Virology for 2nd Year MD Students

(10) Retroviruses 2

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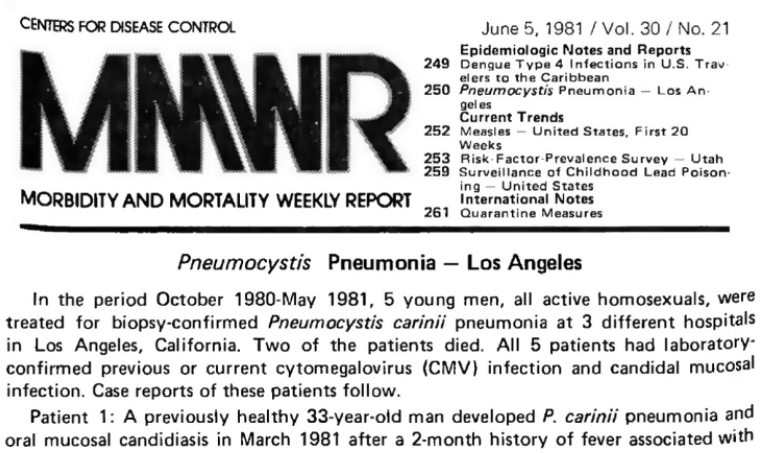
Background on AIDS

الفكرة: انه الـ HIV أخدم بكتير من لما اكتشفناه

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

الاهم وسبب أغلب الإصابات



CENTERS FOR DISEASE CONTROL

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

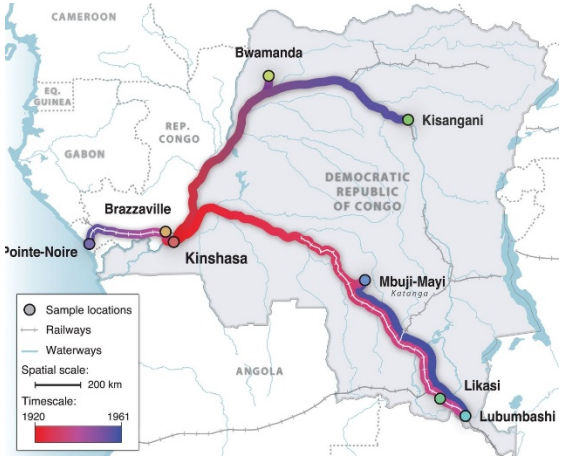
MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

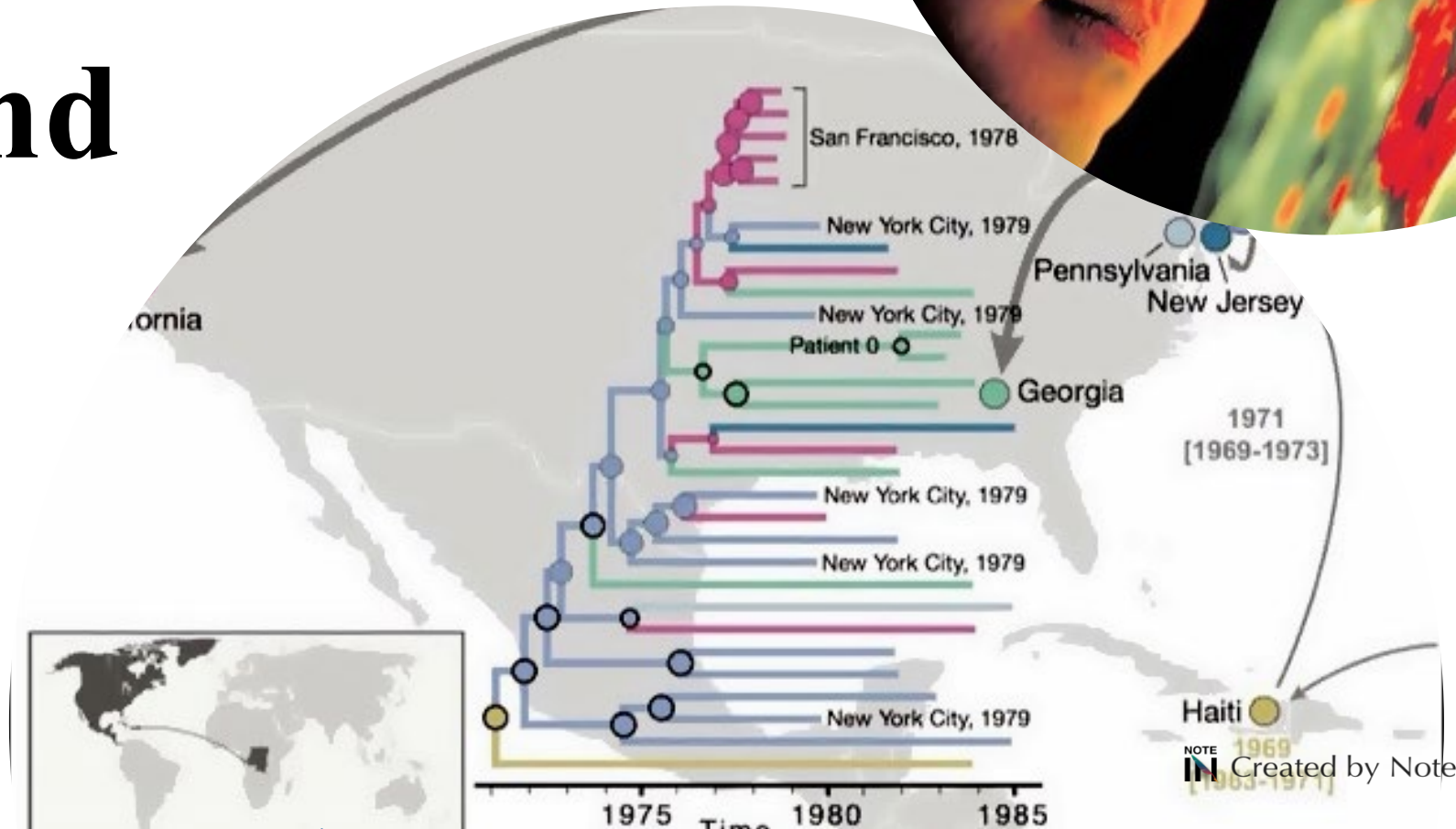
Pneumocystis **Pneumonia — Los Angeles**

