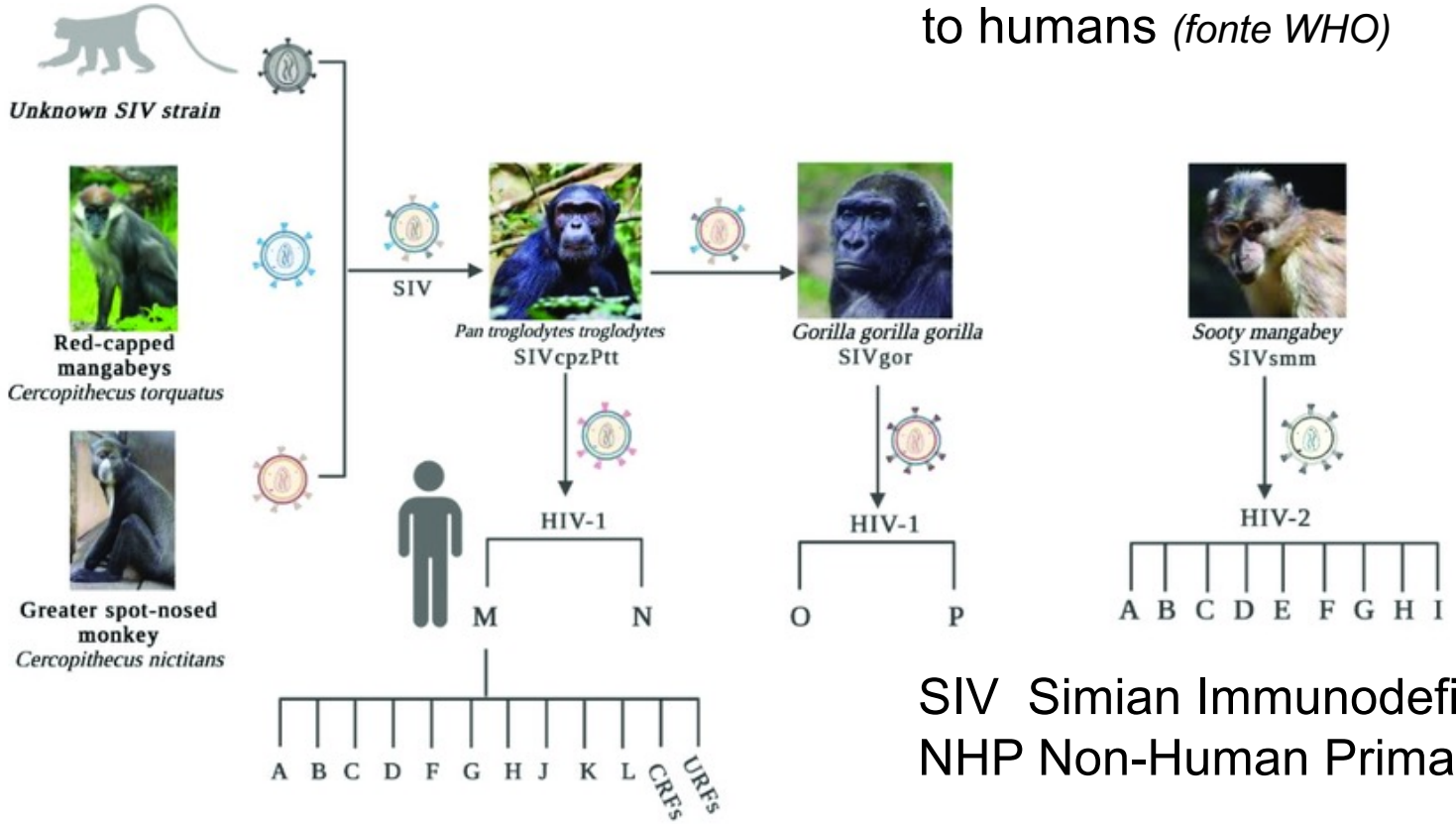
Origins of HIV

Zoonosis=is an infectious disease that has jumped from a non-human animal to humans *(fonte WHO)*



SIV Simian Immunodeficiency Virus
NHP Non-Human Primates

It is likely that HIV first appeared in humans in Africa near the beginning of the twentieth century as a result of infection by SIV from NHP.

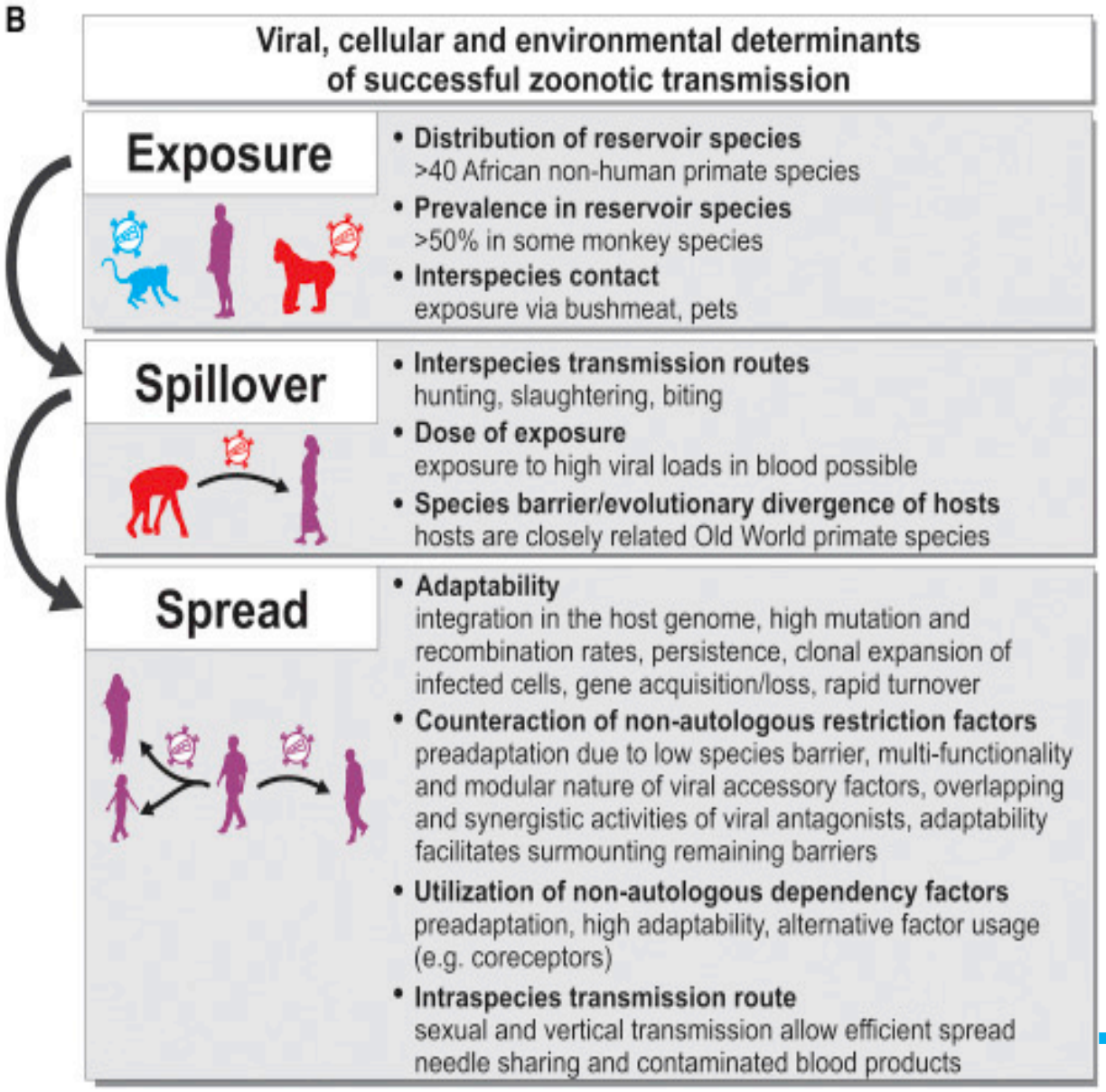
Since there are several groups of HIV, it is likely that humans became infected by SIV on more than one occasion.

The cross-species transmission of lentiviruses from African primates to humans has selected viral adaptations which have facilitated human-to-human transmission.

HIV adapts through mutation and by recombination of regions of its genome in multiply infected individuals

Naturally infected NHP are relatively resistant to AIDS-like disease despite high plasma viral loads and sustained viral evolution.

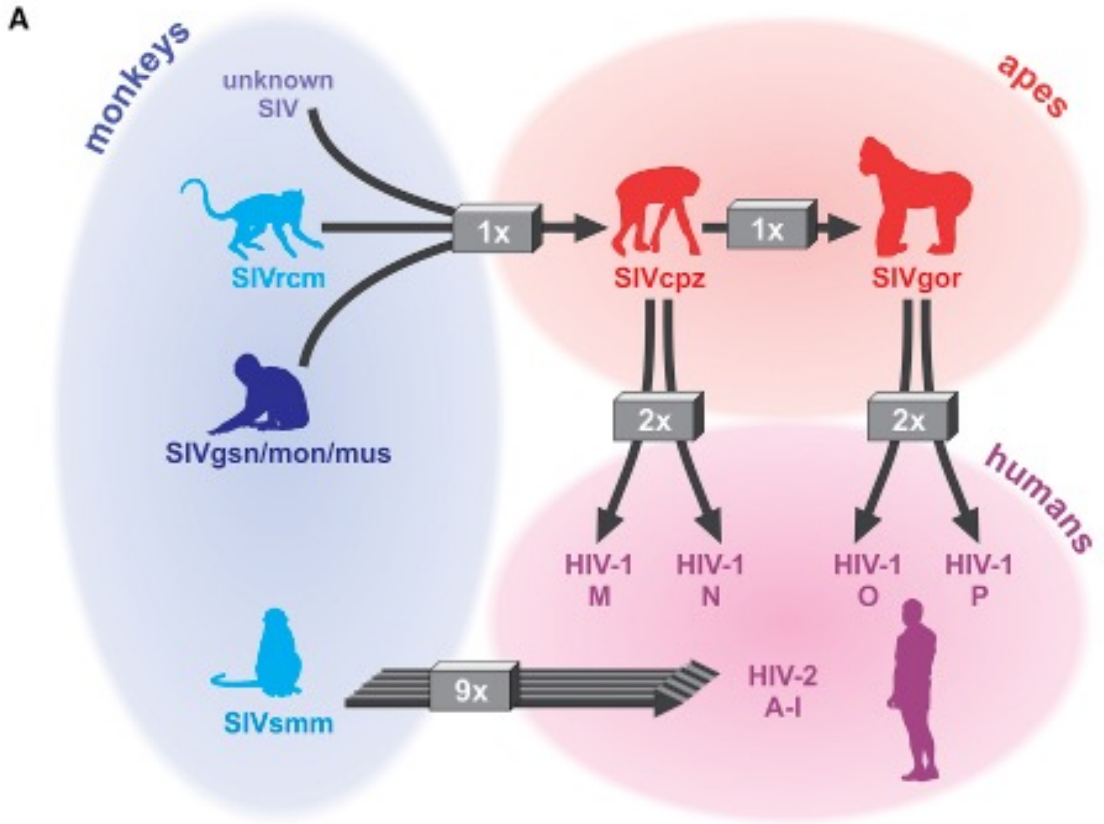
Determinants of succesful zoonotic transmission



