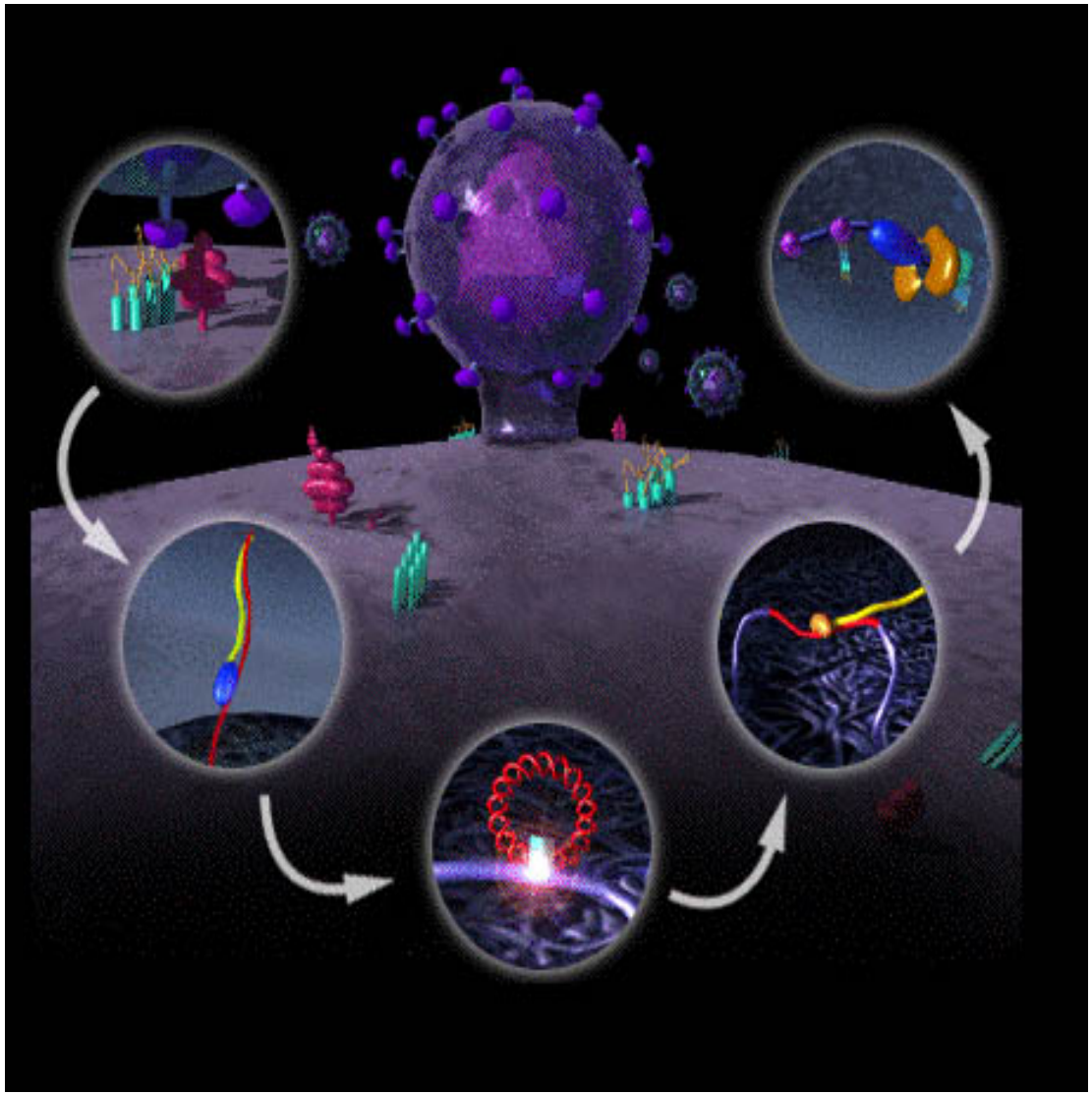

Proviral Transcription
New viral RNA

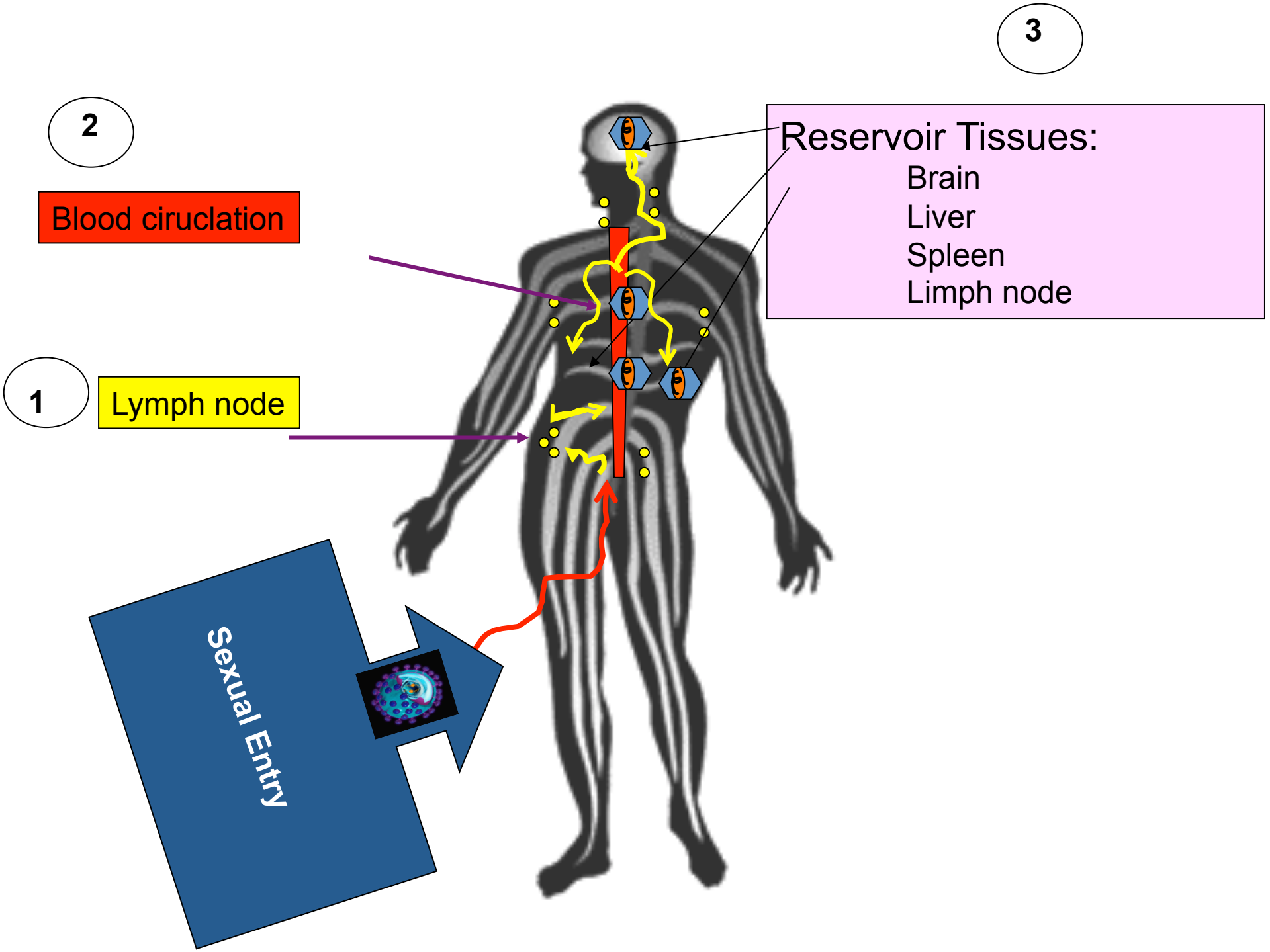

Viral RNA traduction
ribosome
NUCLEUS
New viral proteins are produced
Formation of the new viral capside
The new virus copy is ready to leave the host cell


Budding


Release of the new viral particle that will infect other cells

Vital Cycle of HIV: **8-16 hours**




3
2
Blood ciruclation
Reservoir Tissues:
Brain
Liver
Spleen
Limph node
1
Lymph node
Sexual Entry

Natural history of the infection (1)