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



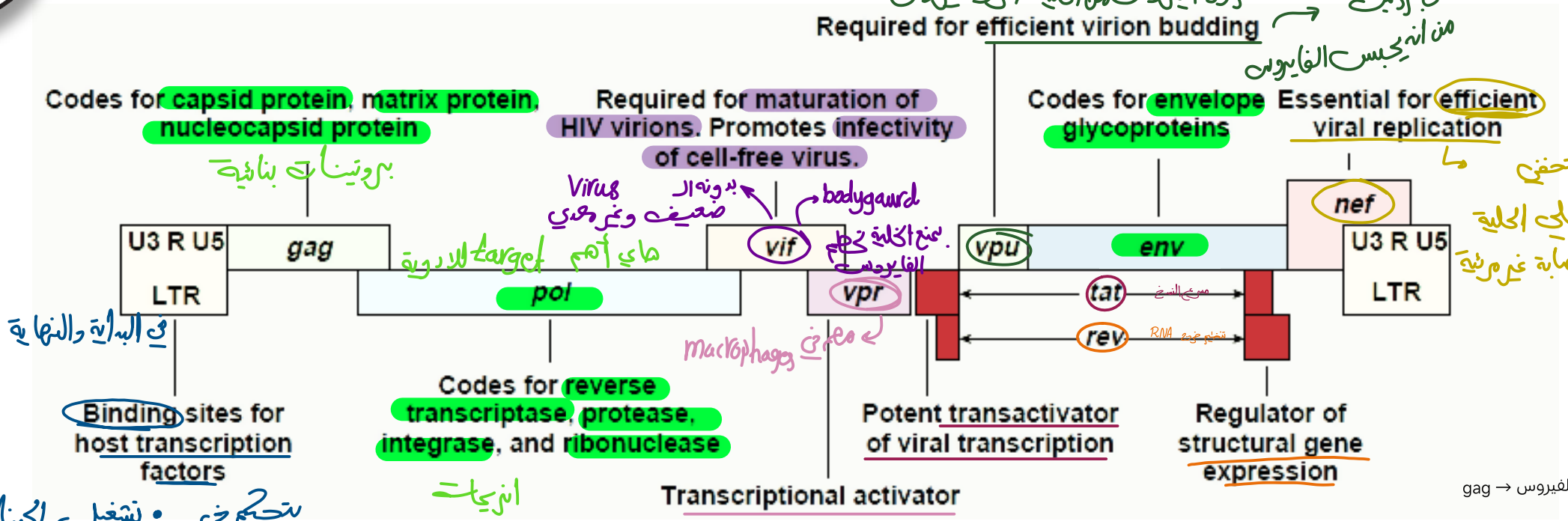
Background



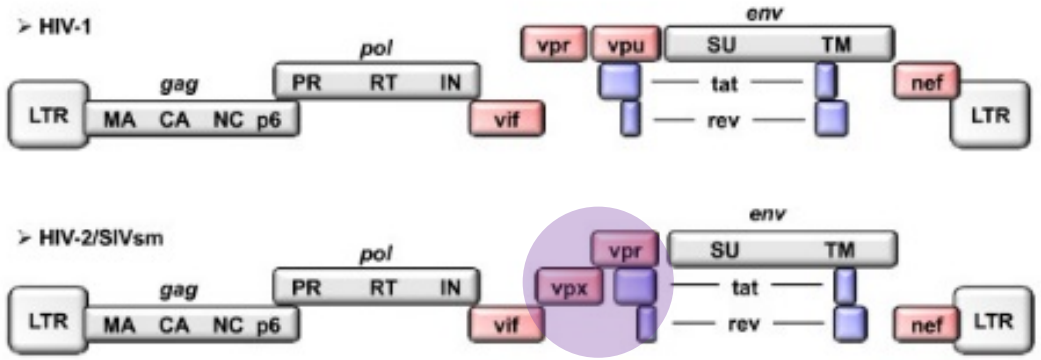
I didn't attend the lecture so I'm not sure about memorizing all of these. But I hope it may help you understand :)

