Virology for 2nd Year MD Students

(10) Retroviruses 2

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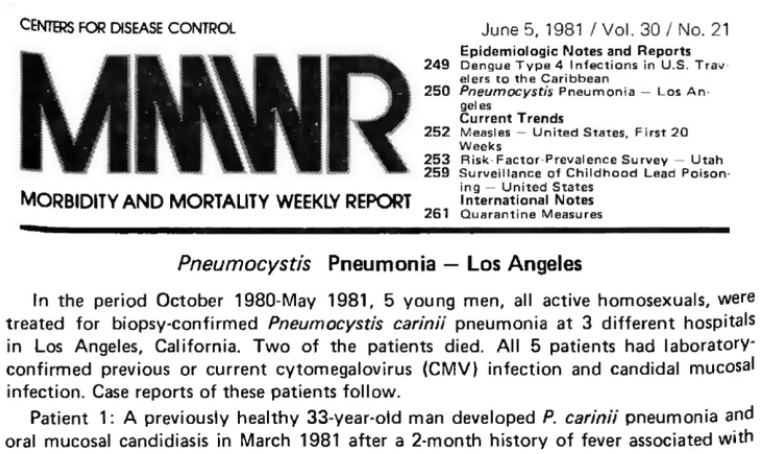
Background on AIDS

1908	HIV-1 tMRCA	1981	Reporting of AIDS
1930	Group M tMRCA	1982	AIDS term coined
1955	Subtype B tMRCA	1983	HIV-1 isolated
1966	Spread to Haiti	1990	AZT approved
1969	Spread to US	1996	Hit early hit hard



CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 21

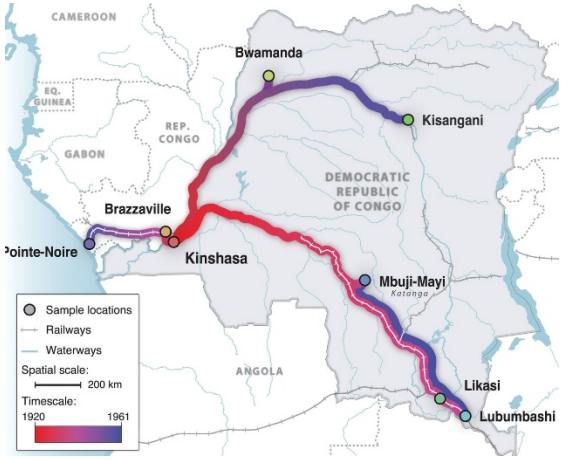
MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Pneumocystis **Pneumonia — Los Angeles**

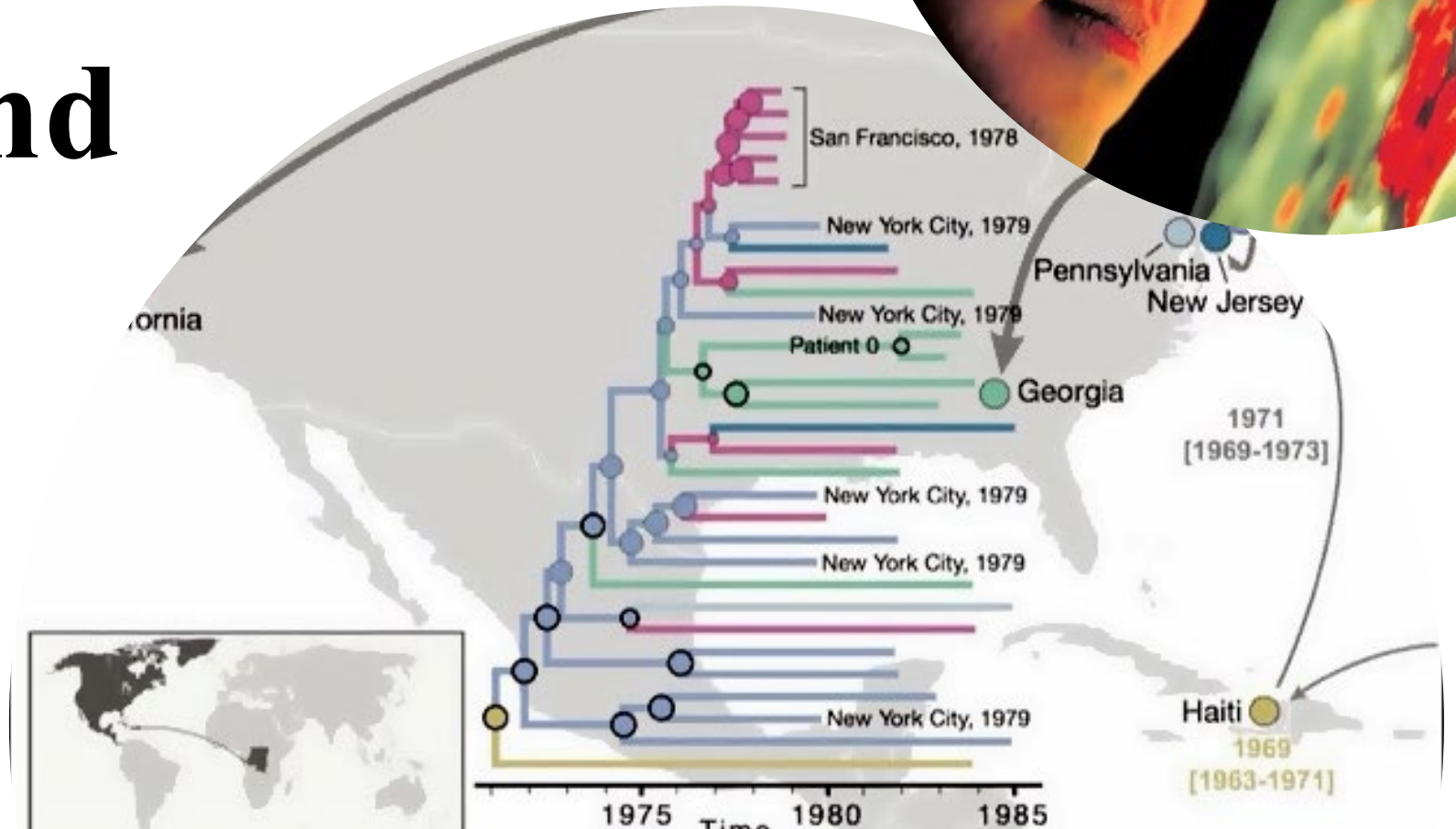
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with