CONTAGION

10-15 days

Flu-like symptoms

Window Period

NO symptoms

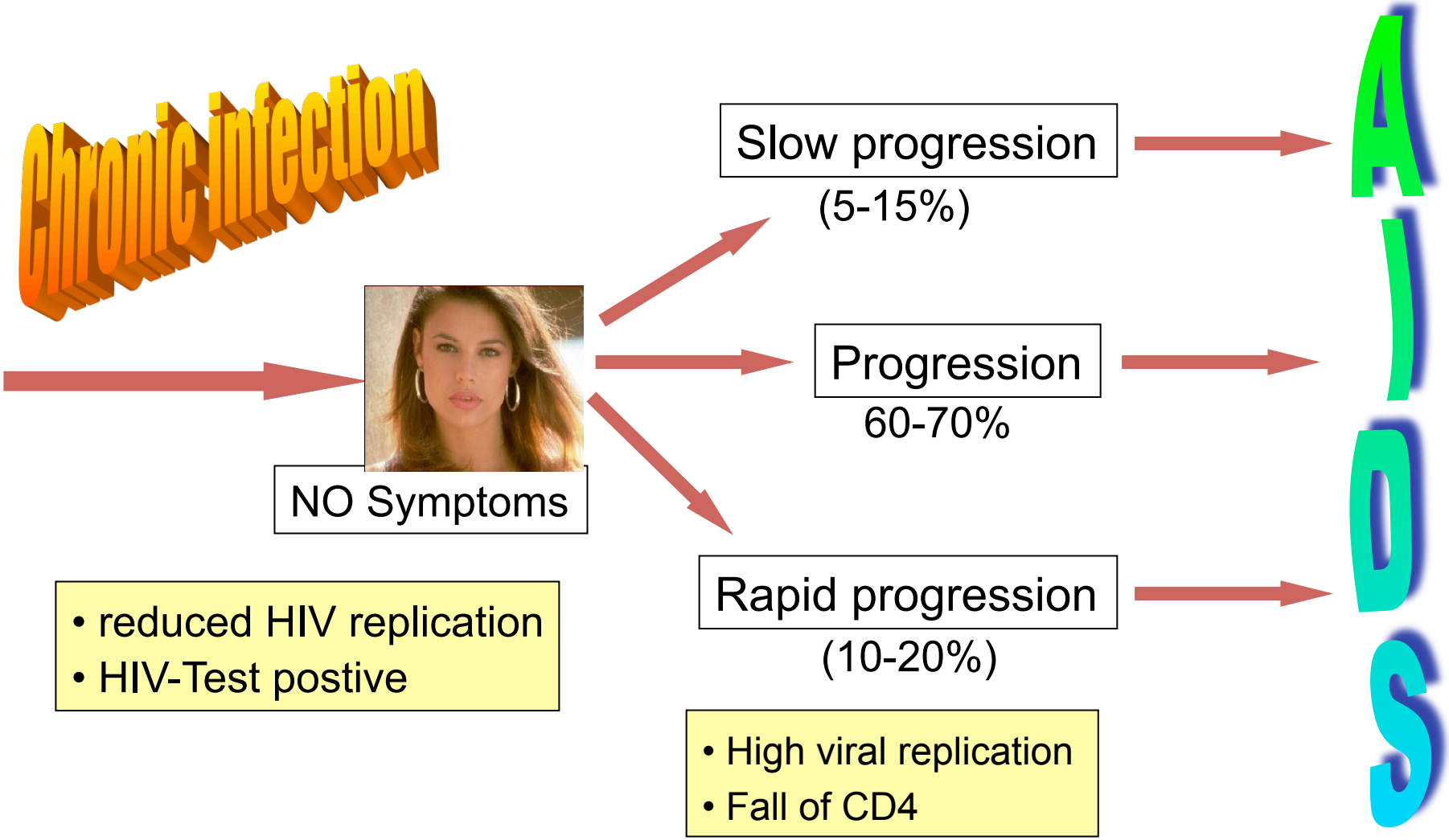
3-6 months

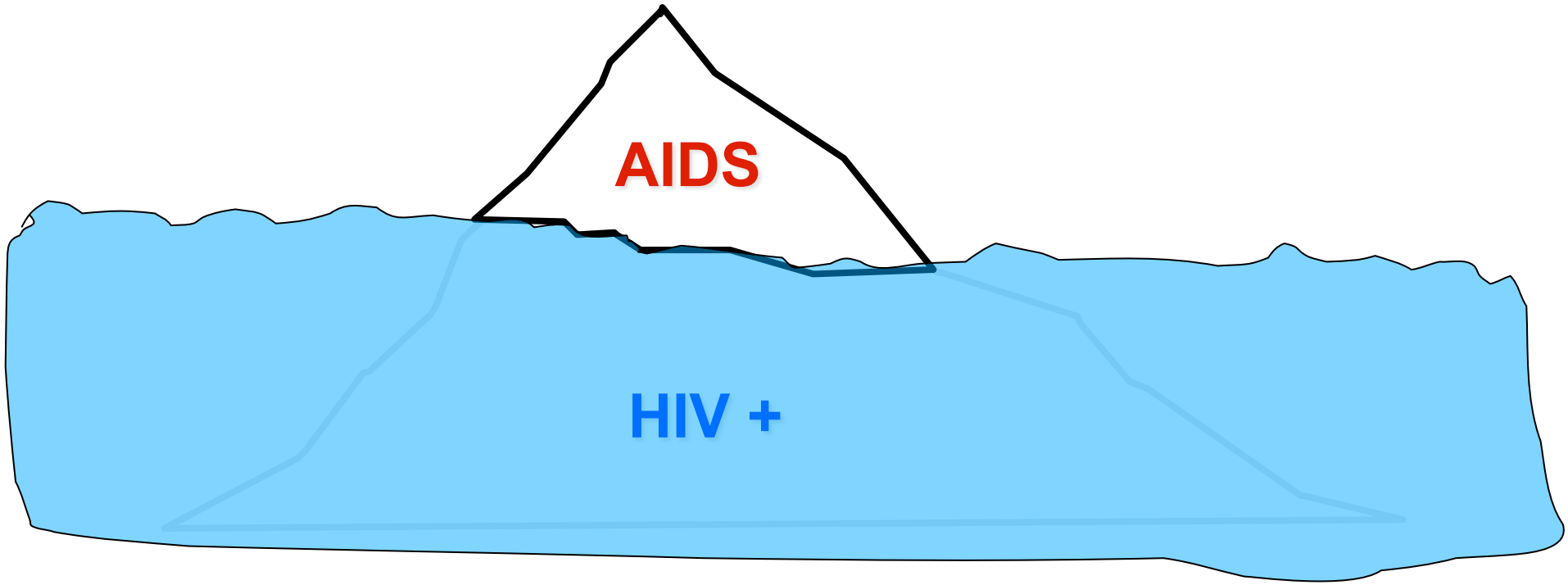
NO Symptoms

- High viral replication