HIV Genome

مشترك مع الـ HTLV genome



يتحكم في
- تشغيل الجينات
- سرعة النسخ
- كم فيروس ينصنع



gag → يبني الفيروس

pol → يشغّل الفيروس

env → يدخل الفيروس

tat → يسرّع النسخ

rev → يطلع RNA

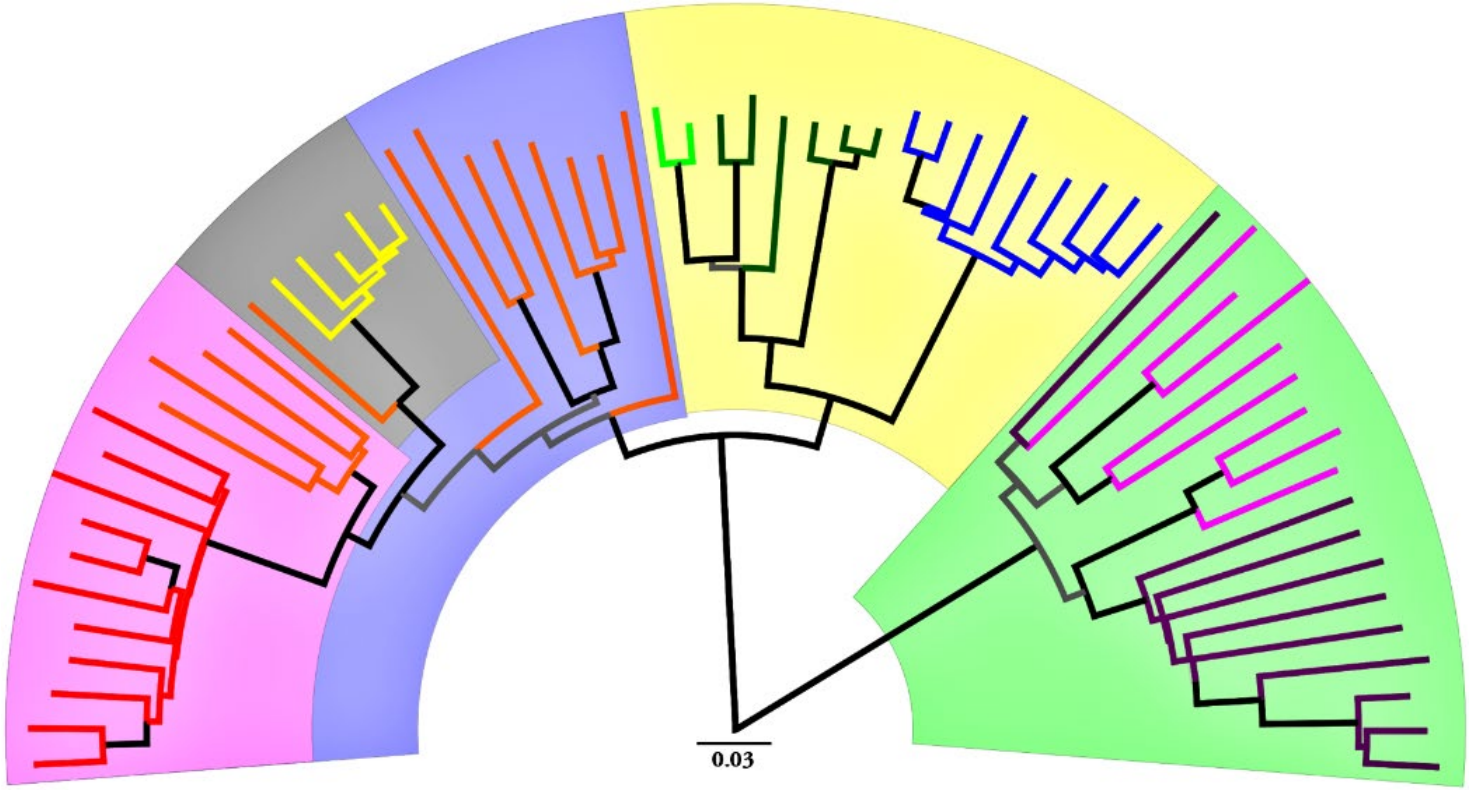
vif → يحمي الفيروس

vpr → يفتح باب النواة

vpu → يخلّي الفيروس يطلع

nef → يخلي الخلية [illegible]

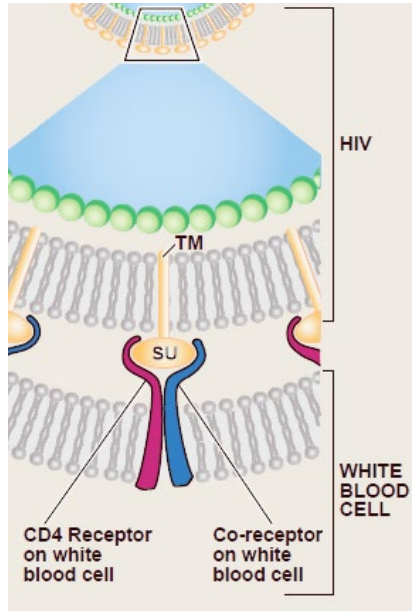
Classification



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)

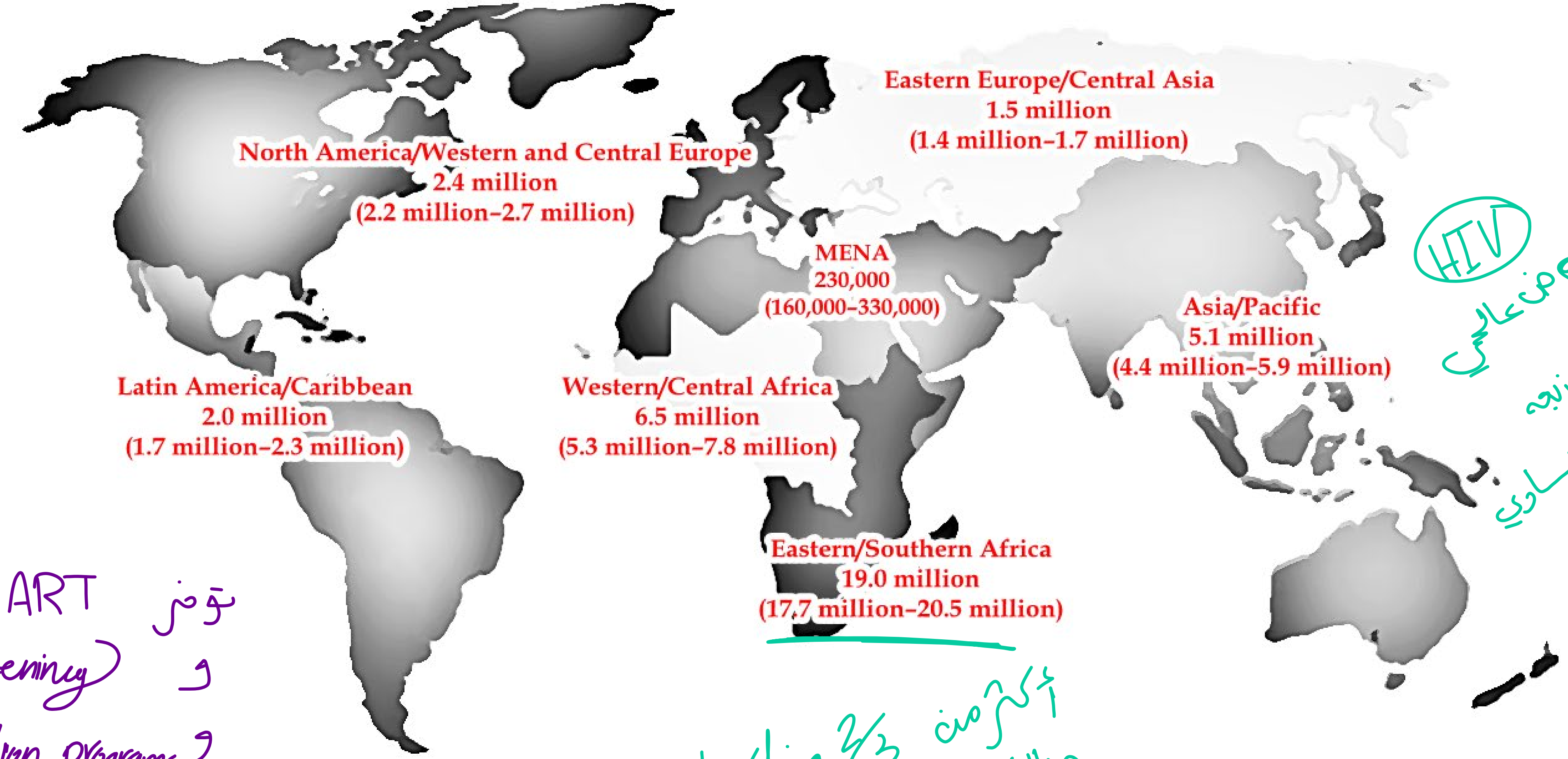
  West Africa (HIV-2)