Unprotected sexual intercourse between discordant couples is by far the most frequent mode of HIV-1 transmission being semen the main vector for HIV-1 dissemination worldwide

Cell Host & Microbe 25, January 9, 2019

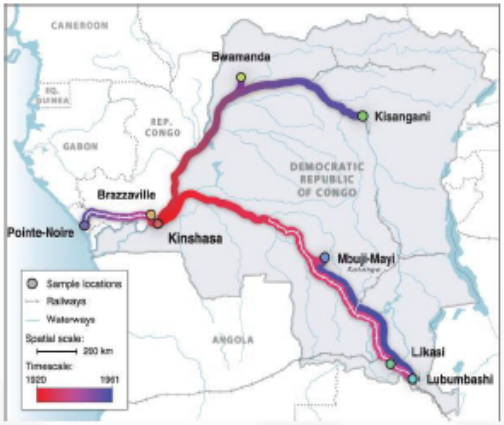
Origins of HIV

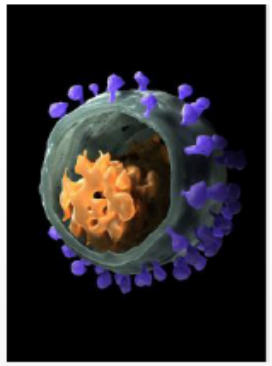


SIVcpz in chimpanzees is the result of recombination events between three different SIV strains. The chimpanzee virus was subsequently transmitted to gorillas and humans, giving rise to SIVgor and HIV-1 groups M and N, respectively.
HIV-1 groups O and P are the result of two zoonotic transmission events of SIVgor.
SIVsmm infecting sooty mangabeys was transmitted to humans on at least nine occasions, resulting in the emergence of HIV-2 groups A through I.

Cell Host & Microbe 25, January 9, 2019

L'origine di HIV-1 è legata al 'salto di specie' tra il Simian Immunodeficiency Virus (SIV) avvenuta probabilmente nell'Africa sub-sahariana tra il ceppo SIVcpz di *Pan troglodytes* e l'uomo, in un periodo imprecisato tra il 1908 e il 1930, presumibilmente per attività di caccia e macellazione



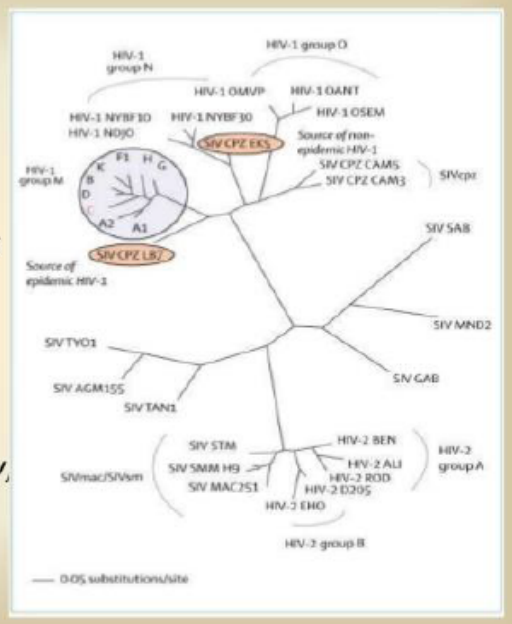


Studi di filogenesi datano i primi episodi di trasmissione di HIV-1 intorno al 1920 nella DRC (Faria et al Science)

L'epidemia si è in seguito diffusa globalmente con modalità non ancora del tutto chiarite intorno al 1960-1970

Evolution of SIV into HIV

- Retroviridae
- *Lentiviridae*
- *Same modes of transmission.*
- *Introduction of simian immunodeficiency virus into the human population.*
- *primate simian immunodeficiency viruses: HIV-2 from SIVsm (sooty mangabey) and HIV-1 from SIVcpz (chimpanzee).*



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Science. 2014 October 3; 346(6205): 56–61. doi:10.1126/science.1256739.

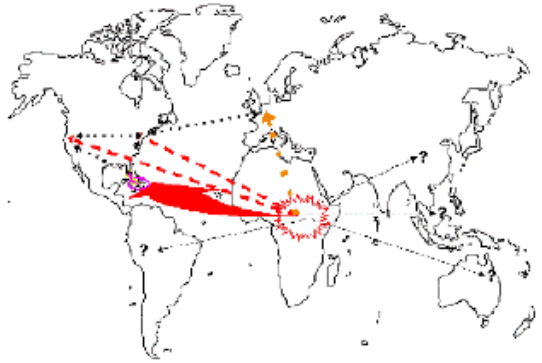
The early spread and epidemic ignition of HIV-1 in human populations

Nuno R. Faria[1,2], **Andrew Rambaut**[3,4,5], **Marc A. Suchard**[6,7], **Guy Baele**[2], **Trevor Bedford**[8], **Melissa J. Ward**[3], **Andrew J. Tatem**[4,9], **João D. Sousa**[2,10], **Nimalan Arinaminpathy**[1], **Jacques Pépin**[11], **David Posada**[12], **Martine Peeters**[13], **Oliver G. Pybus**[1,*,†], and **Philippe Lemey**[2,*,†]

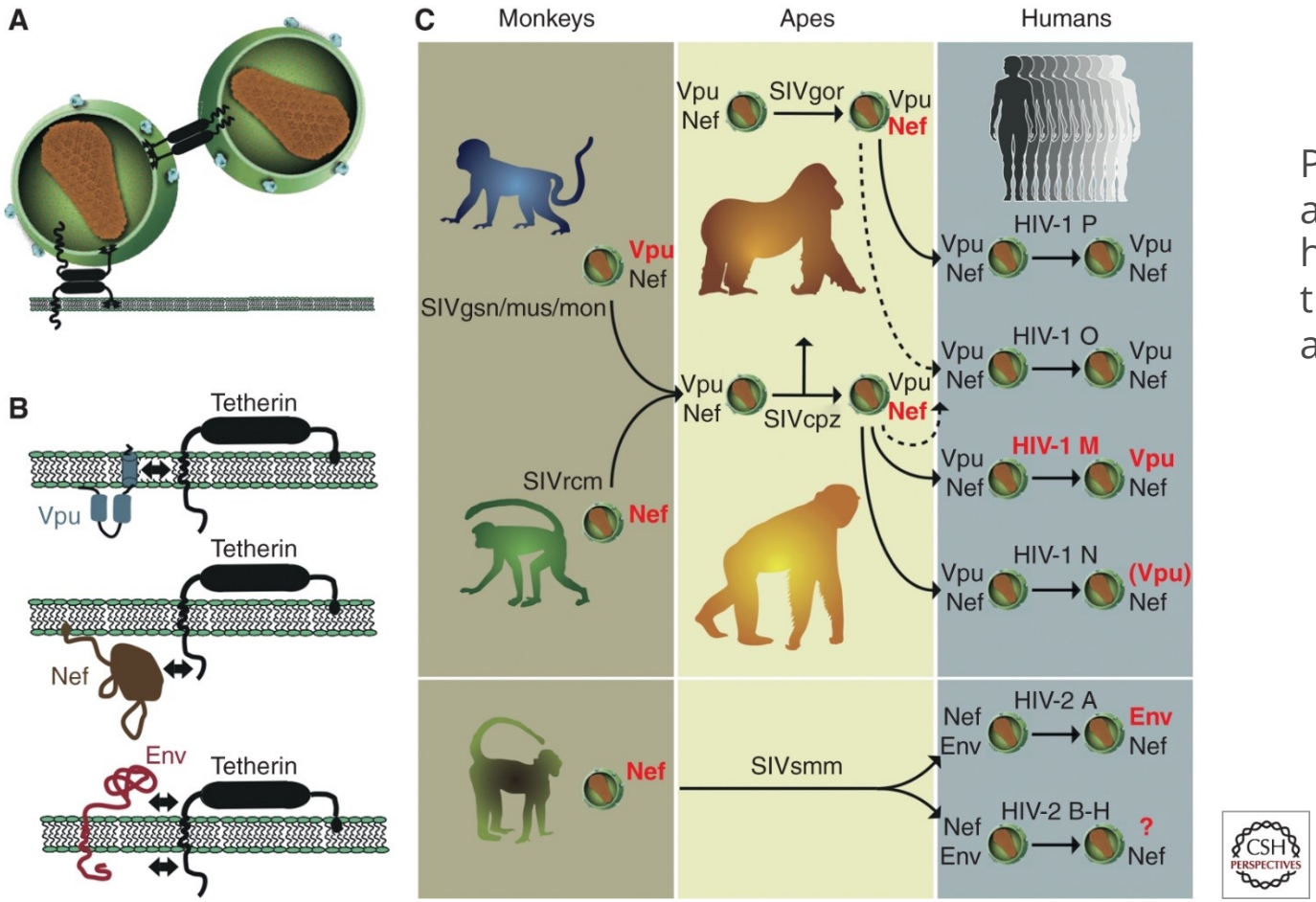
[1]Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK

[2]KU Leuven – University of Leuven, Department of Microbiology and Immunology, Rega Institute for Medical Research, Clinical and Epidemiological Virology, Minderbroedersstraat 10, B-3000 Leuven, Belgium

Probable Routes of Initial Global Spread of HIV-1 in the 1960s and 1970s



Fonte: Faria et al., HIV Epidemiology, Science 346: 56-61, 2014



Proteins that are active against tetherin are highlighted in red, and those that are inactive are shown in gray

Viral antagonists of tetherin and their sites of interaction (indicated by arrows). Vpu associates with the *trans*-membrane domain of tetherin, Nef targets the cytoplasmic domain, and Env interacts either with the extracellular or the cytoplasmic domain. (*C*) Antitetherin function in HIV-1 and HIV-2 and their immediate simian precursors.
SIVcpz acquired *vpu* and *nef* genes from different sources.
During adaptation in chimpanzees, Nef (and not Vpu) evolved to become an effective tetherin antagonist. SIVgor and SIVsmm also use Nef to counteract tetherin.
After transmission to humans, SIVcpz, SIVgor, and SIVsmm Nef were unable to antagonize human tetherin because of a deletion in its cytoplasmic domain.
HIV-1 group M adapted by regaining Vpu-mediated antitetherin activity.
The Nef and Vpu proteins of HIV-1 groups O and P remained poor tetherin antagonists.
The Vpu of HIV-1 group N gained modest antitetherin activity, but lost the ability to degrade CD4.
HIV-2 group A adapted by gaining Env-mediated antitetherin activity; whether HIV-2 groups B–H gained antitetherin function has not been tested.