- NO antibodies (HIV-TEST negative)

- HIV replication reduced
- Appearance of HIV antibodies (HIV Test pos)

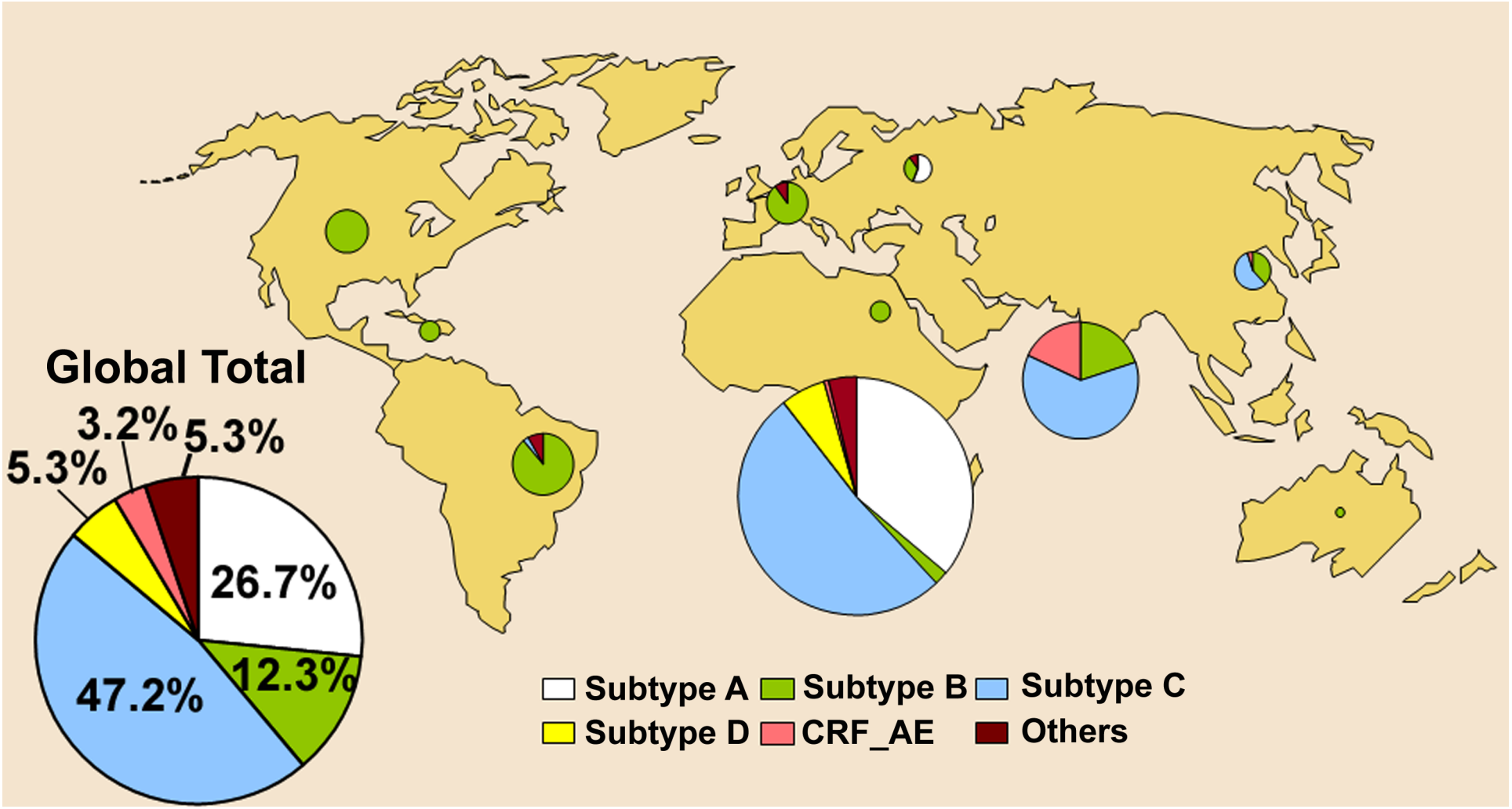
Natural history of the infection (2)