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



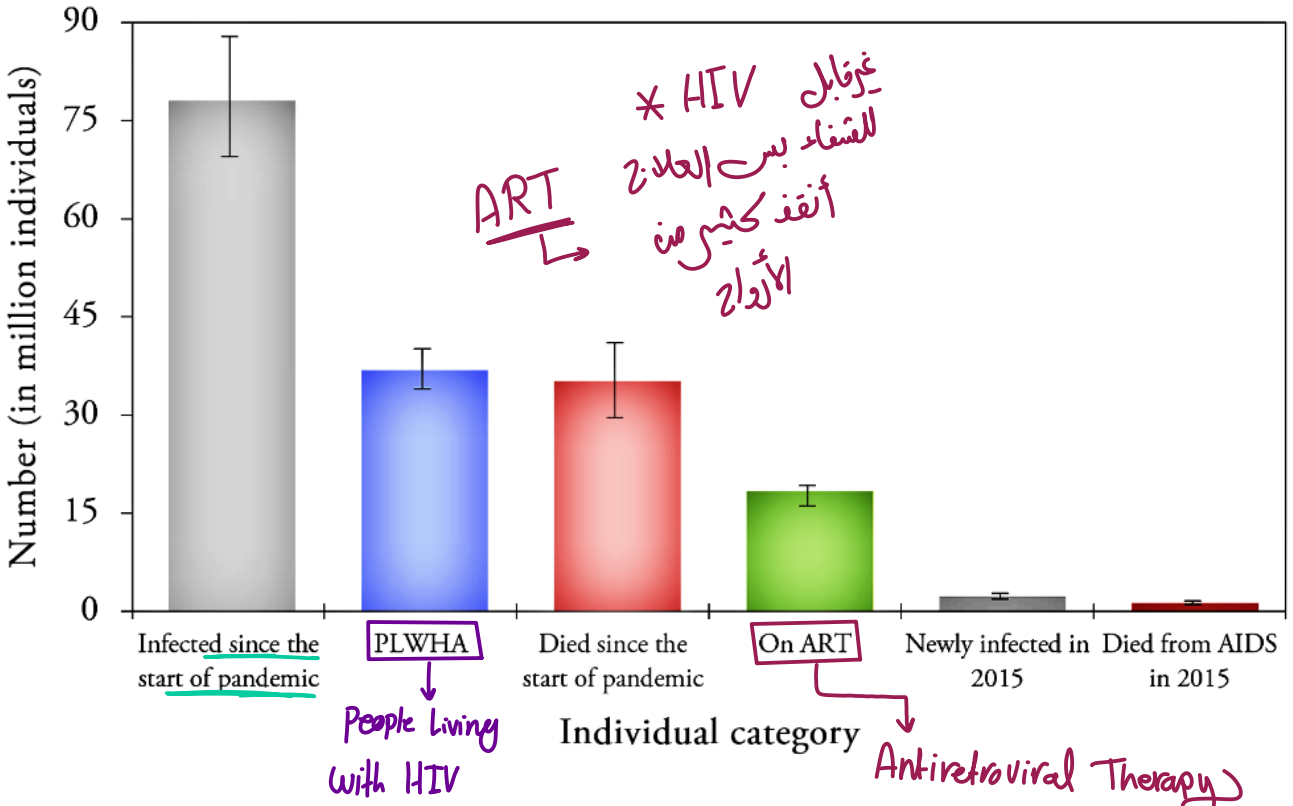
HIV وضع عالمي لكن توزيعه غير متساوي

أكثر من 2/3 من المصابين هناك بسبب الظروف الصحية والاجتماعية

توفر ART (لا بنعت موجود شرح عنه تحت)
و Screening
و Prevention programs
وصول لحلهم بقللوا نسب الانتشار
مثل N.America, Europe

Created by Notein

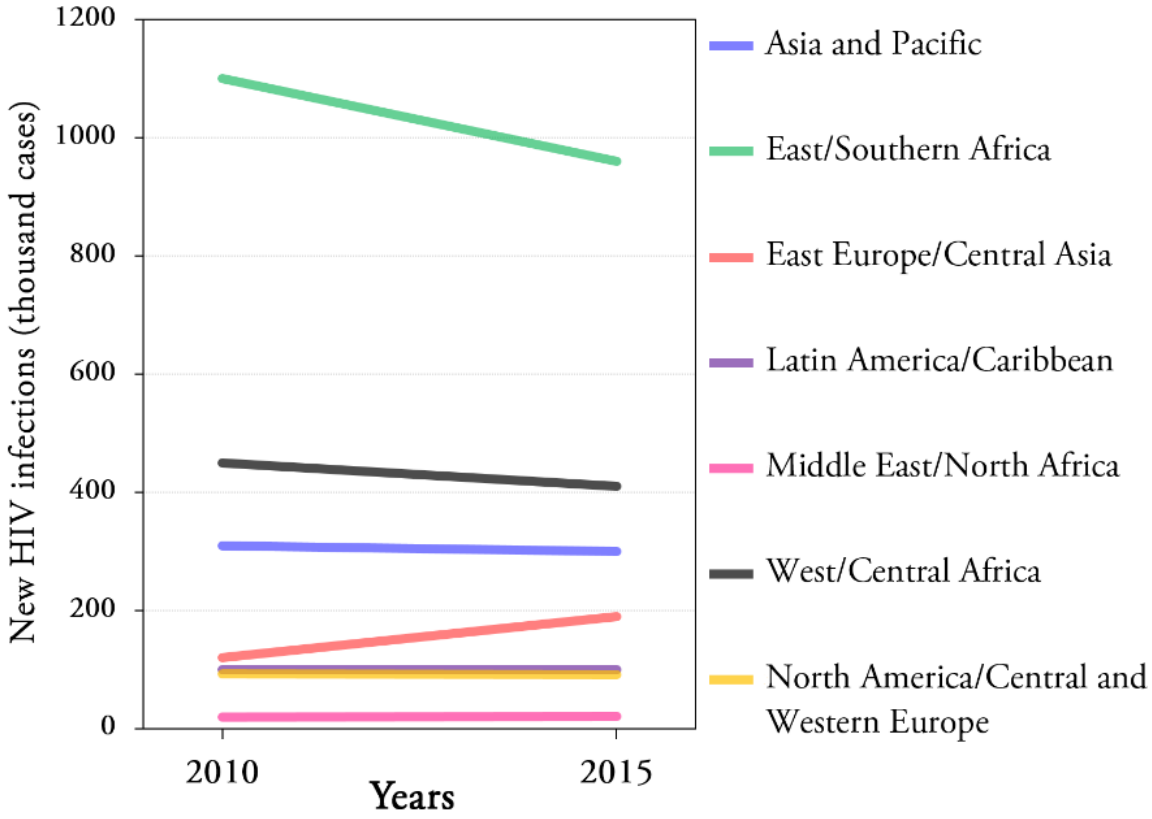
Epidemiologic characteristics of HIV-1/AIDS