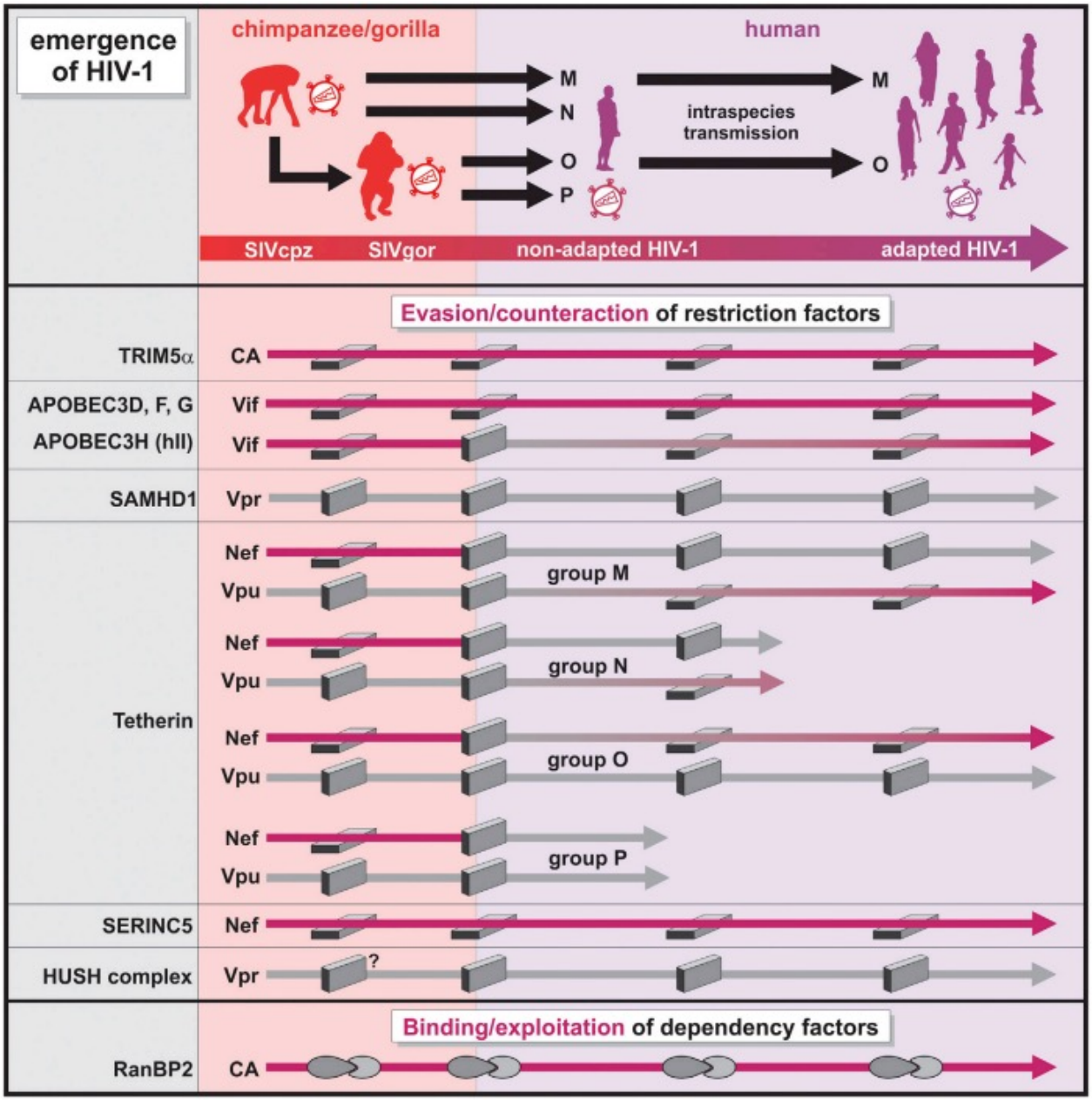


Figure 4. Emergence of HIV-1

The upper panel illustrates the transmission events from chimpanzees to gorillas and humans that ultimately gave rise to HIV-1 groups M, N, O, and P. While groups M and (to a lesser extent) O efficiently spread in the human population, group N and P strains were only identified in few individuals. The lower panel shows the adaptation of viral accessory proteins (Vif, Nef, Vpu, and Vpr) and capsid (CA) to cellular restriction factors (APOBEC3s, TRIM5α, Tetherin, SAMHD1, HUSH complex, and SERINCs) and the dependency factor RanBP2. Barriers to viral spread are represented as intact walls, while successful evasion or counteraction of restriction factors and binding to RanBP2 are illustrated by fallen walls and pink instead of gray arrows.

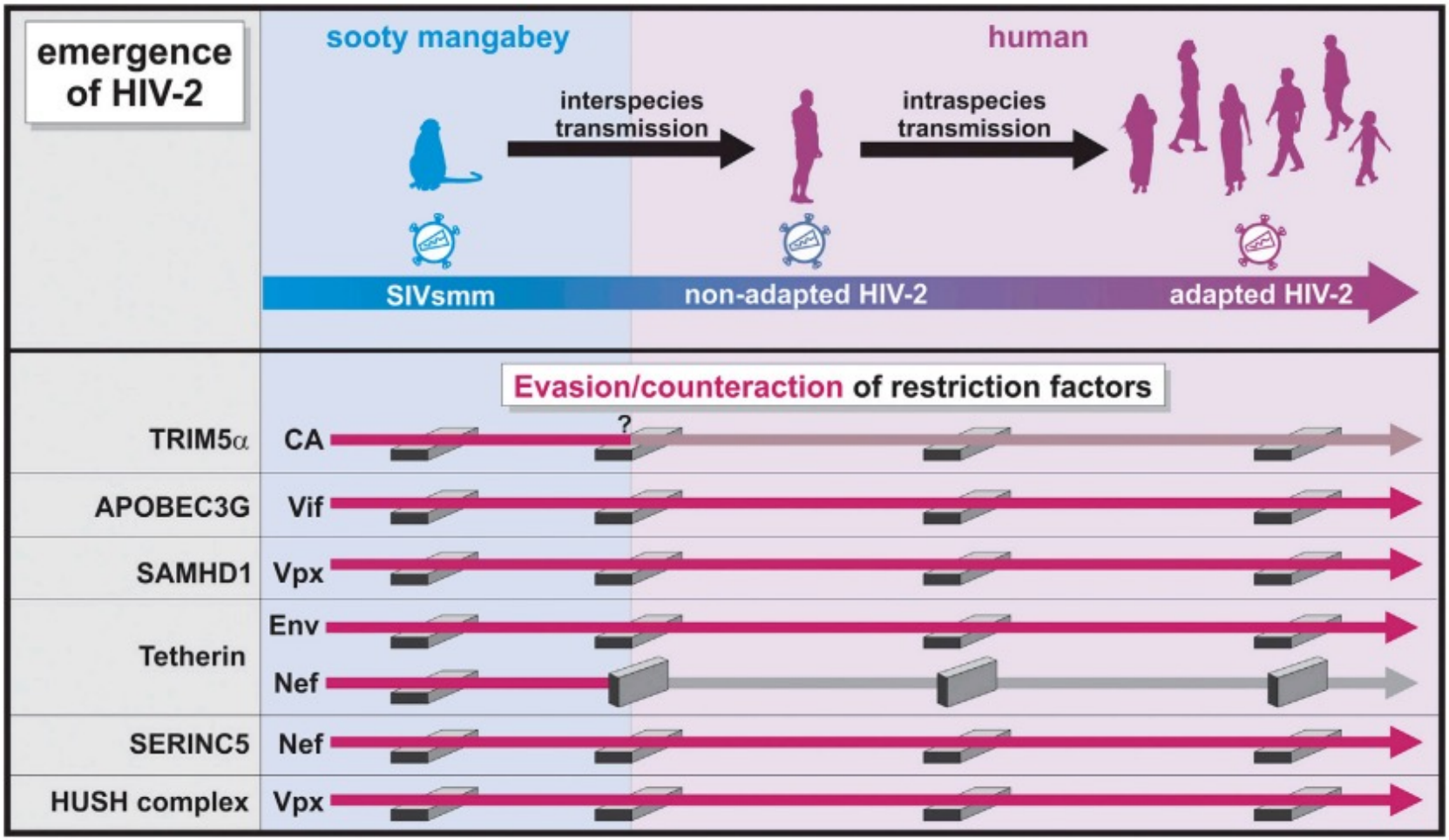


Figure 5. Emergence of HIV-2

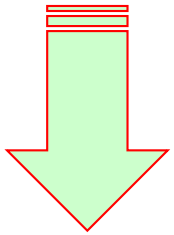
The zoonotic transmission of SIVsmm from sooty mangabeys to humans and the emergence of HIV-2 are shown on top. Adaptation of viral accessory proteins (Vif, Nef, and Vpx), envelope (Env), and capsid (CA) to cellular restriction factors (APOBEC3s, TRIM5α, Tetherin, SAMHD1, HUSH complex, and SERINCs) are illustrated at the bottom. Restriction factors posing potential barriers to viral spread are represented as intact walls, while cleared barriers are illustrated by fallen walls and pink instead of gray arrows.