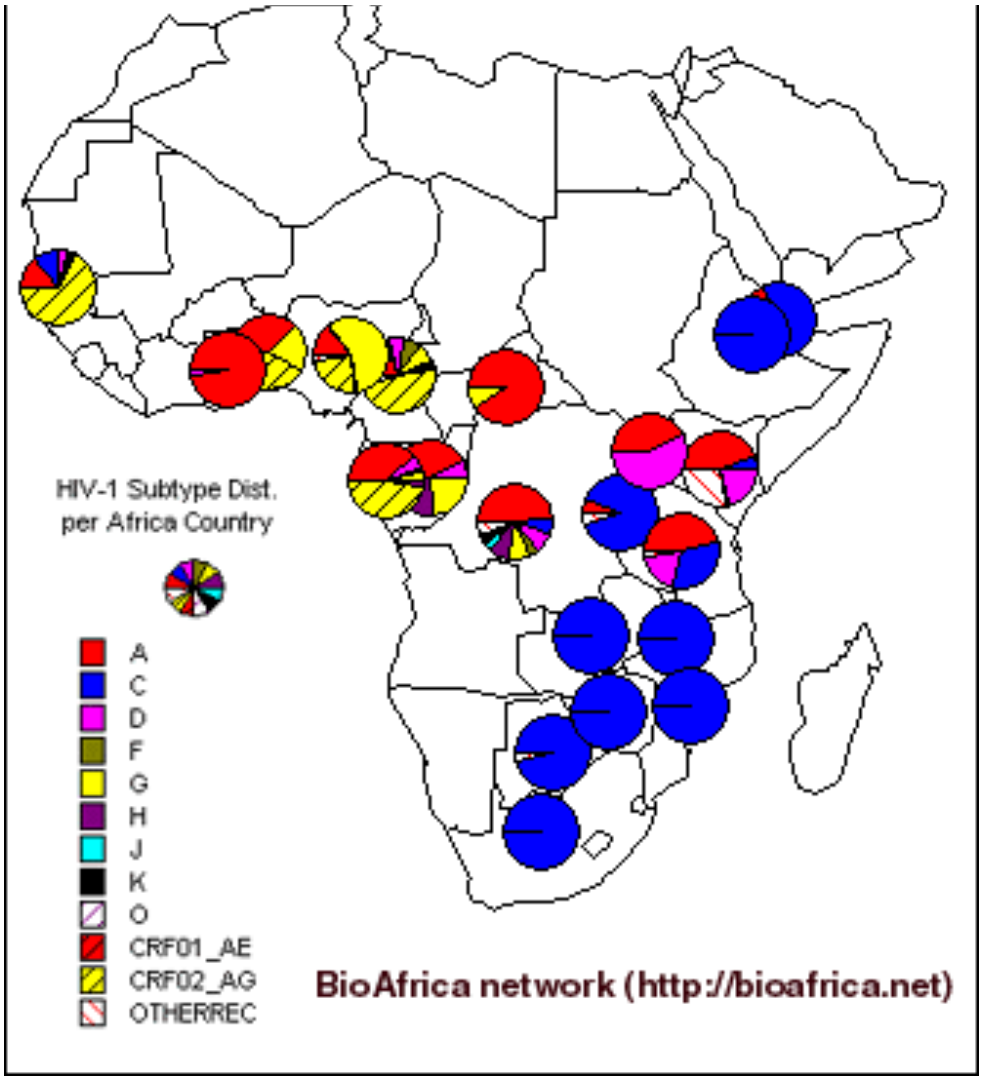


AIDS is the peak of an iceberg

Worldwide genetic diversity of HIV



Genetic diversity of HIV in Africa



Special topics in children

- **High rates of viral replication**
- **High rates of CD4 positive cell destruction** ~ 5% of total per day
- Very high rates of viral mutation
- **Faster rate of disease progression**
- Good immunologic response to ART
- CD4 cell counts are high and variable. CD4% is less variable, and as a result CD4% is used as an immunological marker in young children (<5-6 years)
- **High mortality rate** in perinatally infected children: >60% die by the age of 3 years in resource poor settings

Mode of Transmission

Modes of transmission

- Sexual
- Parenteral (ex. blood exchange)
- Vertical

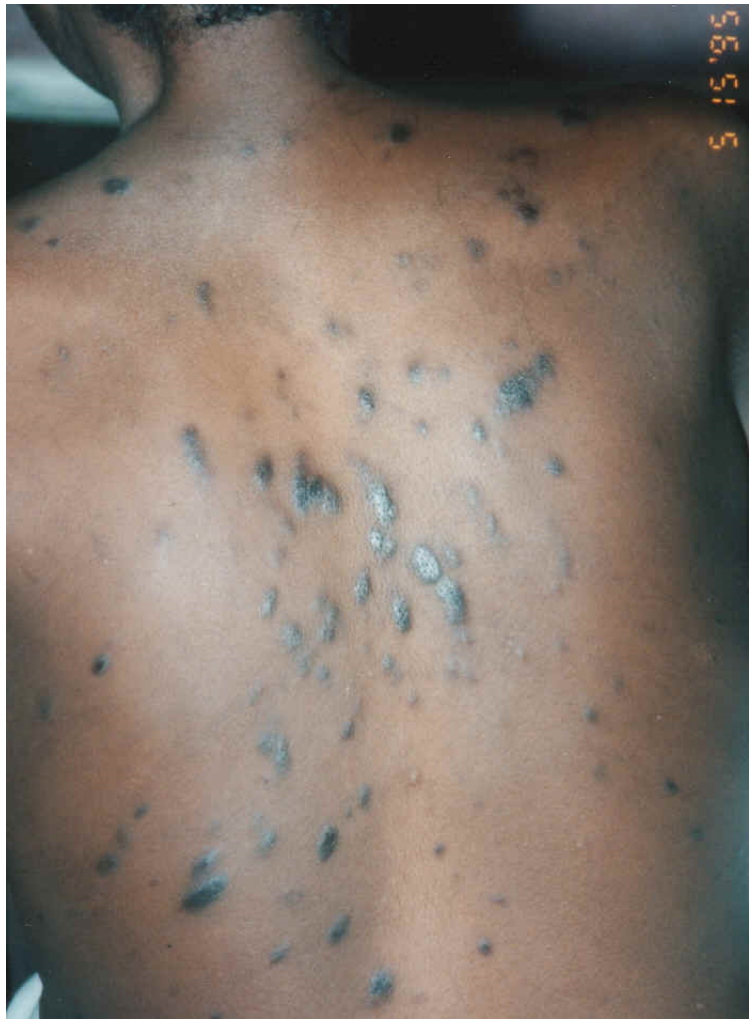
  - **90% of infections in children are by vertical transmission**
    - Overall risk is 25-40%
      - 5-10% in utero
      - 10-20% intrapartum
      - 5-20% breastfeeding
    - Risk period is extended till 6 months later breastfeeding stopping