* HIV غير قابل للشفاء بس العلاج أنقذ كتير من الأرواح

ART

group of drugs given to HIV patients



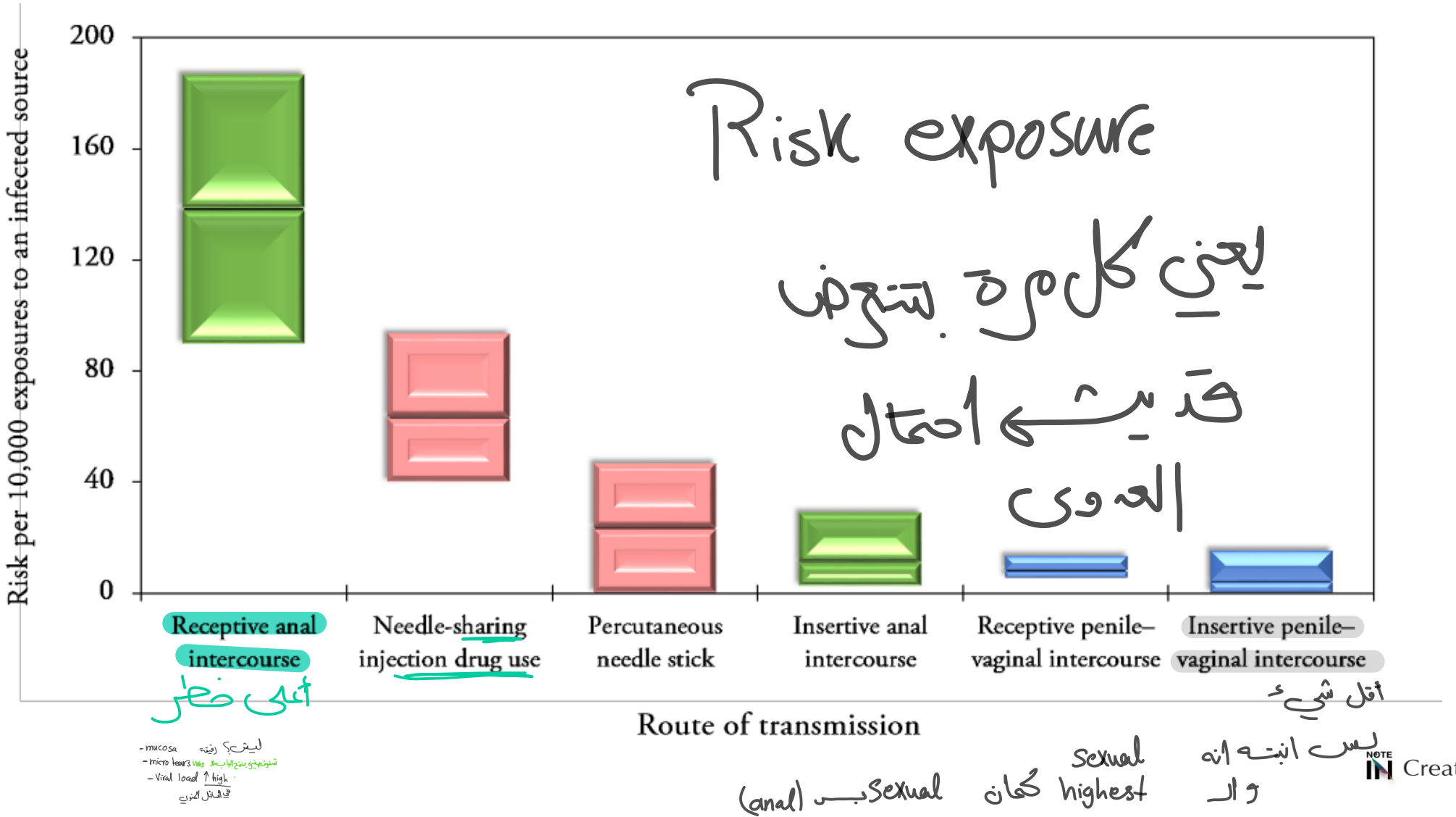
HIV epid. dynamic & region specific

هدفها تمنع تكاثر الفيروس يعني بتسيطر عليه ت مش شفاء

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

كيف نربط كل الخطوط مع بعض؟

🟦 Viral load

عالي بالبداية

ينخفض (set-point)

يرجع يعلى بالنهاية

🔴 CD4 blood

ينخفض بالبداية

يتحسن شوي

ينزل تدريجيًا

ينهار بالنهاية

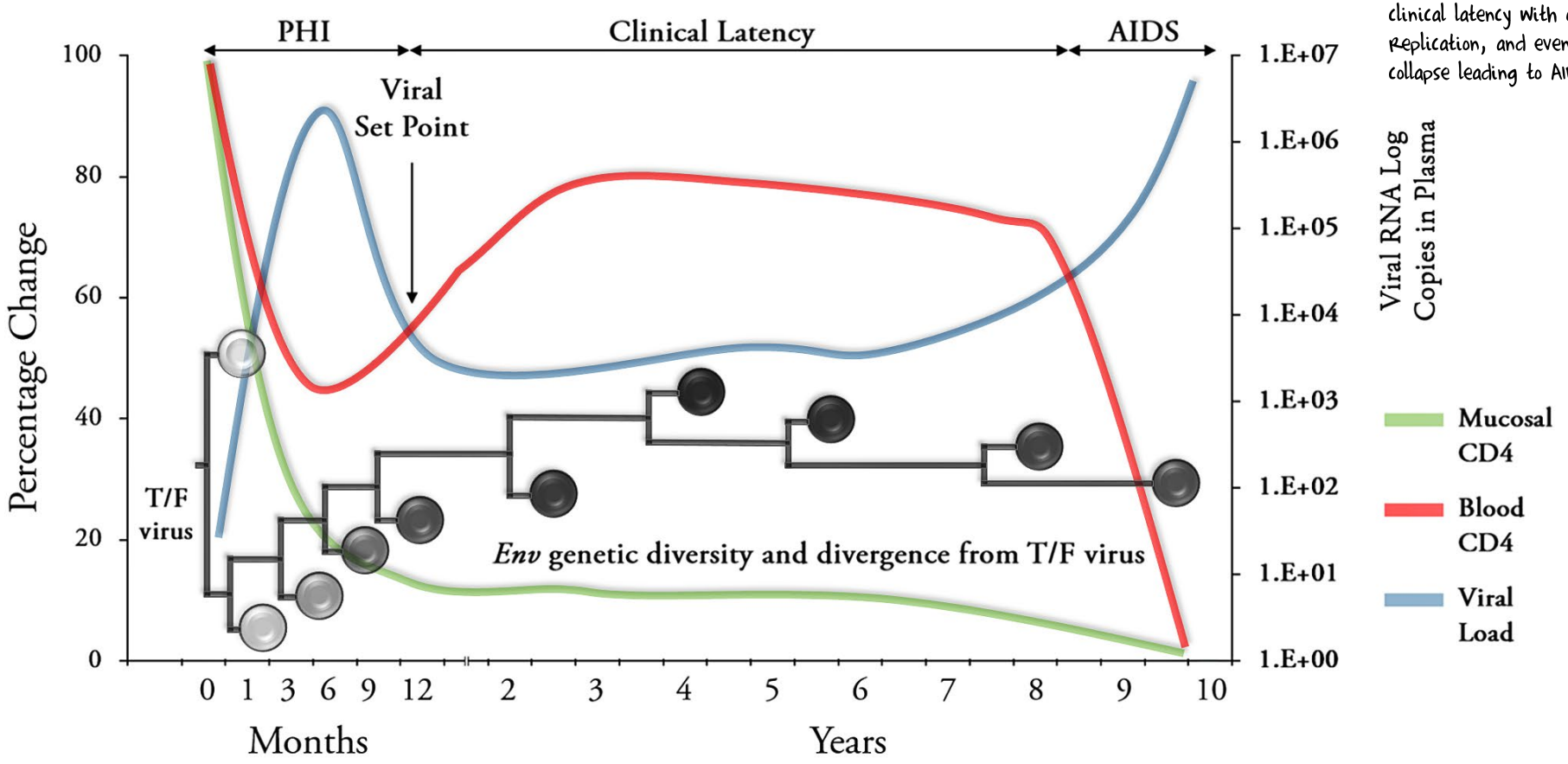
🟢 CD4 mucosal (GALT)