The discovery

1981 AIDS described for the first time as a result of a new infection (anomalous cases of Kaposi's sarcoma and pneumonia induced by Pneumocystis carinii in young men who have sex with men in the areas of New York, Los Angeles and San Francisco)

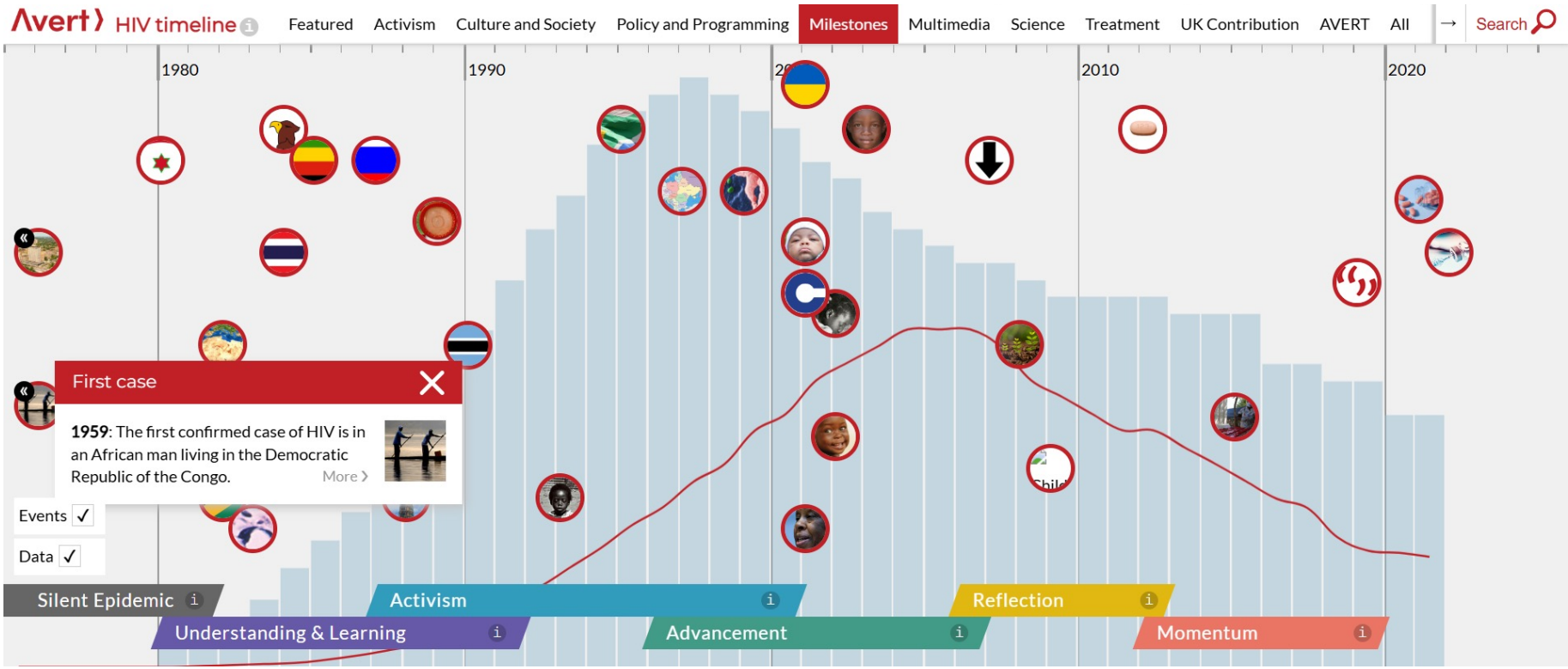
1983 Francoise Barre-Sinoussi, Claude Chermann and Luc Montagnier (Nobel Prize, 2008), at the Pasteur Institute in Paris, isolate a virus from the lymphonodes of a patient with generalized lymphadenopathy of unknown etiology and called the virus Lymphadenopathy-Associated Virus (LAV). The virus, identified as a retrovirus, exhibits characteristics similar to the known human retrovirus HTLV-1

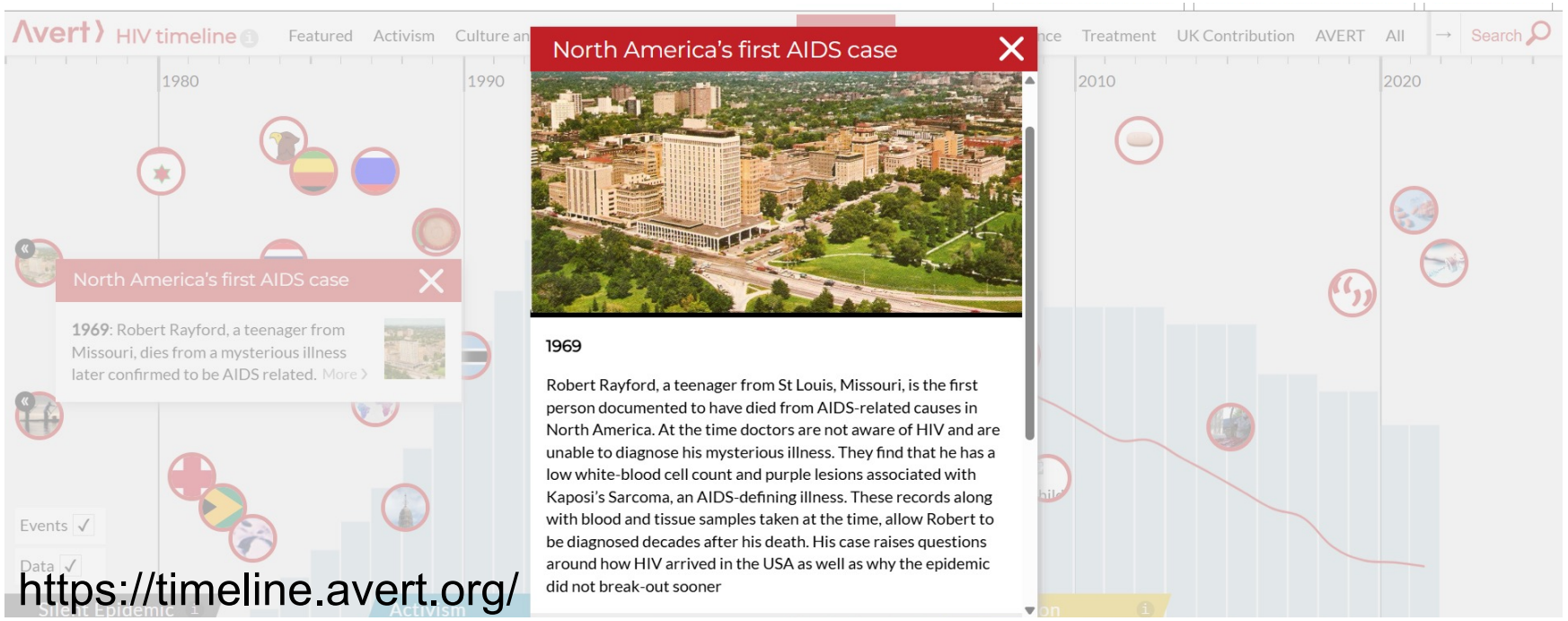
1984 Robert Gallo and coworkers at NIH confirmed the discovery of a human lymphotropic retrovirus (HTLV-III) that unlike HTLV-1 kills CD4 + T cells rather than stabilize them and establish the relationship of the virus with the immune deficiency syndrome AIDS (Acquired immunodeficiency Syndrome)



LAV and HTLV-III represent two strains of the same virus, the Human Immunodeficiency Virus HIV

1986 A second type of HIV is isolated in West Africa (HIV-2).





https://timeline.avert.org/

HIV types and groups

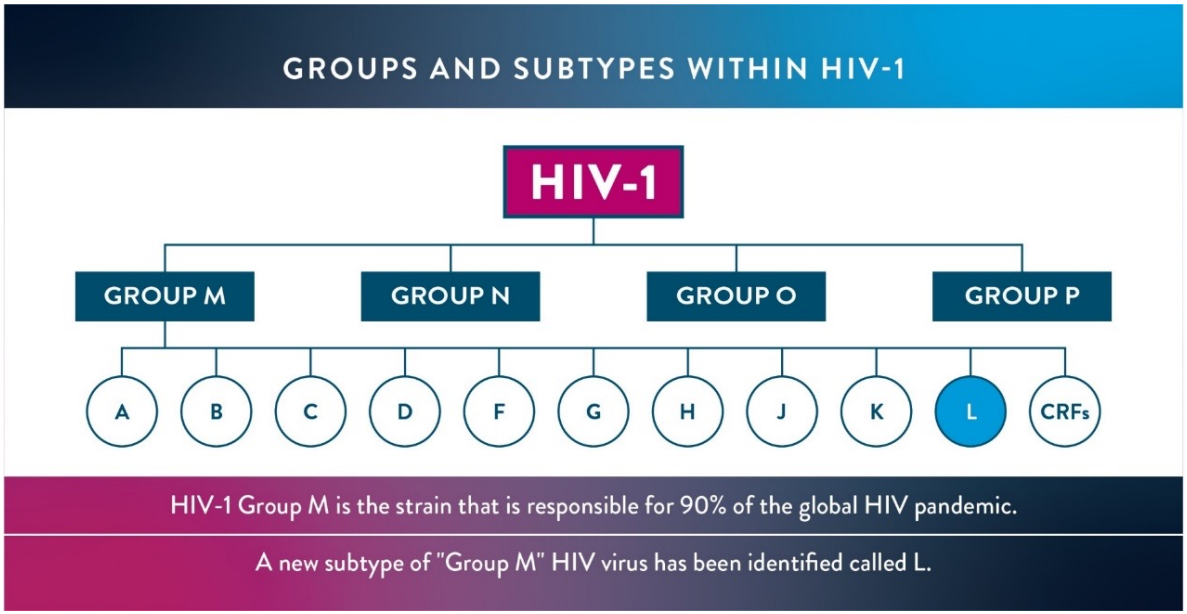
HIV-1 and HIV-2 cause clinically indistinguishable disease, although the time to disease onset is longer for HIV-2. The worldwide epidemic of HIV and AIDS is caused by HIV-1, while HIV-2 is mostly restricted to West Africa.

There are four groups of HIV-1, M (main or major), N (new) and O (outlier). Type O HIV-1 is mostly found in Cameroon and Gabon while the rare N sub-group is also found in Cameroon.