- About 90% of HIV infected children become infected by vertical transmission
- The most important mode of HIV transmission in the world is sexual (by unprotected intercourse with an infected person)
- The women are more susceptible than the men to get infected sexually

Diagnosis and clinical assessment

Conditions very suggestive for HIV infections

- Pneumocystis pneumonia (PCP)
- Oesophageal candidiasis
- Kaposi's sarcoma
- In girls, acquired recto-vaginal fistula.

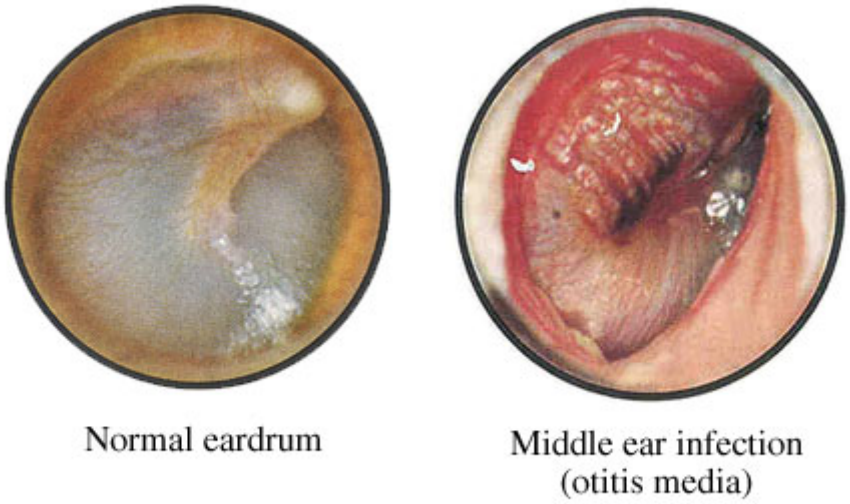


Signs which may indicate a possible HIV infection

- Recurrent bacterial infection
- Oral thrush (candidiasis)
- Chronic parotitis: parotid swelling for >14 days
- Generalized lymphadenopathy
- Hepatomegaly with no apparent cause
- Persistent and/or recurrent fever
- Neurological dysfunction
- Herpes zoster (shingles)
- HIV dermatitis: erythematous purpular rash, extensive fungal infections of the skin, nails and scalp, and extensive molluscum contagiosum.

Signs common in HIV-infected, but also non infected children

- Chronic otitis media: ear discharge lasting more >14 days.
- Persistent diarrhoea: diarrhoea lasting >14 days.
- Moderate or severe malnutrition

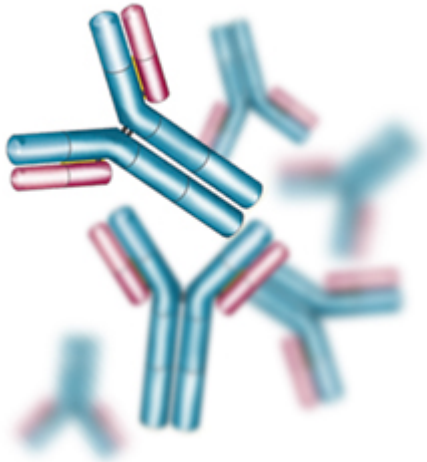


Normal eardrum

Middle ear infection
(otitis media)

Laboratory diagnosis (1)

- Children with HIV-positive mother:
  - Maternal HIV antibodies can be passed to the child and last for up to 15 months, so HIV antibody testing does not reliably indicate HIV infection in children under 15 months of age.
  - Viral testing (e.g. PCR) should be conducted at 4-6 weeks of age for infants known to be HIV exposed, or at the earliest possible opportunity for those seen after 4-6 weeks of age.



Laboratory diagnosis (2)

- Children with HIV-unknown mother status:
  - All infants (<12 months) and children should have their HIV exposure status established at their first contact with the health system, **ideally before 6 weeks of age.**
  - Urgent HIV antibody testing should be carried out for any infant or child presenting with signs, symptoms, or medical conditions that indicate HIV.

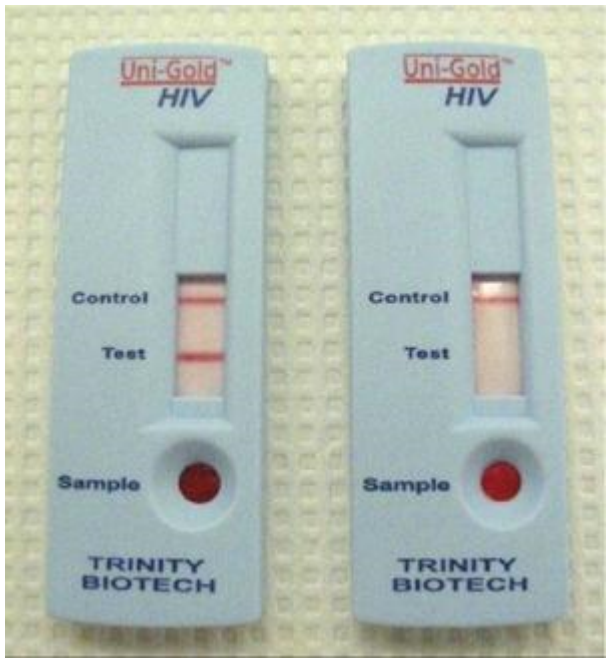
Laboratory diagnosis (3): serology

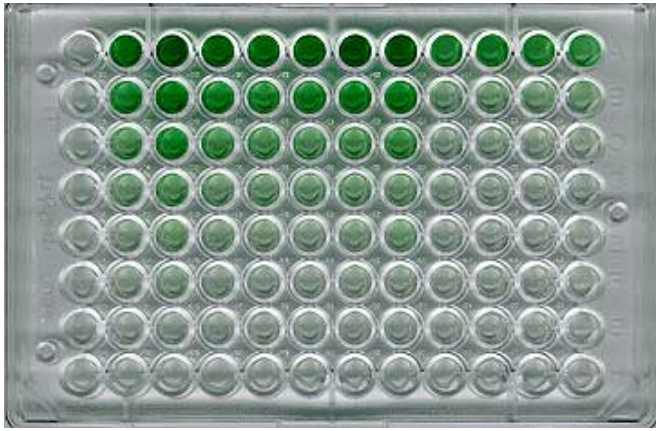
- Antibody Rapid Test
  - This is the most common test available in resource-limited settings
- ELISA test
  - Best performance, but requires laboratory equipment, a regular supply of reagents, and laboratory-trained health personnel

- Both rapid test and ELISA test are useful for diagnosing HIV infection in children aged 18 months and above.