ينخفض بشدة من أول أيام

وما يرجع طبيعي

📌 لذلك:

الفحص بالدم ما بعكس الخسارة الحقيقية بالمناعة بالبداية



HIV causes early massive destruction of mucosal CD4 T cells, followed by partial immune control with establishment of a viral set-point, a prolonged period of clinical latency with ongoing viral replication, and eventual immune collapse leading to AIDS.

🧬 HIV-1 Pathogenesis — الزبدة

1️⃣ أول الإصابة (Acute / PHI)

Viral load ↑ ↑

CD4 ↓ (أكثر شي في GALT)

أعراض تشبه mononucleosis

2️⃣ Viral set-point

المناعة تنزل الفيروس لمستوى ثابت

كل ما set-point أعلى → المرض أسرع

3️⃣ Clinical latency

سنوات بدون أعراض

الفيروس شغال

ينزل ببطء CD4

4️⃣ AIDS

CD4 < 200

Viral load ↑ ↑

Opportunistic infections

[redacted]

أكبر خسارة CD4 بالبداية = GALT

مؤشر إنذار = Viral set-point

الفيروس يتحوّر → ما بنشفي

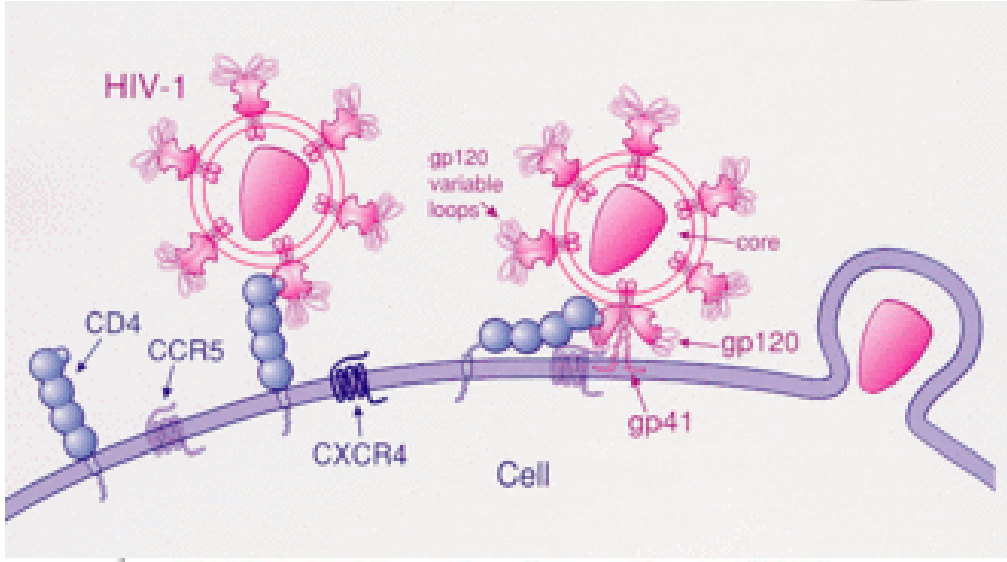
بدون ART → نهاية المرض AIDS

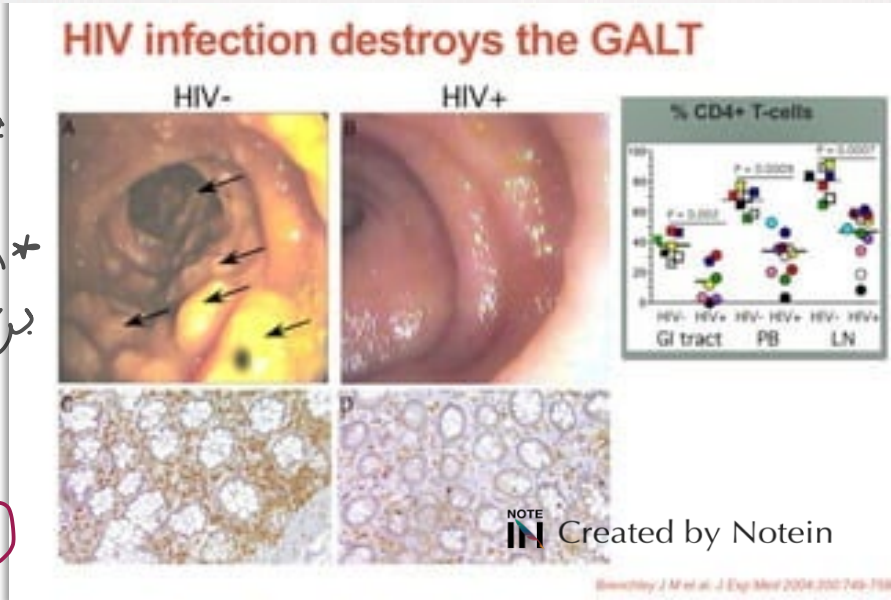
الاسهم غالبًا معكوسة 🙃

Sorry.