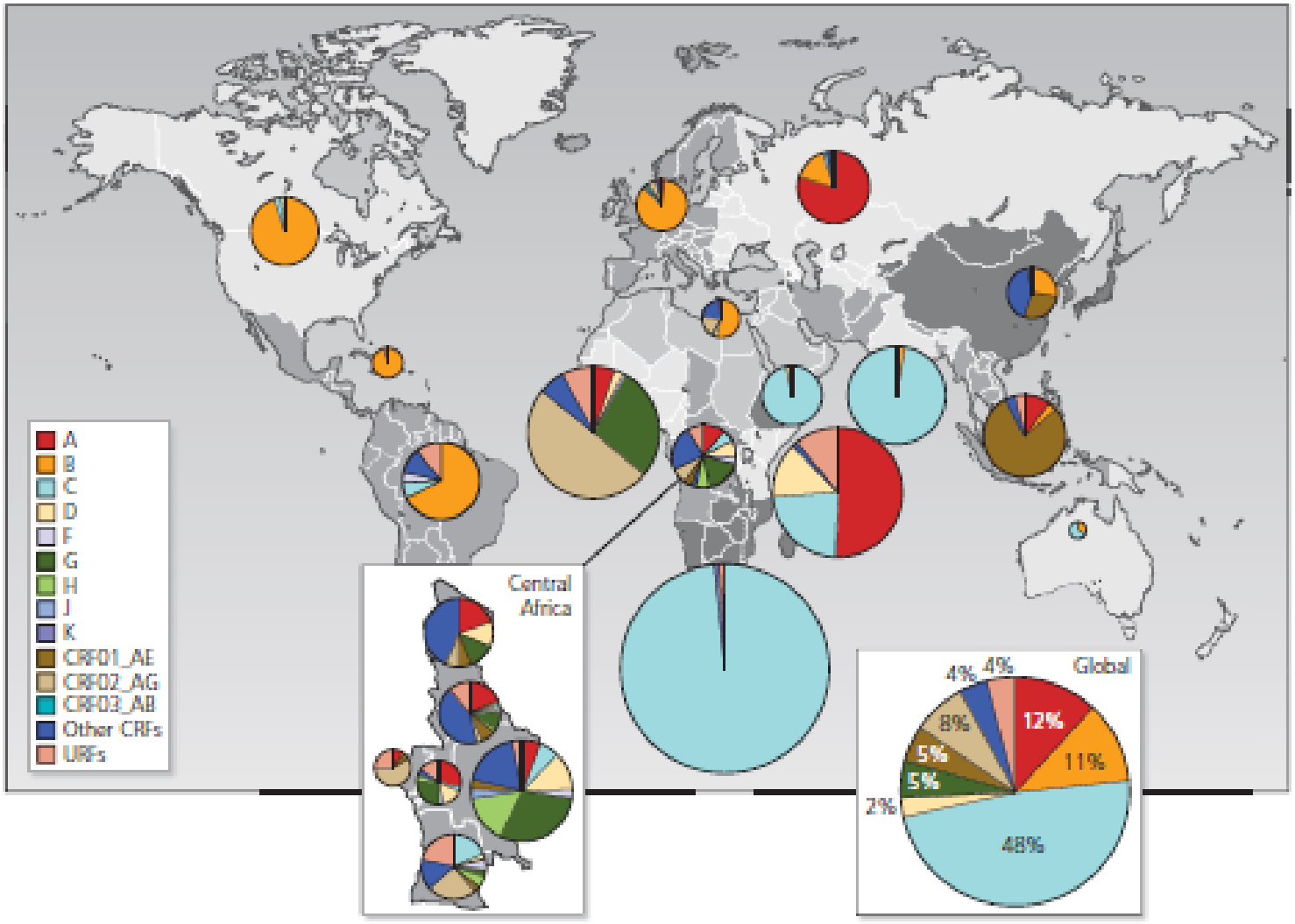
In 2009 a new strain closely related to gorilla simian immunodeficiency virus was discovered in a Cameroonian woman. It was designated HIV-1 group P.

HIV-1 groups and sub-types

Based on nucleotide sequence analyses of the *env* and *gag* genes, it has been found that there are also at least ten different HIV-1 subtypes within the M group - these are designated A to L.

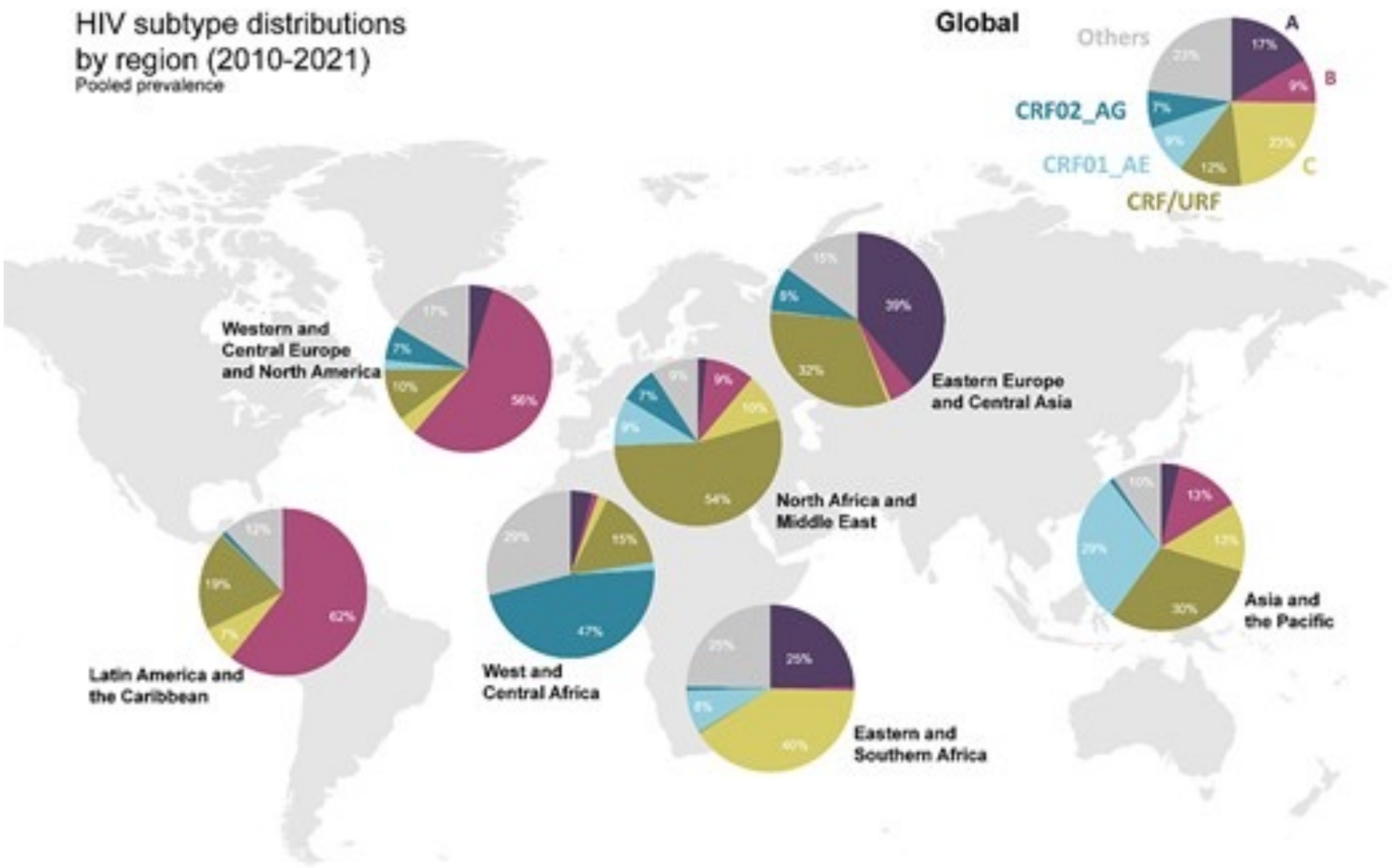


CRF-Circulating recombinant form. In some countries, mosaics (recombinants) between different subtypes have been found. These arise when two different subtypes infect a person at the same time and recombination occurs.



World map showing the relative contribution of different HIV-1 subtypes to the total burden of infection globally (inset) and in different regions (main map) from 2004–7. The overall size of each pie chart reflects the numbers of infected people in each region, with the coloured segments of the charts representing the particular subtypes (A–K) and recombinant forms (CRF) present. The situation in Central Africa is represented in greater detail in an inset which shows the greater heterogeneity in the virus present in this region as compared with other parts of the world.

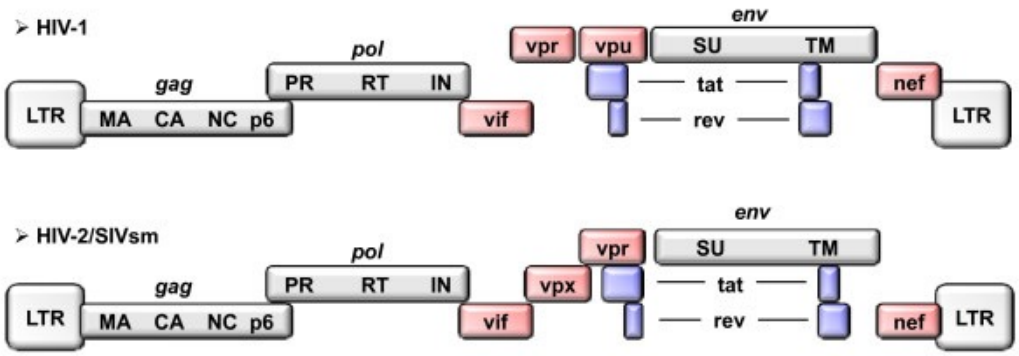
Trends in Molecular Medicine, 18: 2012

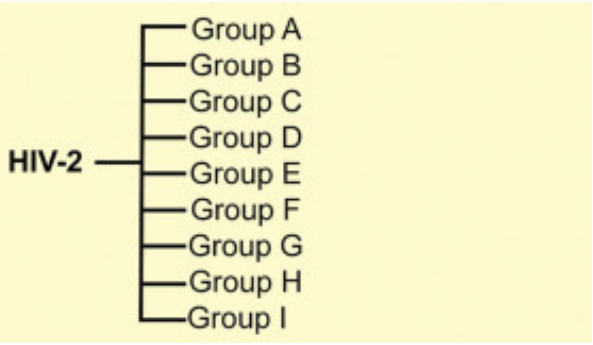


Understanding the prevalent HIV subtypes in key populations is crucial for designing targeted prevention and intervention strategies.

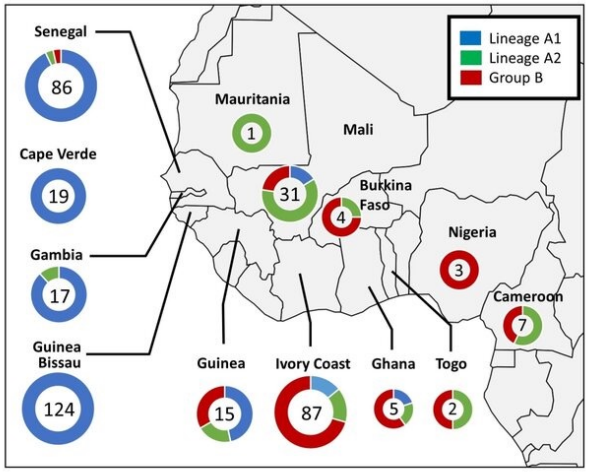
The Journal of Infectious Diseases, Volume 228, Issue 11, 2023, Pages 1583–1591

HIV-2


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
vpx
vpr
SU
TM
tat
rev
nef
LTR