Laboratory diagnosis (4): serology

- Collect blood in a tube for whole blood (serum tube)





Laboratory diagnosis (5): viral tests

- The most reliable method for diagnosing HIV infection in infants and children less than 15 months of age who have anti-HIV antibodies
- Expensive, and requires a sophisticated laboratory set up with trained staff
- Types of test:
  - HIV DNA on whole blood specimen
  - HIV RNA on plasma
  - Up24 Ag on plasma

- All infants with an initial positive virological test result should be started on ART without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result.

Baseline clinical assessment (1)

- Following confirmation of HIV infection status the baseline, clinical assessment for children should include:
  - clinical staging of HIV disease;
  - identification of concomitant medical conditions (e.g. TB, pregnancy in adolescent girls);
  - detailing of concomitant medications, including co-trimoxazole and traditional or herbal therapies;
  - weight, height, head circumference and other measures of growth and nutritional status;
  - developmental status;

Baseline clinical assessment (2)

- Laboratory assessment should include:
  - Blood count with haemoglobin and white blood cells
  - pregnancy test for sexually active adolescent girls
  - screening for TB and malaria (and diagnostic testing where clinically indicated)
  - CD4 monitoring and viral load (desirable but not essential).

Clinical staging (1)

Classification of HIV-associated clinical disease	WHO clinical stage
Asymptomatic	1
Mild	2
Advanced	3
Severe	4

Clinical staging (2)

WHO Paediatric HIV Clinical Staging

WHO Paediatric Clinical Staging for HIV	
Stage 1	**Stage 2**
Asymptomatic	Hepatomegally
Persistent generalized lymphadenopathy (PGL)	Parpular pruritic eruptions
	Seborrhhoeic dermatitis
	Extensive human papilloma virus infection
	Extensive molluscum contangiosum
	Fungal nail infections
	Recurrent oral ulcerations
	Lineal gingival erythema
	Angular cheilitis
	Parotid enlargement
	Herpes zoster
	Recurrent or chronic URTIs (otitis media, ottorhoea, sinusitis)

Clinical staging (3)

Stage 3	Stage 4
Moderate unexplained malnutrition, not adequately responding to standard therapy	Unexplained severe wasting or malnutrition not responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)	Pneumocystis pneumonia
Unexplained persistent fever (intermittent or constant for longer than one month)	Recurrent severe bacterial infections (empyema,pyomyositis, bone or joint infections, meningitis, excluding pneumonia)
Oral candidiasis (outside the neonaltal period)	Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
Oral hairy leukoplakia (OHL)	Extrapulmonary Tubeculosis
Pulmonary Tuberculosis	Kaposi Sarcoma
Severe recurrent presumed bacterial pneumonia (2 or more episodes in 6 months)	Oesophageal candidiasis (or candida of the trachea, bronchi or the lungs)
Acute necrotizing ulcerative gingivitis/ periodontitis	Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age over one month
Lymphoid interstitial pneumonia (LIP)	Central nervous system toxoplasmosis (after the neonatal period)
Unexplained anaemia (<8gm/dl), neutorpaenia (<500/mm^3) or thrombocytopaenia (<30000/ mm^3)	Extrapulmonary cryptococcosis , including meningitis
	HIV encephalopathy
	Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiodomycosis)
	Chronic cryptosporidiosis
	Chronis isosporiasis
	Disseminated non-tuberculous mycobacteria infection
	Cerebral or B cell non-Hodgkin lymphoma
	Progressive multifocal leucoencephalopathy
	HIV-associated cardiomyopathy or nephropathy.

Bioethical focus

- HIV testing should be voluntary and free of coercion
- All diagnostic HIV testing must be:
  - confidential
  - accompanied by counselling
  - only conducted with informed consent (from a child's parent or guardian) is required, so that it is both informed and voluntary.

Antiretroviral therapy

When to initiate antiretroviral therapy (ART)? (1)

Age	Infants and children <24 months of age[a,b]	≥24 months of age to 59 months of age	Five years of age or older
%CD4+	All[c]	≤25	NA
Absolute CD4	All[c]	≤750 cells/mm^3	≤350 cells/mm^3 (As in adults)

	Clinical stage	Immunological
<24 months	Treat all	
>24 months	Stage 4[a]	Treat all[b]
	Stage 3[a]	Treat all
	Stage 2	Treat if CD4 below age-adjusted threshold Don't treat if no CD4 available:
	Stage 1	