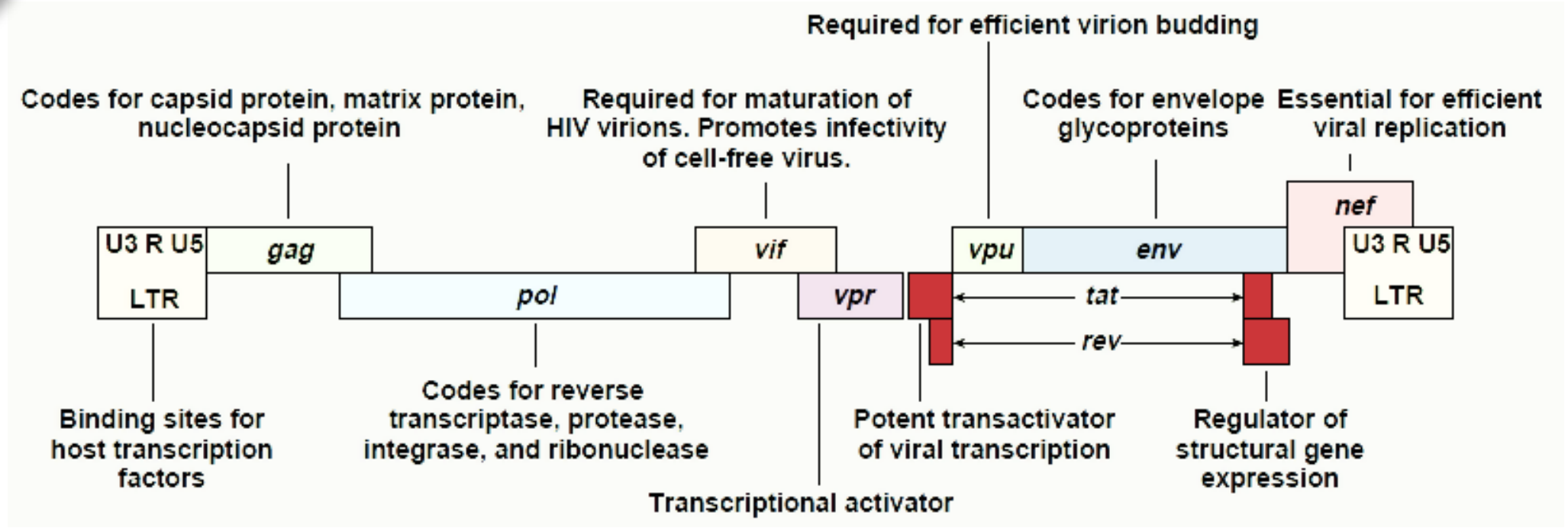


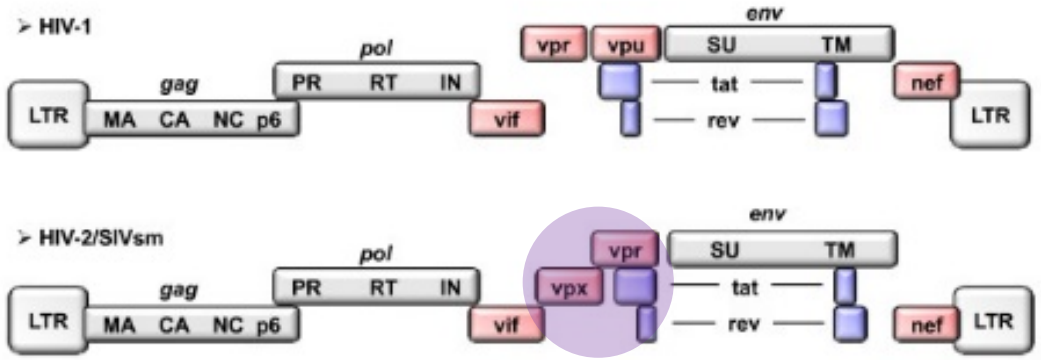
Background


MAN OF THE YEAR

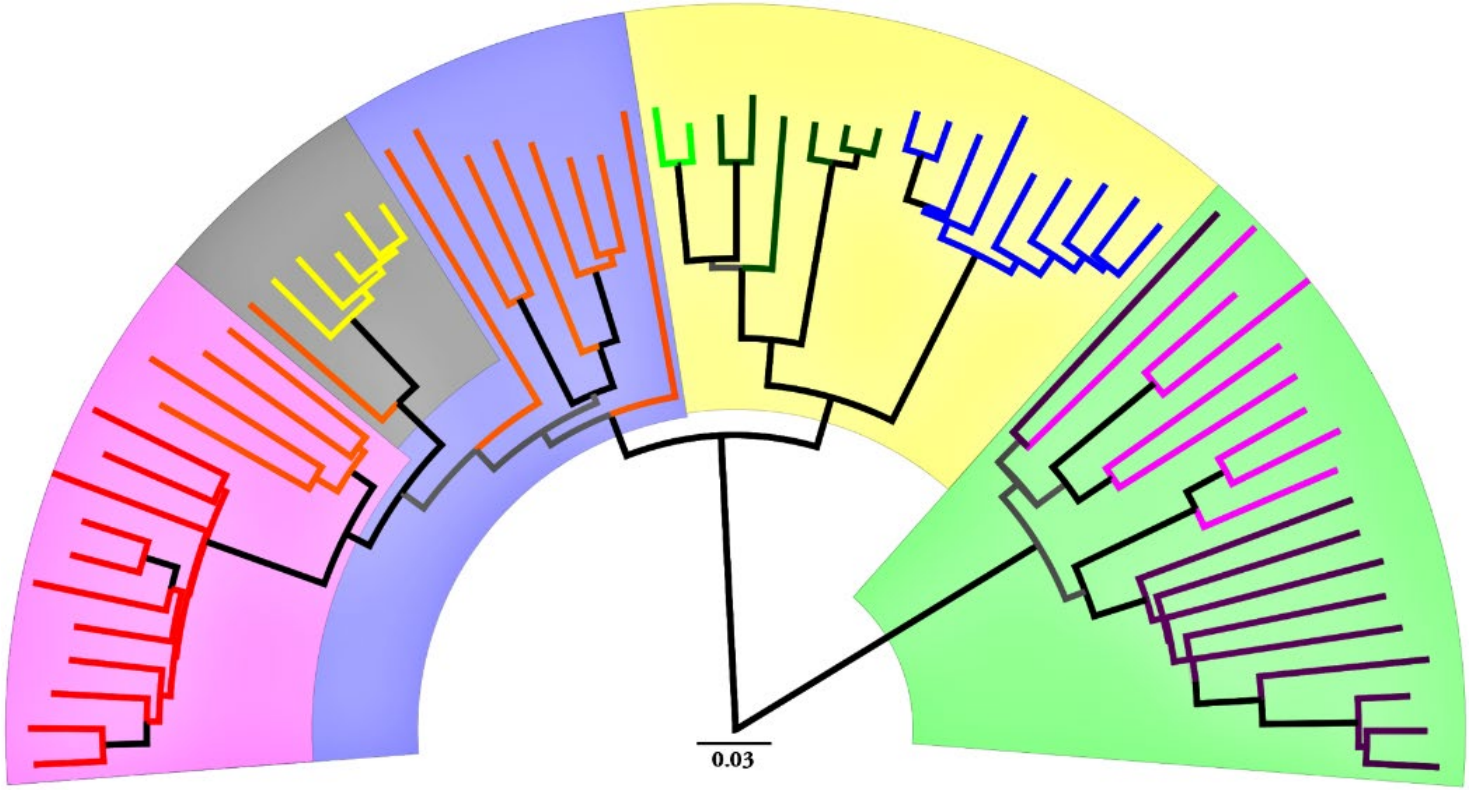

San Francisco, 1978
New York City, 1979
New York City, 1979
Patient 0
Georgia
New York City, 1979
New York City, 1979
New York City, 1979
Pennsylvania
New Jersey
1971
[1969-1973]
Haiti
1969
[1963-1971]
1975
1980
1985

HIV Genome


Required for efficient virion budding
Codes for capsid protein, matrix protein, nucleocapsid protein
Required for maturation of HIV virions. Promotes infectivity of cell-free virus.
Codes for envelope glycoproteins
Essential for efficient viral replication
U3 R U5
LTR
gag
pol
vif
vpr
vpu
env
nef
U3 R U5
LTR
tat
rev
Binding sites for host transcription factors