HIV-2
Group A
Group B
Group C
Group D
Group E
Group F
Group G
Group H
Group I

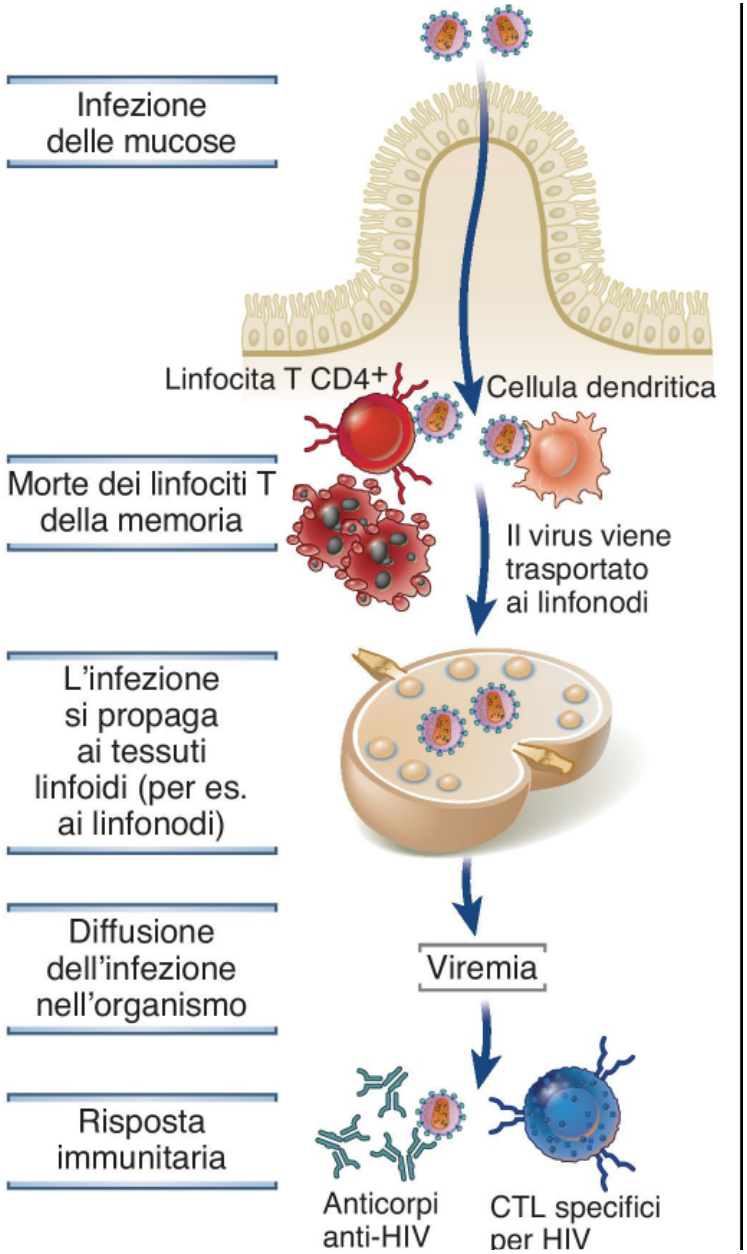

Luxembourg
UK
France
Spain
Portugal
Senegal
Cape Verde
Gambia
Guinea-Bissau
Côte d'Ivoire
Nigeria
South Korea
HIV-2 prevalence >1%
HIV-2 prevalence <1%
Absent/no data
Phylogeographic links


Lineage A1
Lineage A2
Group B
Senegal
86
Cape Verde
19
Gambia
17
Guinea Bissau
124
Mauritania
1
Mali
31
Bukkina Faso
4
Nigeria
3
Cameroon
7
Guinea
15
Ivory Coast
87
Ghana
5
Togo
2

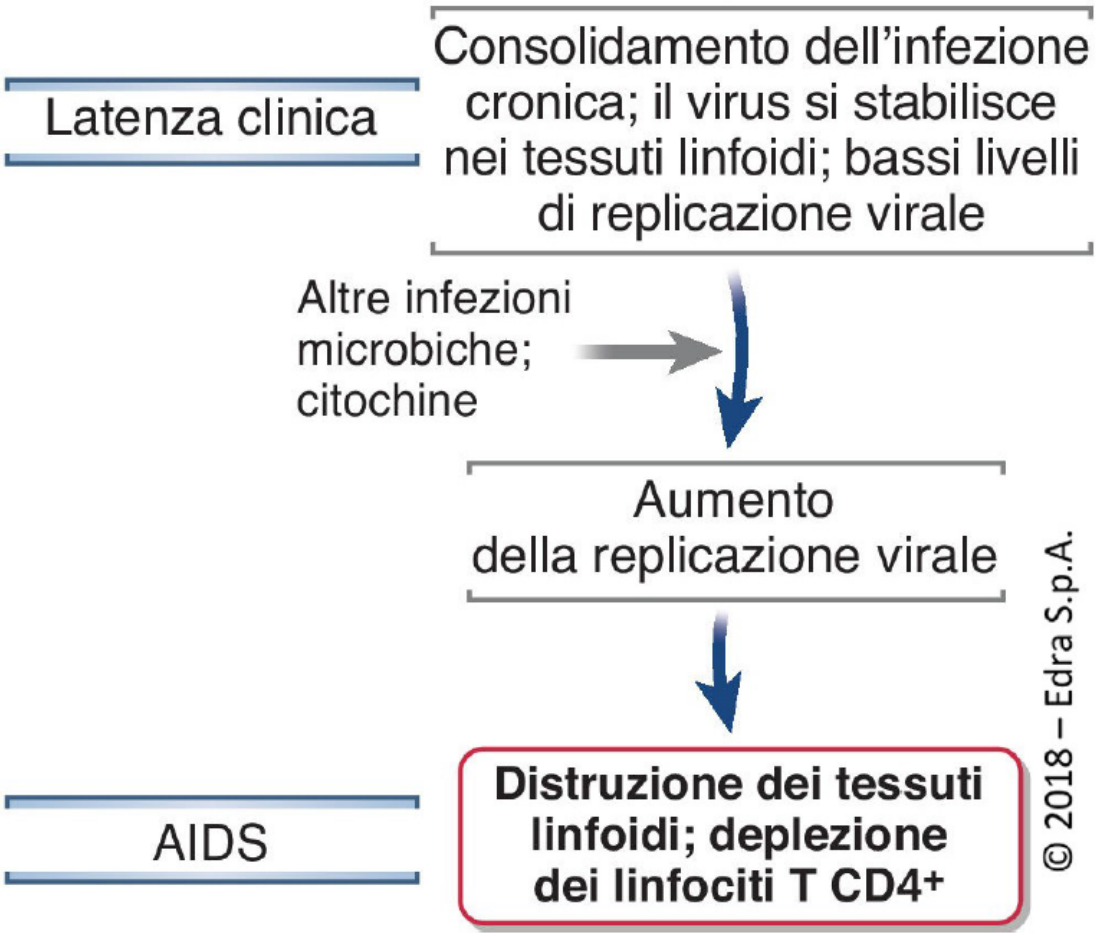
Patogenesi dell'infezione da HIV

L'infezione acuta precoce è caratterizzata dall'infezione dei linfociti T **CD4+ di memoria che esprimono CCR5** dei tessuti linfoidi mucosali che si riflette in una considerevole perdita di linfociti T CD4+ a livello sistemico evidente dopo 2 settimane dal contagio

La viremia favorisce la disseminazione sistemica del virus con infezione di TCD4+, macrofagi e cellule dendritiche nei tessuti linfoidi periferici



Patogenesi dell'infezione da HIV



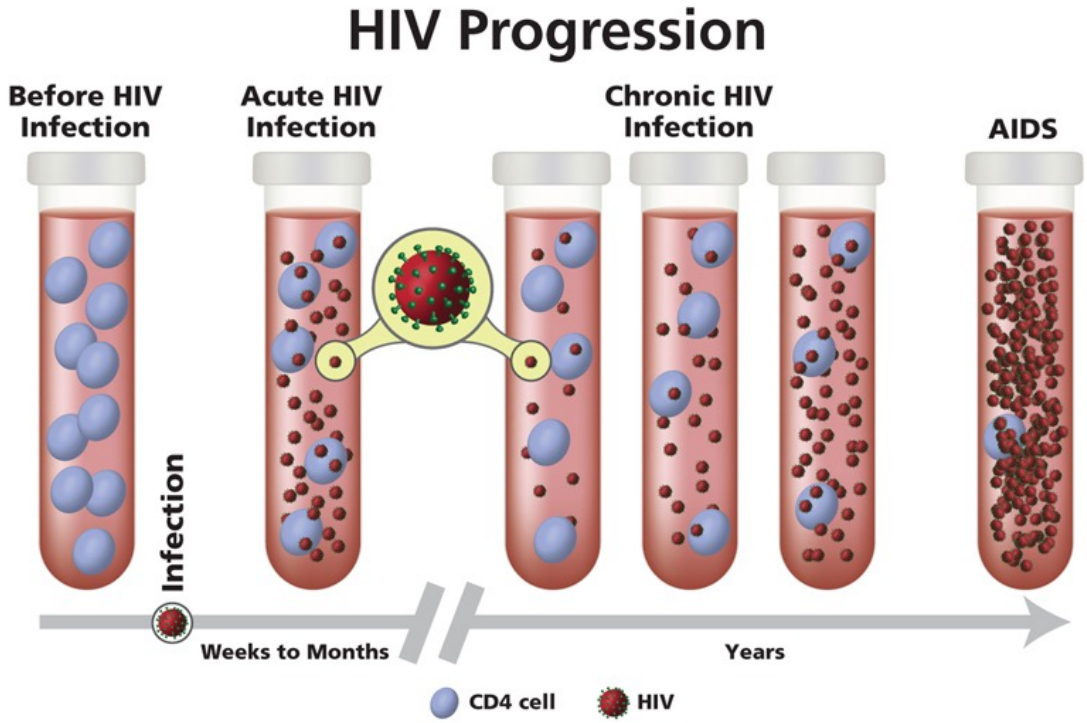


Tabella 20–7. Caratteristiche cliniche dell'infezione da HIV

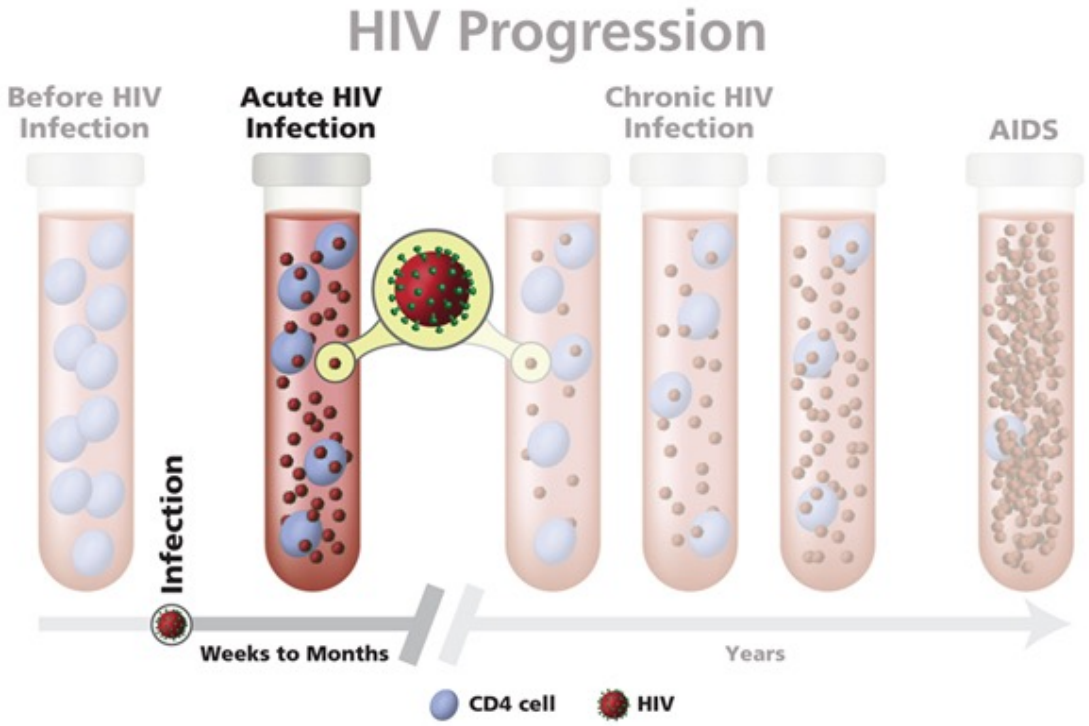
Fase della malattia	Caratteristiche cliniche
Sindrome acuta	Febbre, cefalea, mal di gola con faringite, linfoadenopatia generalizzata, eruzioni cutanee
Periodo di latenza clinica	Diminuzione del numero di linfociti T $CD4^+$
AIDS	**Infezioni opportunistiche:** Protozoi *(Toxoplasma Cryptosporidium)* Batteri *(Mycobacteruim avium, Nocardia, Salmonella)* Miceti *(Candida, Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Pneumocystis)* Virus *(cytomegalovirus, herpes simplex, varicella-zoster)* **Tumori:** Linfomi (linfomi B associati a infezione da EBV) Sarcoma di Kaposi Carcinoma della cervice **Encefalopatia** **Sindrome da deperimento**

AIDS, sindrome da immunodeficienza acquisita; EBV, virus di Epstein-Barr.