HIV-1 Pathogenesis

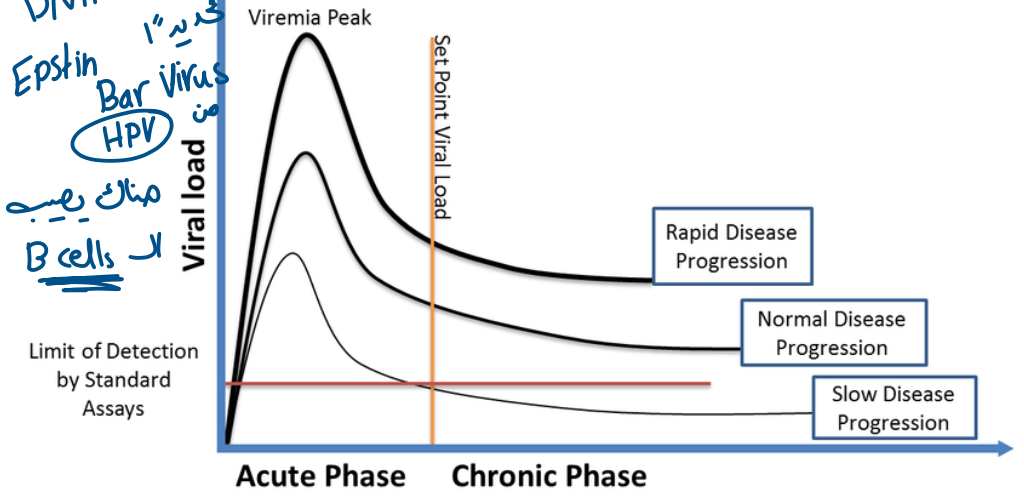
- The distinctive feature of HIV-1 infection is the progressive quantitative and qualitative deficiency of **CD4+ T cells**.
- After HIV-1 inoculation, the virus infects its target cells, mostly macrophages through binding of **gp120** (part of *ENV*) to **CD4** and chemokine receptors **CCR5** or **CXCR4**.
- 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

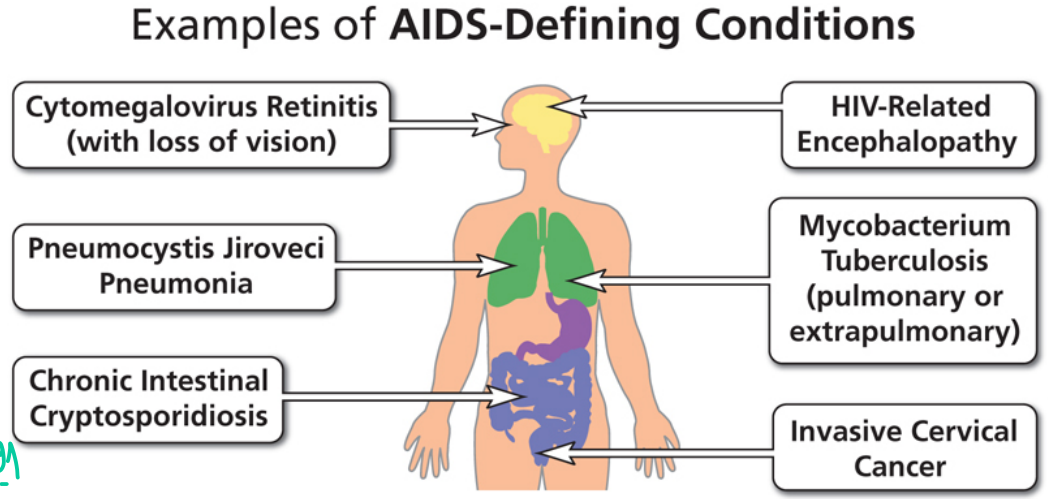
- Viremia follows, which remains at high levels for about 8-12 weeks, coinciding with **mononucleosis-like features** in a majority of infected individuals.
- **The significant decline of CD4 cells at this phase is related to loss of memory cells in the GALT**.
- The adaptive immune response takes over 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

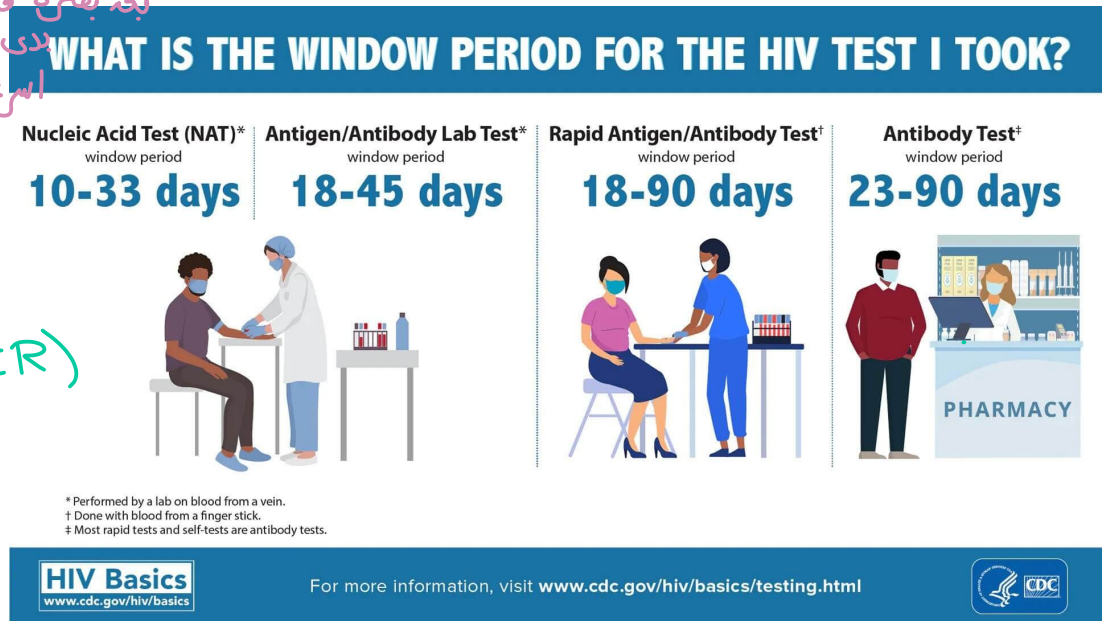
- **Primary infection (first few months):** Nonspecific and resemble those of infectious mononucleosis.
- **Clinical latency (3-20 years, average 8-10 years):** The majority of HIV-1 infected individuals remain **asymptomatic** during the clinical latency period, nevertheless, *generalized lymphadenopathy* 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

window period
مصاب بس الفحص
Negative

- 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. (PCR)
- 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**. → Highly Active Antiretroviral Therapy → يعني أعطي أكثر من دواء مع بعض
- 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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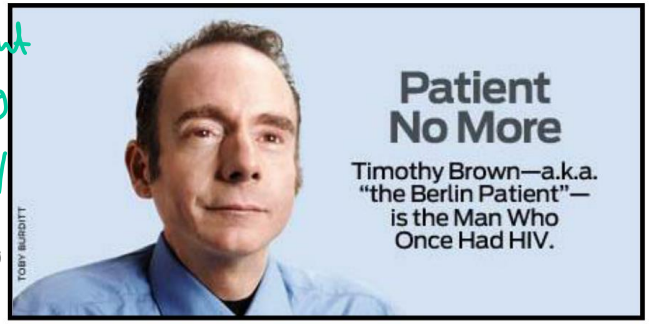
I Am the Berlin Patient:
A Personal Reflection

Timothy Ray Brown

ضد HIV

"The Berlin Patient"



recieved stem cell transplant والاول بالعالم الي Cured of HIV

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

لا أدري إذا الدكتور جبي عنه/هم للامتحان بس لخايات اشباع الفضول !!