Codes for reverse transcriptase, protease, integrase, and ribonuclease
Potent transactivator of viral transcription
Regulator of structural gene expression
Transcriptional activator


HIV-1
gag
pol
env
LTR
MA CA NC p6
PR RT IN
vif
vpr
vpu
SU TM
tat
rev
nef
LTR
HIV-2/SIVsm
gag
pol
env
LTR
MA CA NC p6
PR RT IN
vif
vpr
vpx
SU TM
tat
rev
nef
LTR

Classification



Pan troglodytes

SIV_{cpz}

HIV-1 group M

HIV-1 group N

Homo sapiens

HIV-2

HIV-1 group O

HIV-1 group P

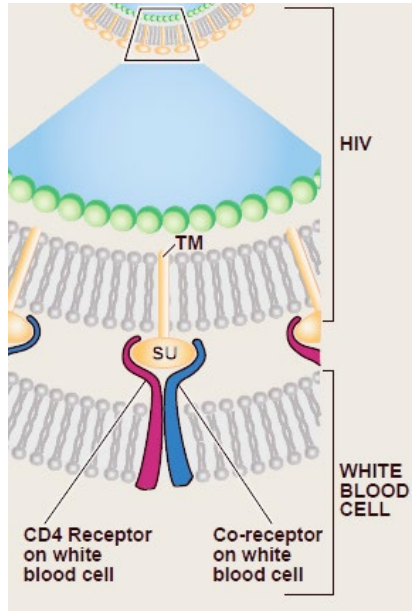
Gorilla gorilla

SIV_{gor}

HIV, Important Features

- *Natural Host:* Human.
- *Tropism:* CD4+ T cells, MΦ and DCs
- *Cellular receptors:* CD4 + (CCR5 and/or CXCR4)
- *Geography:* Worldwide (HIV-1 group M)

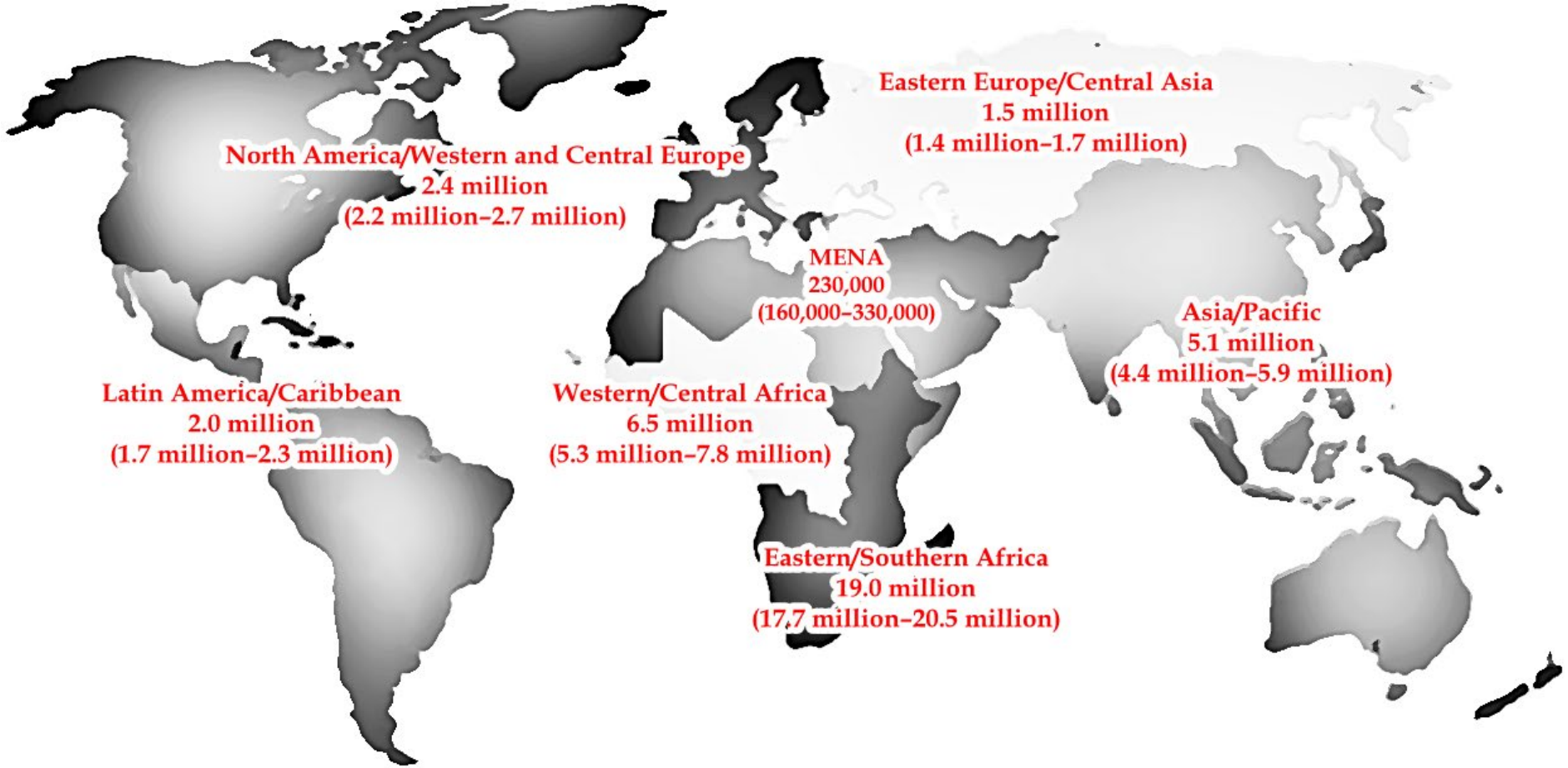
  West Africa (HIV-2)