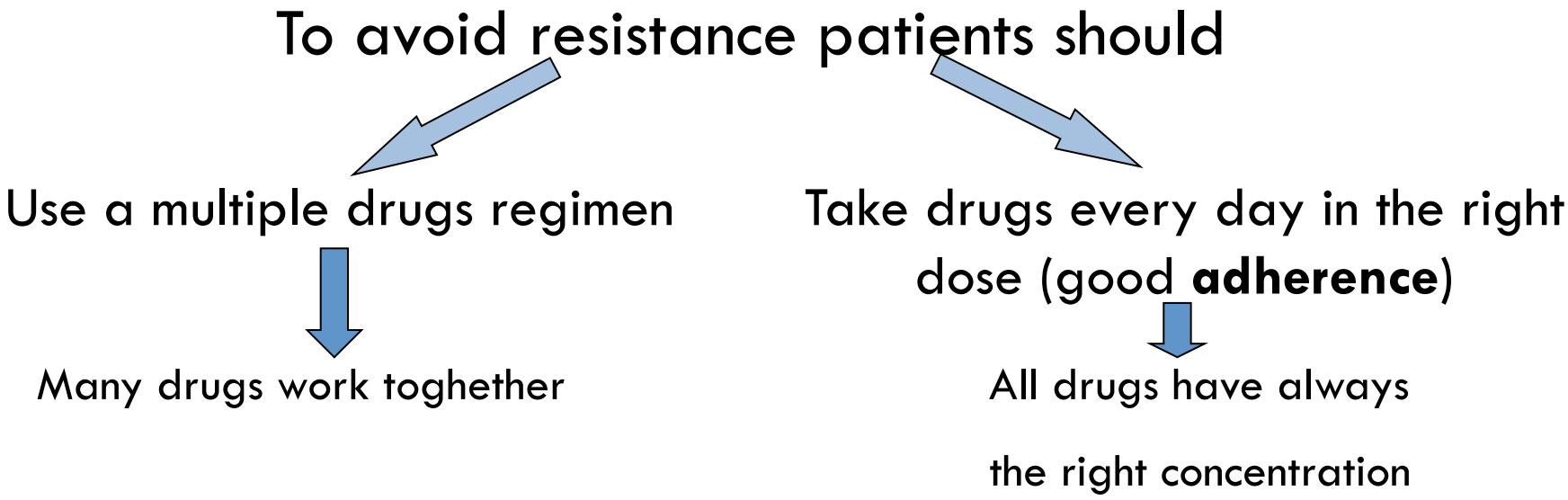
When to initiate antiretroviral therapy (ART)? (2)

A presumptive diagnosis of severe HIV disease should be made if:	
1. The child is confirmed as being HIV antibody-positive **AND**	2a. The infant is symptomatic with two or more of the following: • oral thrush • severe pneumonia • severe sepsis **OR** 2b. A diagnosis of any AIDS-indicator condition(s) a can be made
Other findings that support the diagnosis of severe HIV disease in an HIV-seropositive infant include: – Recent HIV-related maternal death or advanced HIV disease – Child's %CD4+ <20%	
Confirm the diagnosis of HIV infection as soon as possible.	

- If presumptive diagnosis is made, start ART

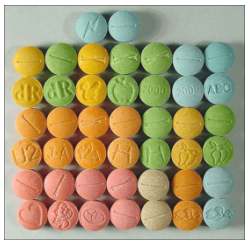
ART “rules”

- Antiretroviral drugs are not a definitive cure for HIV, but they reduce mortality and morbidity
- The current standard treatment for HIV infection uses three ARV medications (triple drug therapy)



Adherence

- Maximize adherence (>90%) is essential to avoid resistance and preserve ART regimen efficacy
  - Education
  - Taking the medications properly-for example, if medications are mixed with food or not
  - Identifying a back-up informed caregiver
  - Continuously assessing adherence
  - Use of calendars or other visual aids to illustrate dosing
  - Directly observed therapy (DOT)



Antiretroviral drugs available for pediatric usage

1. Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)	
Zidovudine	ZDV (AZT)
Lamivudine	3TC
Stavudine	D4T
Didanosine	Ddl
Abacavir	ABC
Emtricitabine	FTC

2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Nevirapine	NVP
Efavirenz	EFV

3. Protease Inhibitors (Pis)	
Nelfinavir	NFV
Lopinavir/ritonavir	LPV/r
Atazanavir	ATZ

First line regimens (1)

- The standard regimen for first-line ART consists of 2 NRTIs + 1 NNRTI
  - Zidovudine (AZT) or Abacavir (ABC) or Stavudine (d4T)

    +

    Nevirapine (NVP) or Efavirenz (EFV)

  - Notes
    - d4T is no longer preferred
    - Avoid EFV if < 3 aa or fertile girls (teratogenic)
    - Avoid NVP in adolescent girls if CD4+ >250/mmc (hepatotoxicity)

First line regimens (2)

- In infants, if Nevirapine has been used during pregnancy
  - Avoid NVP
  - Use Lopinavir/ritonavir (LPV/r)

- If poor adherence is suspected
  - Triple NRTI regimen
    - AZT/d4T+ABC+3TC

First line regimens (3)

Patient group	Standard first-line regimen
INFANTS	
Infant or child <24 months not exposed to ARVs	NVP + 2 NRTI
Infant or child <24 months exposed to NNRTI	LPV/r + 2 NRTI
Infant or child <24 months with unknown ARV exposure	NVP + 2 NRTI
CHILDREN	
Children 24 months to 3 years	NVP + 2 NRTI
Children >3 years	NVP or EFV + 2 NRTI

Treatment failure

- **Clinical failure:** when clinical stage 3 or 4 events develop in a child who has been on therapy for at least 24 weeks
  - Switch regimen!

- **Virological failure:** persistent viral load above 5000 copies/ml, after at least 24 weeks on ART
  - Switch regimen!

Second line regimens

- In the event of treatment failure, the entire regimen should be changed from a first-line to a second-line combination.
- The new second-line regimen should include at least three new drugs, one or more of them from a new class.

Follow-up (1)

- Children who are not yet eligible for ART
  - Every 3-6 months the same parameters used in baseline assessment. As the child approaches the clinical or immunological threshold for initiating ART, clinical evaluation

Follow up (2)

- Children on ART

Diagnosis and monitoring laboratory tests	Baseline (at entry into care)	At initiation of first-line or second-line ARV regimen	Every six months	As required or symptom-directed
HIV diagnostic testing: viral and Ab testing	✓	-	-	-
Haemoglobin[a]	✓	✓	-	✓
WBC and differential[b]	✓	✓	-	✓
%CD4+ or absolute CD4 cell count[c]	✓	✓	✓	✓
Pregnancy testing in adolescent girls	✓[d]	✓	-	✓
Full chemistry (including, but not restricted to, ALT,[e] liver enzymes, renal function, glucose, lipids, amylase, lipase and serum electrolytes)[f]	-	-	-	✓
HIV viral load measurement[g]	-	-	-	✓

Follow up (3)

- Children on ART
  - CD4 values every six months
  - If AZT containing regimen: haemoglobin measurement at weeks 4, 8 and 12 after initiation of ART or in a symptom-directed approach.
  - If NVP containing regimen: AST and ALT during the first few months of treatment, or who have co-infection with hepatitis

More common toxicity: NRTI

- AZT
  - Anemia and/or neutropenia
  - Lactic acidosis
  - Gastro-intestinal intolerance
- d4T
  - Lactic acidosis
  - Peripheral neuropathy
  - Pancreatitis
  - Lipoatrophy/metabolic syndrome
- ABC
  - Hypersensitivity reactions