Management

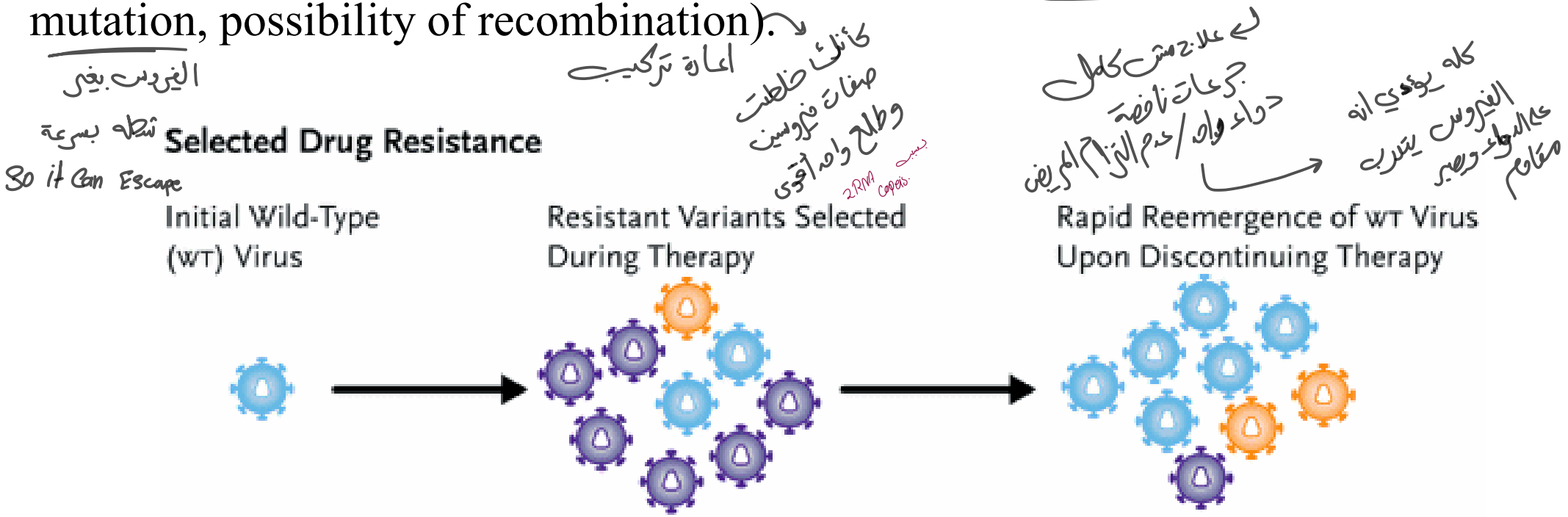
- The latency of HIV-1 infection is evident upon treatment interruption which will lead to resurgence of viral replication.

- 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).



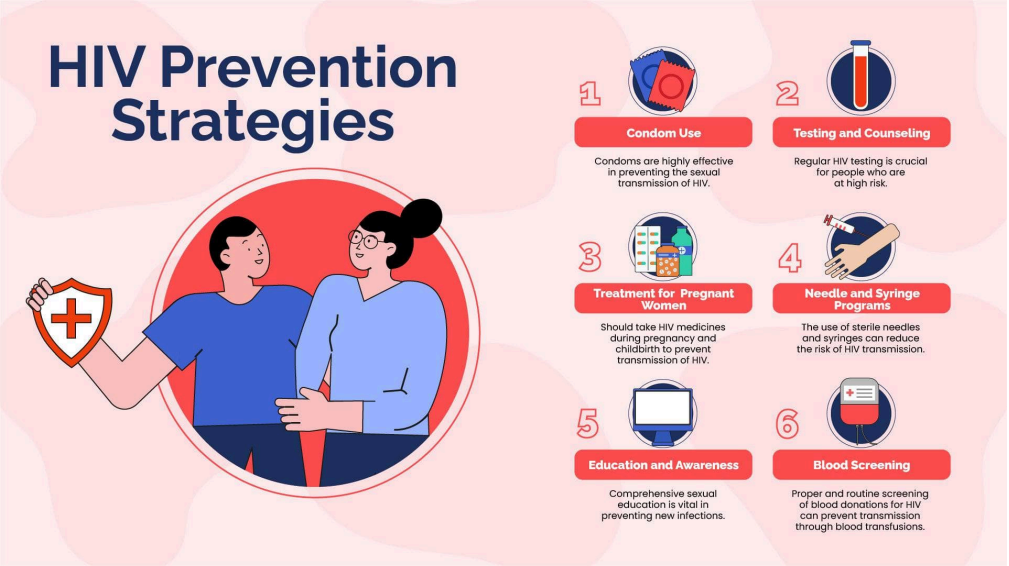
Prevention

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!

🧬 Retroviridae – Summary Table (High-Yield)

Virus	Genome	Target cells	Main receptors	Key feature	Main diseases
HIV-1	+ssRNA (diploid)	CD4⁺ T cells, macrophages, DCs	CD4 + CCR5 / CXCR4	نقص مناعة تدريجي	AIDS, opportunistic infections, cancers
HIV-2	+ssRNA (diploid)	CD4⁺ T cells	CD4 + CCR5	أبطأ وأقل عدوى	AIDS (أخف)
HTLV-1	+ssRNA (diploid)	CD4⁺ T cells	غير محدد بدقة	**Oncovirus (Tax)**	Adult T-cell leukemia, HAM/TSP
HTLV-2	+ssRNA (diploid)	T cells	غير محدد بدقة	أقل مرضية	asymptomatic نادر، غالبًا

🔑 خصائص مشتركة لكل Retroviruses

Feature	Description
Envelope	نعم
Enzyme	Reverse transcriptase
Integration	Viral DNA → **Provirus**
Infection	مزمنة (lifelong)
Genome copies	**2 RNA copies (diploid)**

🧠 فروقات امتحانية سريعة

Point	HIV	HTLV
المشكلة الأساسية	نقص مناعة	سرطان / تكاثر خلايا
الانتقال	فيروس حر + خلايا	**Cell-associated**
أشهر بروتين	gp120, nef	**Tax**
أهم مرض	AIDS	Adult T-cell leukemia