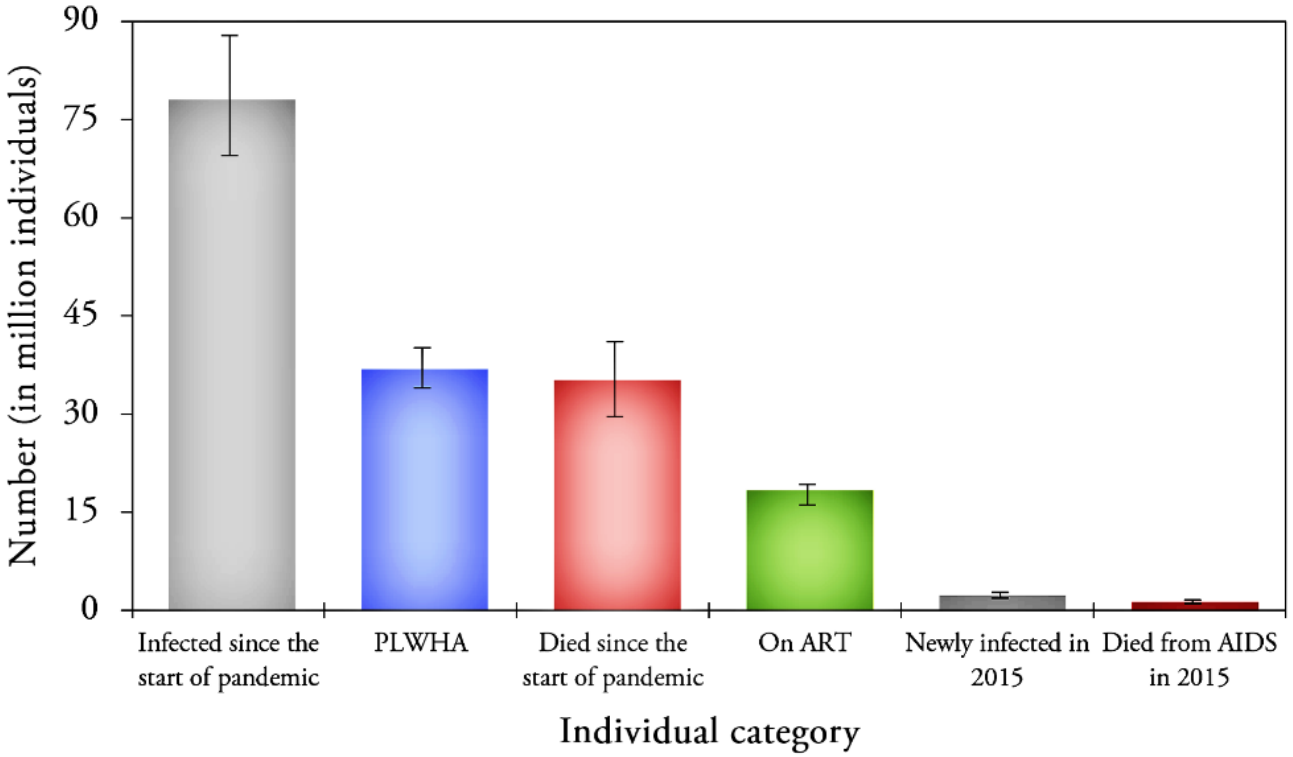
Epidemiologic characteristics of HIV-1/AIDS

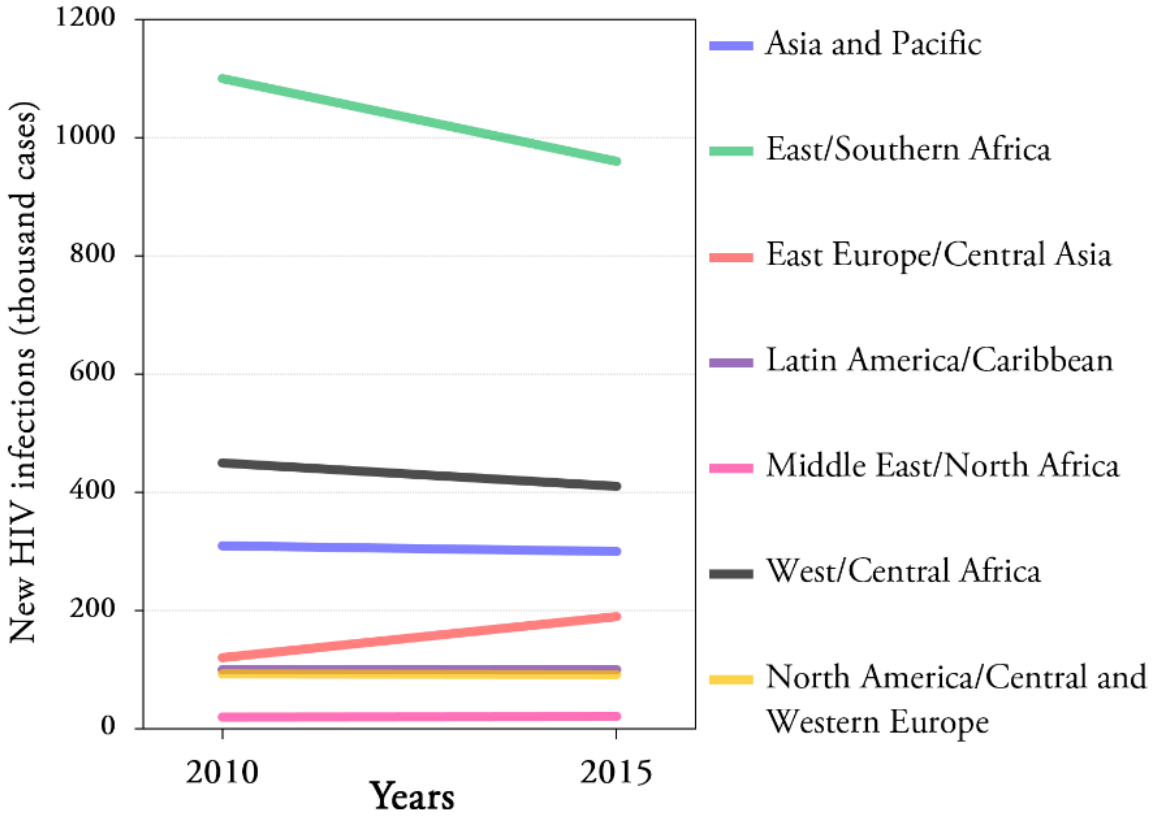
- According to UNAIDS, and by the end of 2024, 40.8 million people globally were living with HIV/AIDS, of which 1.3 million people became newly infected with HIV in 2024.
- 91.4 million people have become infected with HIV since the start of the epidemic.
- 44.1 million people have died from AIDS-related illnesses since the start of the epidemic.
- The unequal distribution of HIV/AIDS around the world is notable mostly in **Sub-Saharan Africa**, with more than two-thirds of PLWHA.