The three stages of HIV infection are (1) acute HIV infection, (2) chronic HIV infection, and (3) acquired immunodeficiency syndrome (AIDS).

There is no cure for HIV, but treatment with HIV medicines (called antiretroviral therapy or ART) can slow or prevent HIV from advancing from one stage to the next. HIV medicines help people with HIV live longer, healthier lives.

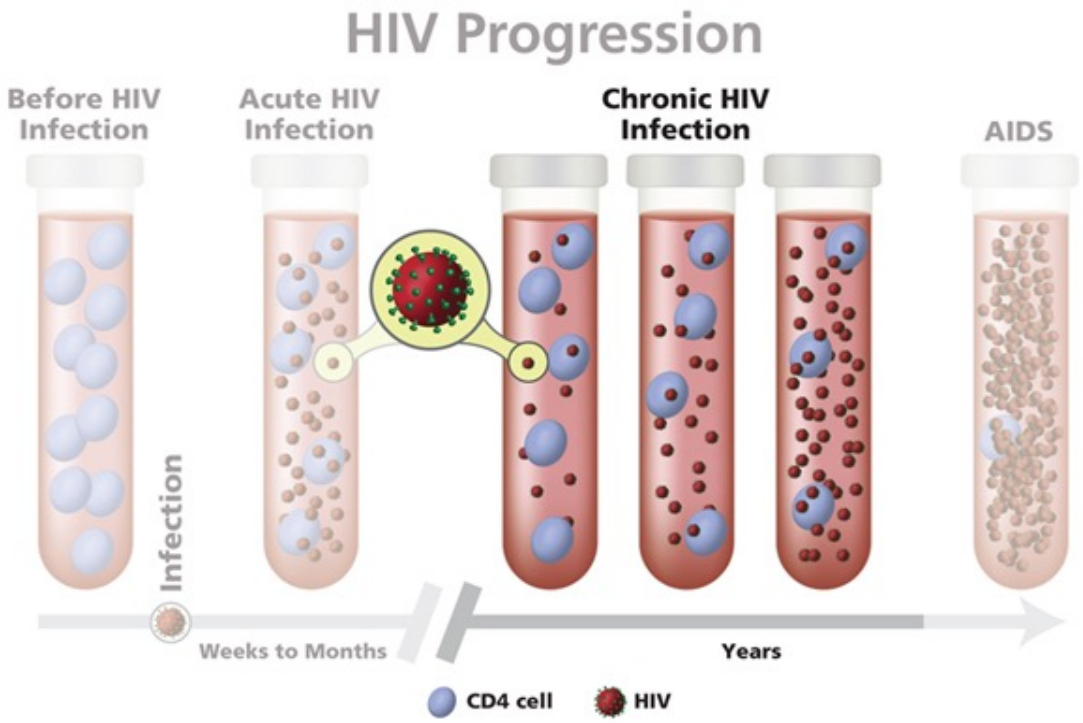
https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/46/the-stages-of-hiv-infection



Acute HIV infection

Early stage of HIV infection that extends approximately 2 to 4 weeks from initial infection until the body produces enough HIV antibodies to be detected by an HIV antibody test. During acute HIV infection, HIV is highly infectious because the virus is multiplying rapidly. The rapid increase in HIV viral load can be detected before HIV antibodies are present. During this time, some people have flu-like symptoms, such as fever, headache, and rash. The virus attacks and destroys the infection-fighting CD4 cells of the immune system. A person may experience significant health benefits if they start ART during this stage.

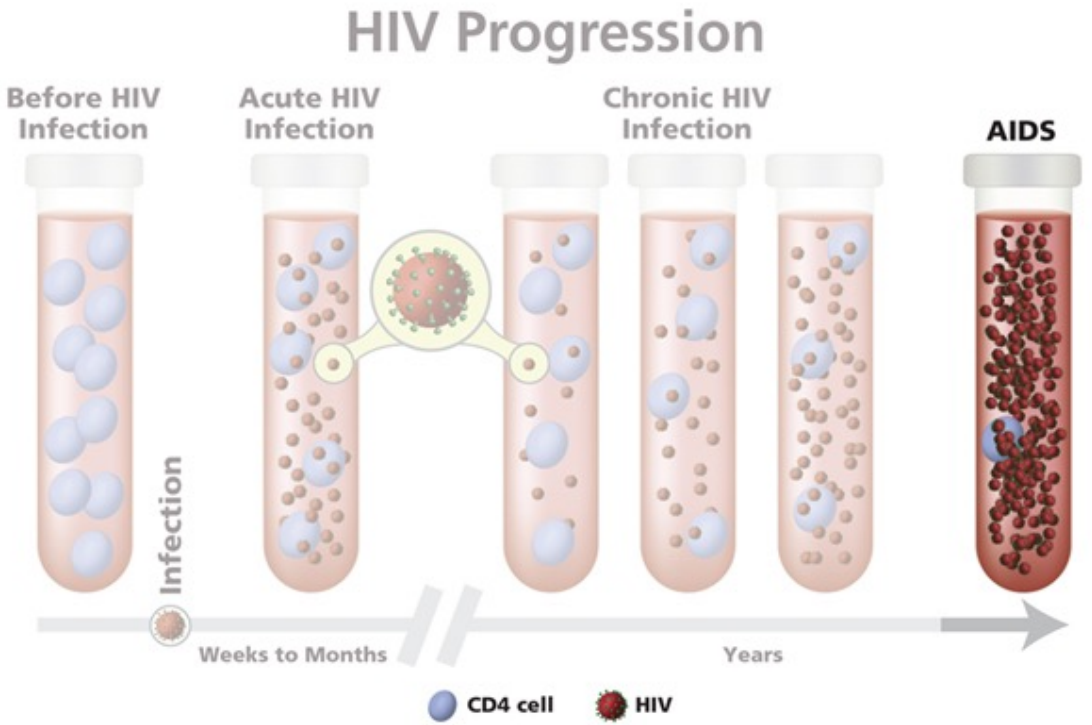
https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/46/the-stages-of-hiv-infection



Chronic HIV Infection

The second stage of HIV infection is chronic HIV infection (also called asymptomatic HIV infection or clinical latency). During this stage, HIV continues to multiply in the body but at very low levels. People with chronic HIV infection may not have any HIV-related symptoms. Without ART, chronic HIV infection usually advances to AIDS in 10 years or longer, though in some people it may advance faster. People who are taking ART may be in this stage for several decades. While it is still possible to transmit HIV to others during this stage, people who take ART exactly as prescribed and maintain an undetectable viral load have effectively no risk of transmitting HIV to an HIV-negative partner through sex.

https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/46/the-stages-of-hiv-infection

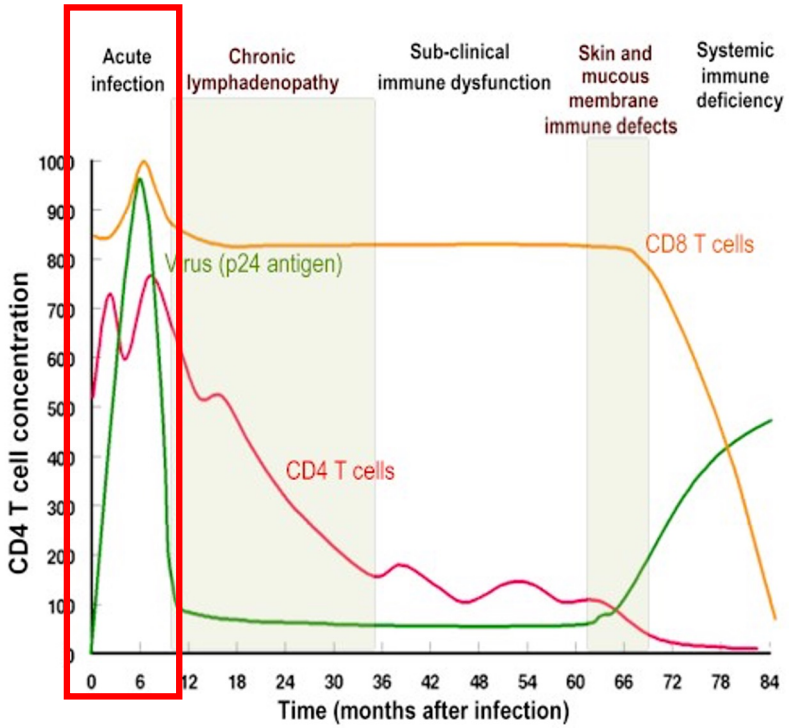


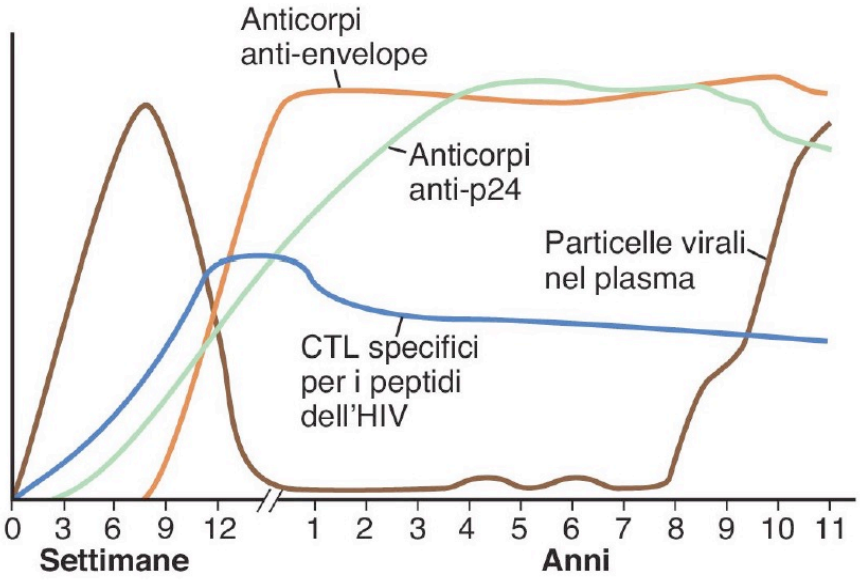
AIDS

AIDS is the final, most severe stage of HIV infection. Because HIV has severely damaged the immune system, the body can't fight off opportunistic infections. (Opportunistic infections are infections and infection-related cancers that occur more frequently or are more severe in people with weakened immune systems than in people with healthy immune systems.) People with HIV are diagnosed with AIDS if they have a CD4 count of less than 200 cells/mm3 or if they have certain opportunistic infections. Once a person is diagnosed with AIDS, they can have a high viral load and are able to transmit HIV to others very easily. Without treatment, people with AIDS typically survive about 3 years.