More common toxicity: NNRTI and PI

- NVP
  - Acute symptomatic hepatitis
  - Hypersensibility reaction
- EFV
  - Central nervous system toxicity (nightmares, psycotic reactions…)
  - Teratogenicity
- LPV/r
  - Lipoatrophy/metabolic syndrome
  - Gastro-intestinal intolerance

Other cares

Nutritional support (1)

- Prevent of mother-to-child-transmission (MTCT) of HIV via breast feeding,
- The type and quantity of food, and the frequency of feeding should be appropriate for the infant/ child's age
- Infants and children require adequate micronutrient intake, particularly in the case of vitamin A, iron, iodine and zinc
- Monitoring wasting syndrome

Nutritional support (2)

- Ensure household consumption of iodized salt.
- Inform the mother about the importance of hygiene when preparing food because her child can easily get sick.
- She should wash her hands after going to the toilet and before preparing food

Prophylaxis: Co-trimoxazole

- Starting at 4-6 weeks of age
- Prevents pneumocystis pneumonia (PCP)
- Protects against common bacterial infections, toxoplasmosis, and malaria

- Doses:
  - <6 months: 100 mg sulfamethoxazole/20 mg trimethoprim
  - 6 months– 5 years: 200 mg sulfamethoxazole/ 40 mg trimethoprim
  - 6 – 14 years: 400 mg sulfamethoxazole/80 mg trimethoprim
  - >=15 years: 800 mg sulfamethoxazole/160 mg trimethoprim

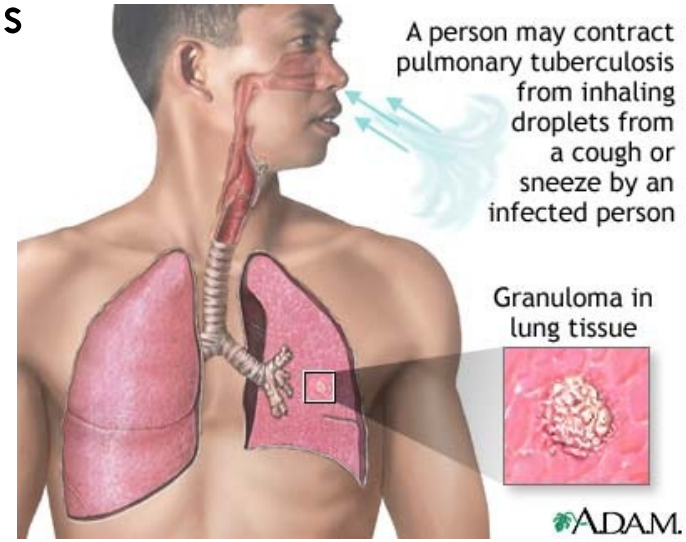
Who needs co-trimoxazole prophylaxis?

Situation			
HIV-exposed infants and children	**Infants and children confirmed to be living with HIV infection**		
	< 1 year	1 – 4 years	≥ 5 years
Co-trimoxazole prophylaxis is universally indicated, starting at 4-6 weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection.	Co-trimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage OR Any WHO stage and CD4 <25%	Follow adult recommendations

Once a child with HIV infection is started on co-trimoxazole, prophylaxis should continue until five years of age regardless of clinical symptoms or CD4 percentage.

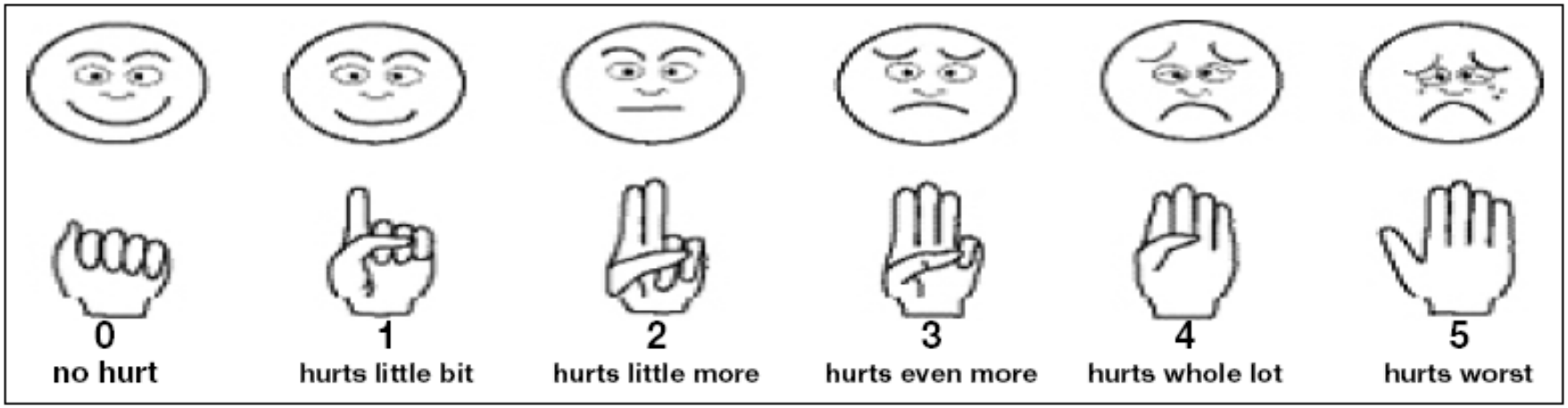
Prophylaxis: Isoniazid (INH)

- In case of TB contacts:
  - < 5 years
    - Establish that children do not have TB or possible TB
    - Give 10 mg/kg Isoniazid daily for at least 6 months
  - > 5 years
    - TST: if positive give prophylaxis



Pain management

- May be useful assessing pain using facial expressions



Vaccines

- HIV-exposed infants and children should receive all vaccines under the Expanded Programme for Immunization (EPI), including Haemophilus influenzae type B and pneumococcal vaccine
- Common schedules, with following exceptions:
  - Measles: 1st dose of standard measles vaccine at six (or nine) months of age, with a second dose as soon as possible after nine (or twelve) months of age, unless they are severely immuno-compromised at that time
  - Pneumococcal vaccine: delay if the child is severely immuno-compromised.
  - Haemophilus influenzae: delay if the child is severely immuno-compromised
  - BCG: should not be given to children known to be HIV-infected (if symptomatics)

Thank you!