Epidemiologic characteristics of HIV-1/AIDS



Epidemiologic characteristics of HIV-1/AIDS

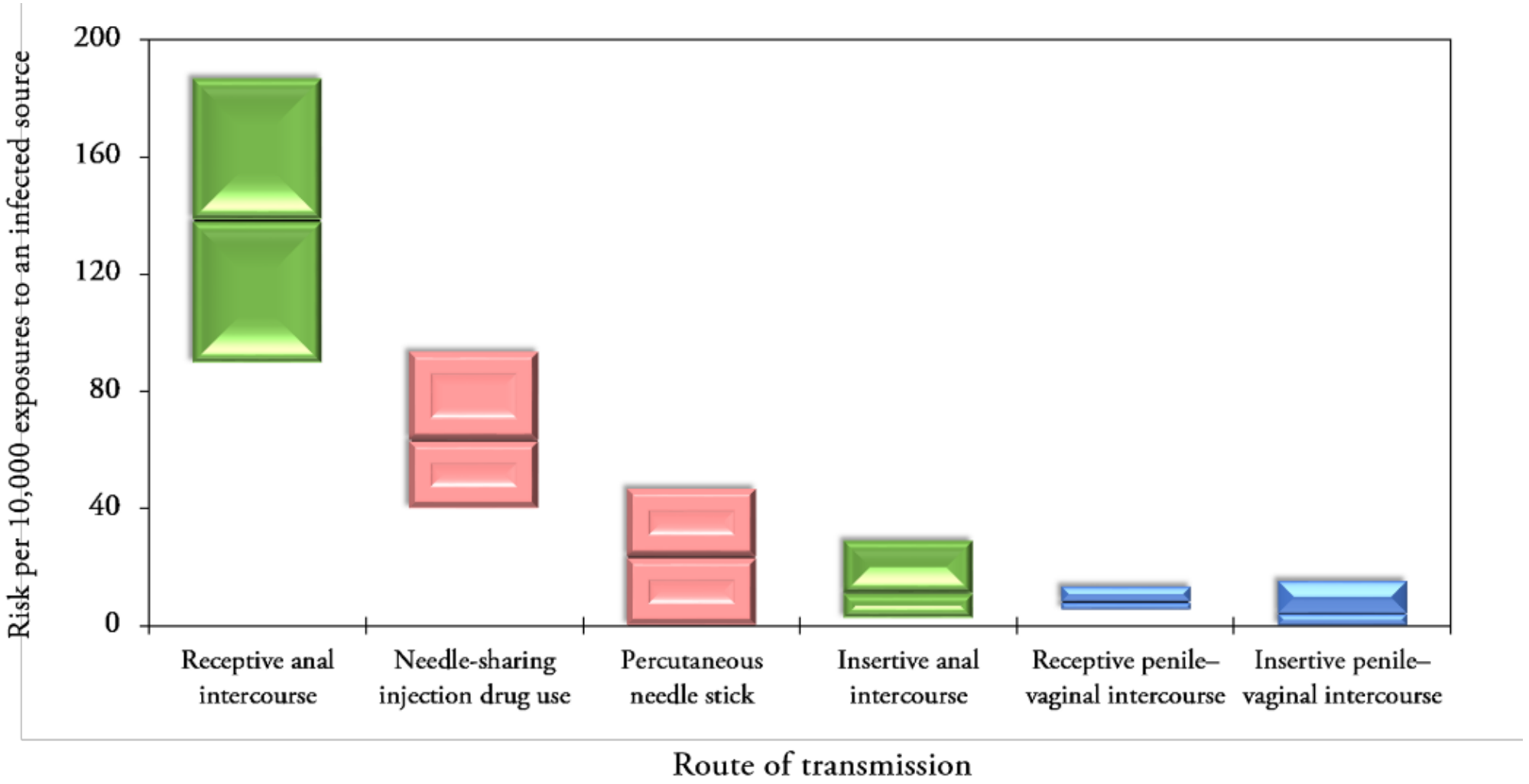




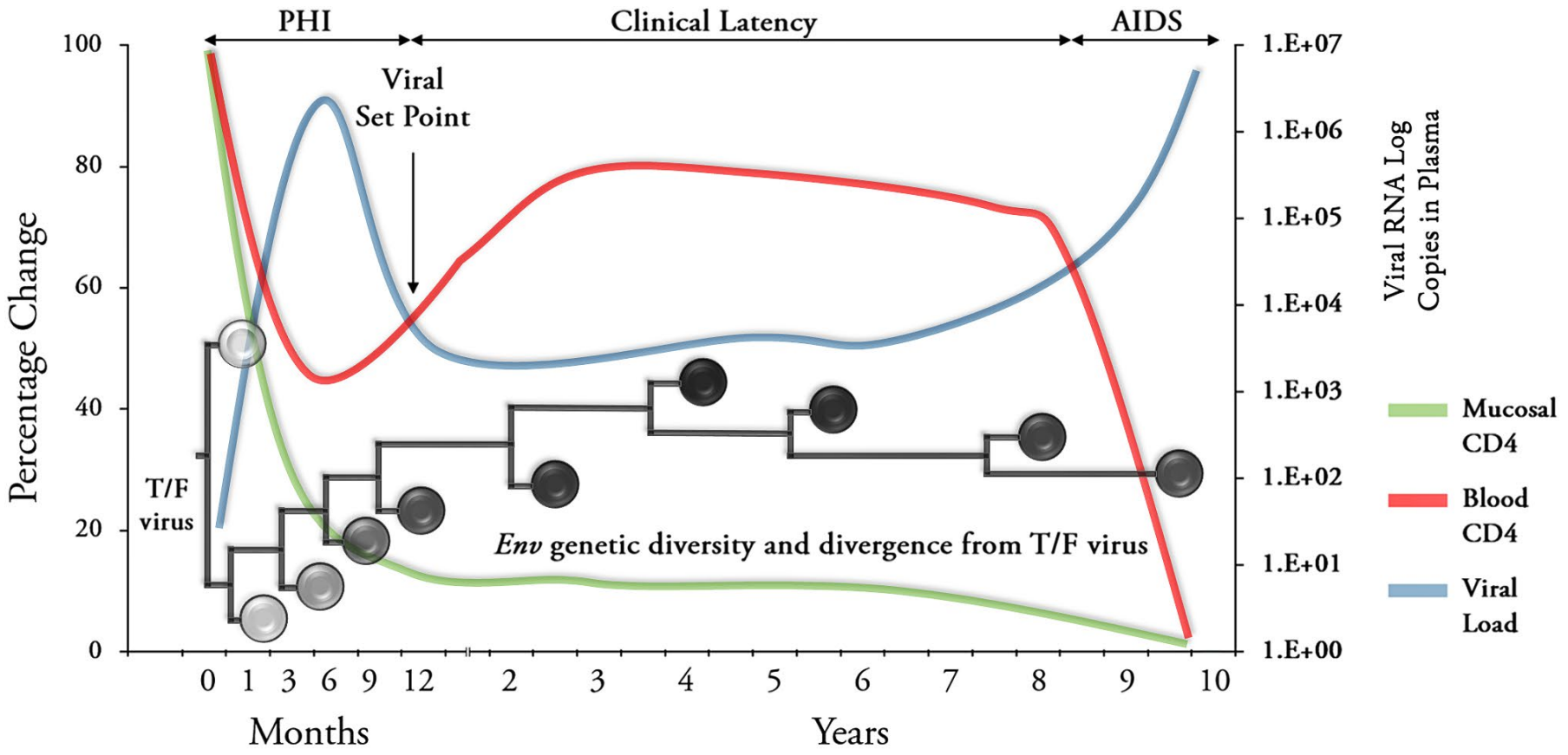
HIV-1 Transmission

- HIV-1 is a **blood-borne virus** (i.e. it can be transmitted through *transfusion*, *needlestick injury* and *IDU*) and the infection can be considered an **STI** (occurring through homosexual and heterosexual practices via vaginal, penile and anal mucosa).
- **Vertical transmission** can occur in utero, perinatally and through breast milk of infected mothers.
- Nowadays, the most common mode of transmission globally is **HET** contact but different regions differ in the most common route (e.g. **MSM** in US and Western Europe, **IDU** in Former Soviet Union countries and **HET** in sub-Saharan Africa).

HIV-1 Transmission

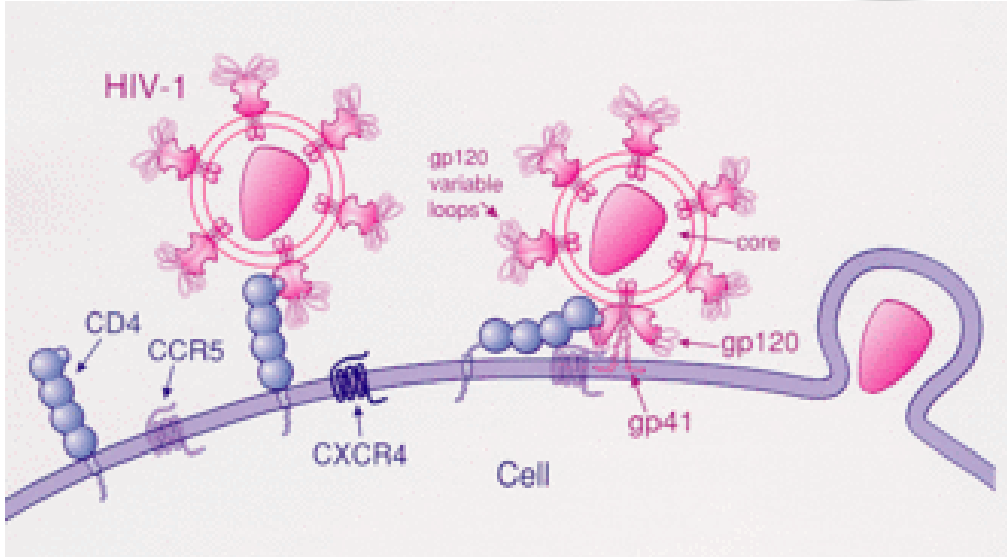


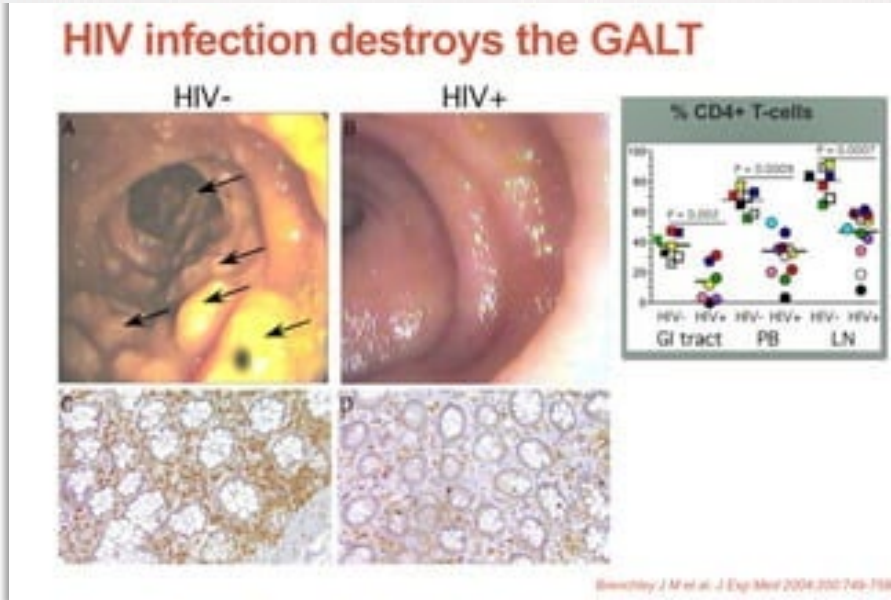
HIV-1 Pathogenesis



HIV-1 Pathogenesis

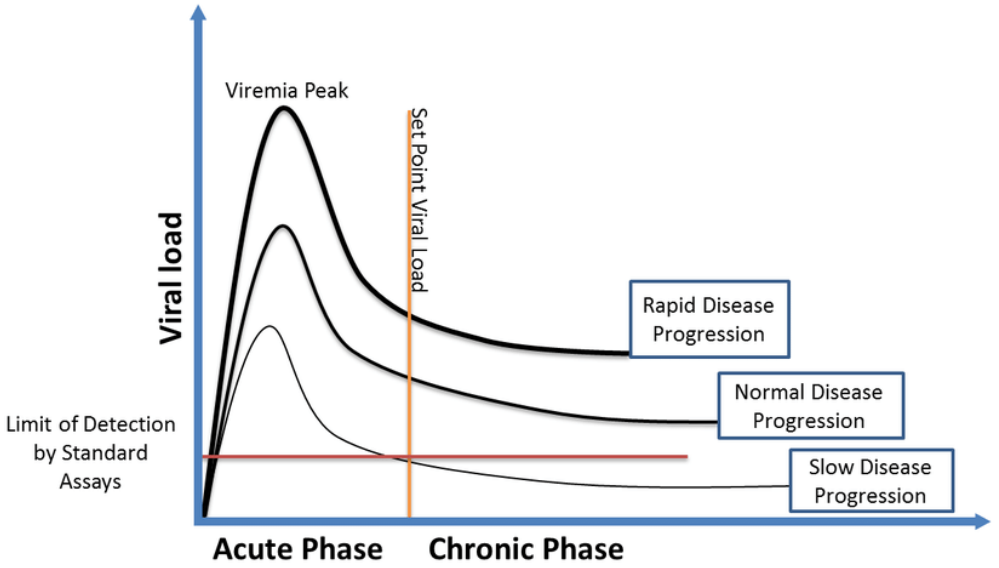
- The distinctive feature of HIV-1 infection is the progressive quantitative and qualitative deficiency of **CD4+ T cells**.
- After HIV-1 inoculation, the virus infects its target cells, mostly macrophages through binding of **gp120** (part of *ENV*) to **CD4** and chemokine receptors **CCR5** or **CXCR4**.
- The virus starts to establish the infection for about 10 days locally before **systemic** spread.
- Subsequent virus spread into the lymphoid tissues including the gut-associated lymphoid tissue (**GALT**), ends-up in the establishment of infection chronically.





HIV-1 Pathogenesis

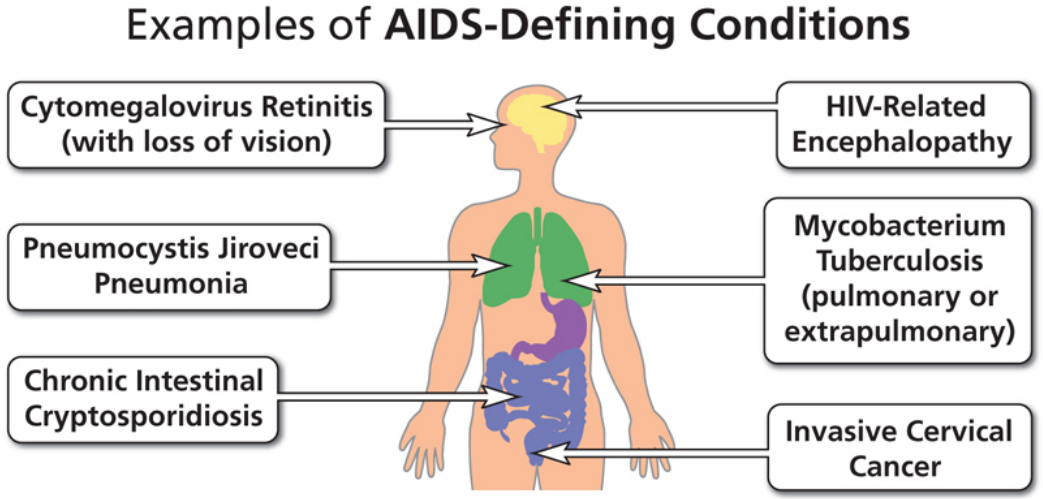
- Viremia follows, which remains at high levels for about 8-12 weeks, coinciding with **mononucleosis-like features** in a majority of infected individuals.
- **The significant decline of CD4 cells at this phase is related to loss of memory cells in the GALT**.
- The adaptive immune response takes over at this stage to control viral replication manifested in the decline of viral load to a nadir "**viral set-point**", which fluctuates at low level throughout the clinical latency.
- **HIV-1 set-point** is considered an important **prognostic marker for assessment of disease progression**.



Source: Yaseen, M. M., Yaseen, M. M., & Alqudah, M. A. (2017). Broadly neutralizing antibodies: An approach to control HIV-1 infection. International Reviews of Immunology, 36(1), 31–40.

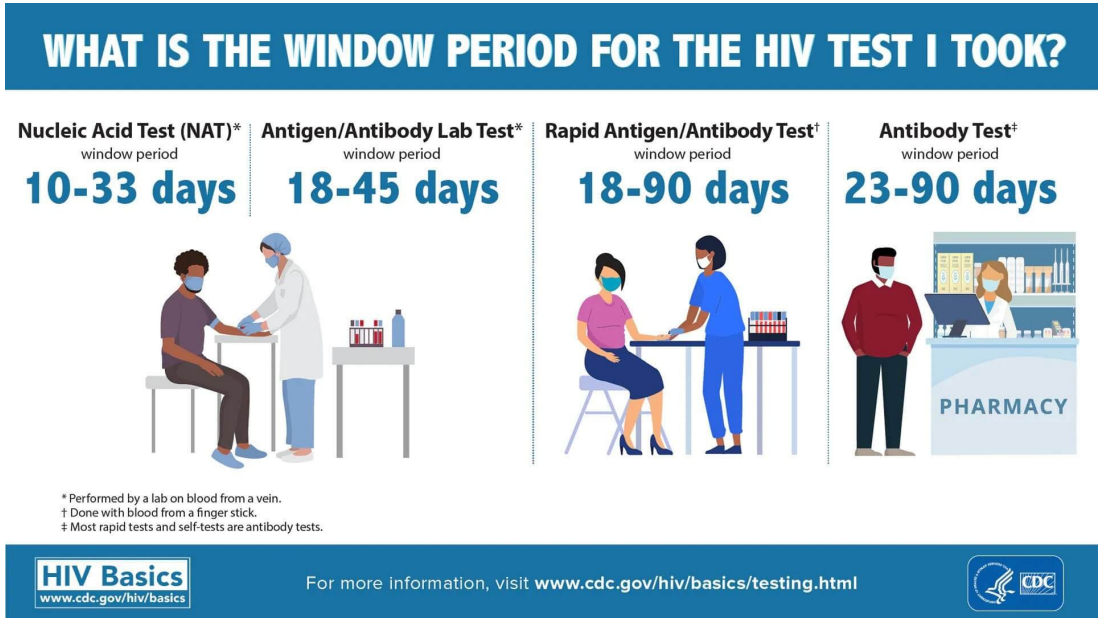
Clinical features

- **Primary infection (first few months):** Nonspecific and resemble those of infectious mononucleosis.
- **Clinical latency (3-20 years, average 8-10 years):** The majority of HIV-1 infected individuals remain **asymptomatic** during the clinical latency period, nevertheless, *generalized lymphadenopathy* might persist from the primary infection period.
- **AIDS:** The diagnosis of AIDS is made at **CD4 T cell count of less than 200/µL** or **the presence of an AIDS defining condition** (MAC, PCP, extrapulmonary TB, **PML**, **KS**, toxoplasmosis, cryptococcosis, esophageal candidiasis, lymphomas, etc.).



Diagnosis

- Screening for HIV-1 infection relies on **enzyme immune assays** with fourth-generation assays combining the detection of Abs (IgM and IgG) to HIV-1 (groups M, O, and N) and HIV-2 together with detection of p24.
- This is followed if positive by a confirmatory test, mostly **western blot** or detection of HIV-1 RNA.
- The biggest challenge in diagnosis is the presence of an interval between infection and detection (**window period**) and refinements of different diagnostic tests aimed to shrink this period particularly in testing of blood/blood products.



Management

- For management of the HIV-1 infected individuals, ***CD4 T cell count*** and ***plasma viral load*** measurements are indispensable for evaluation of disease progression and response to ART.
- The cornerstone of HIV-1 management is the so-called **HAART**.
- Despite the incurable nature of HIV-1 infection so far (with the exception of the Berlin patient) the treatment with combinations of antiretroviral drugs aims to suppress viral replication to a degree that permits the recovery of immune system responses in order to prolong the infected-individuals' survival.

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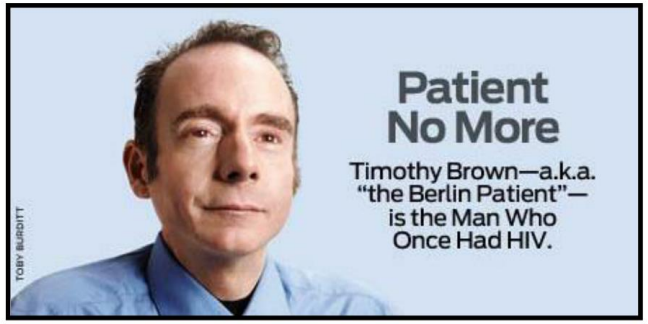
I Am the Berlin Patient:
A Personal Reflection

Timothy Ray Brown

"The Berlin Patient"



- **HIV + leukemia → chemotherapy and stem cell tx → 5 yrs; No HIV detected (R. Siliciano)**
- **2012: 2 more patients – Brigham Hospital, Boston (IAS Conference 2012)**

Management

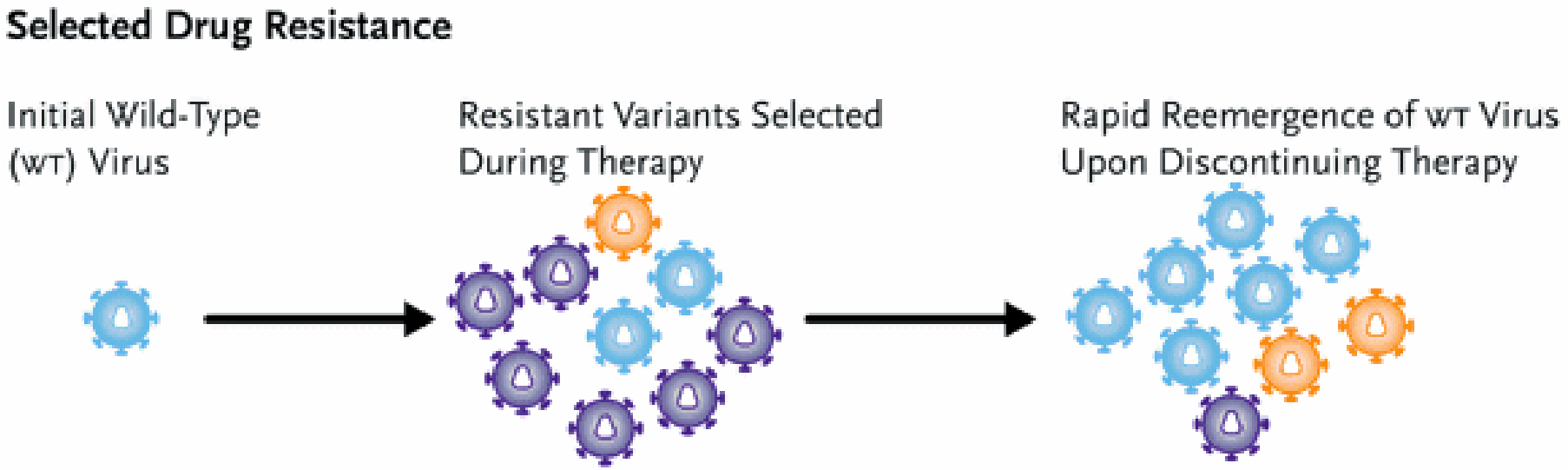
- The latency of HIV-1 infection is evident upon treatment interruption which will lead to resurgence of viral replication.

- ARV drugs are classified currently based on its mechanism of action into six classes:

NRTI	NNRTI	PI	Integrase Inhibitor	Fusion Inhibitor	CCR5 antagonist
Zidovudine	Nevirapine	Saquinavir	Raltegravir	Enfuvirtide	Maraviroc
Didanosine	Delavirdine	Ritonavir	Dolutegravir		
Stavudine	Efavirenz	Indinavir	Elvitegravir		
Lamivudine	Etravirine	Nelfinavir			
Abacavir	Rilpivirine	Atazanavir			
Tenofovir		Tipranavir			
Emtricitabine		Darunavir			

Management

Several biologic properties of HIV-1 make the emergence of drug resistance an inevitable outcome in the individuals receiving suboptimal ART (high rate of mutation, possibility of recombination).



Prevention

In the absence of an effective vaccine towards HIV-1 infection, the preventive efforts rely on the following measures:

(1) **HIV-1 testing** particularly among most-at-risk groups.

(2) Consideration of (**PrEP**) and (**PEP**) among individuals at risk along with *early initiation of ART among HIV-1 infected individuals*.

(3) Counselling and education of most-at-risk groups regarding the behavioural practices that are associated with higher probability of transmission (e.g. needle-sharing, unprotected sex, etc.), along with implementing protective measures (needle exchange program [**NEP**], STI screening and condom use).

Thank You…
Wishing you all the best!