https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/46/the-stages-of-hiv-infection

Course of the disease

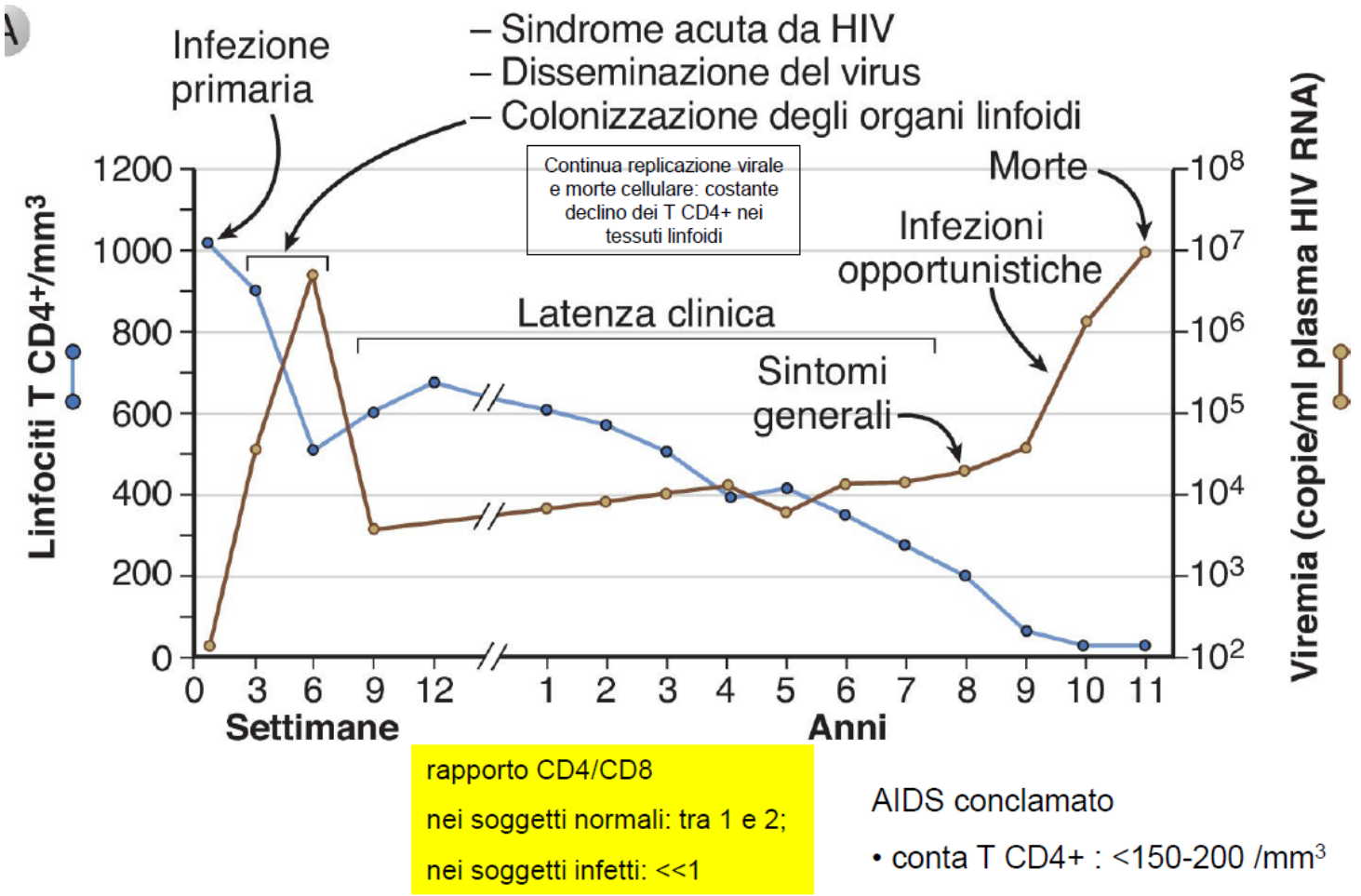




Cytotoxic B and T lymphocytes mount a strong defense and virus largely disappears from the circulation. After the increased cell-mediated immune response, there is a rise in humoral anti-HIV antibodies. During this period of strong immune response to the virus, more than 10 billion new HIV particles are produced each day, but they are rapidly cleared by the immune system and have a half-life of only 5 to 6 hours

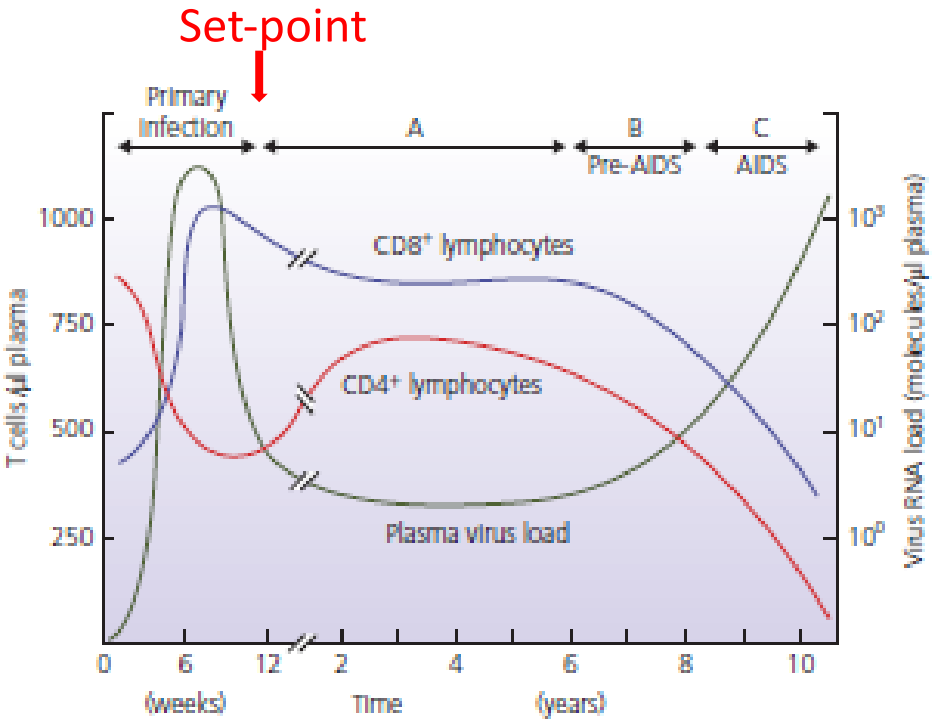
The infected cells that are producing the virus are destroyed either by the immune system or by the virus and have a half-life about 1 day. However, the rate of production of $CD4^+$ cells can compensate for the loss of cells and a steady state is set up in which most CD4+ cells are uninfected.

Course of the disease



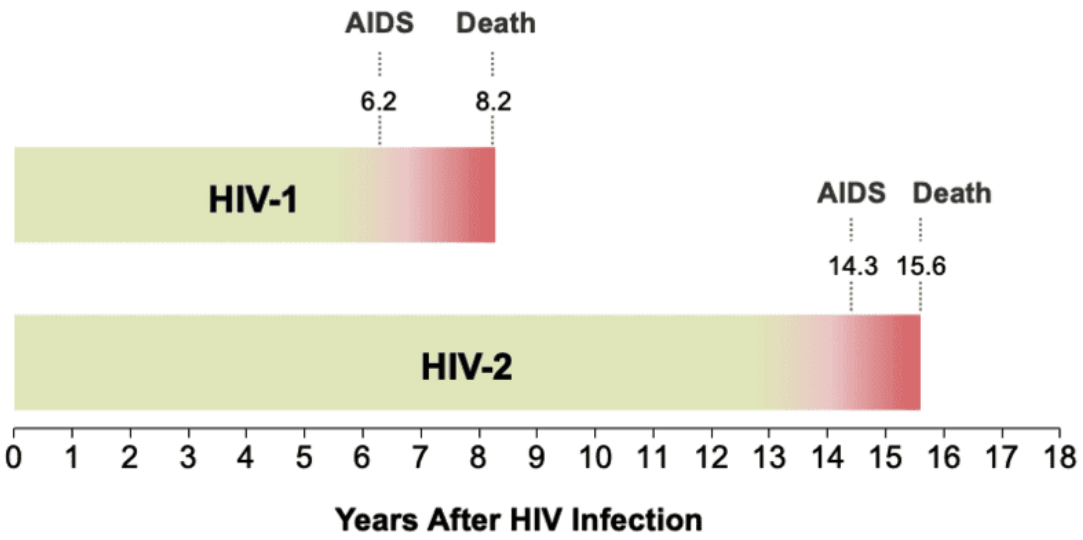
As a result of the strong immune defense, the number of viral particles in the blood stream declines and the patient enters *clinical latency* . Little virus can now be found in the bloodstream or in peripheral blood lymphocytes and, initially, the number of blood CD4+ cells is only slightly decreased. Nevertheless, the virus persists elsewhere, particularly in lymph nodes and here viral replication continues as follicular dendritic cells interact with more CD4+ cells that become infected. The virus is also replicated by macrophages. The killer cells needed to control HIV also damage the helper T cells that they need to function efficiently. With the lack of CD4+ cells, new cytotoxic T cell responses cannot occur as helper cells are lacking and such new responses are required as the virus mutates.

Course of the disease



During the initial/primary infection by HIV-1, virus-specific CD4+ T cells are stimulated to proliferate by viral antigens. As virus infects and replicates in activated CD4+ cells, these same cells are preferentially destroyed. At the same time, there is a dramatic expansion of virus-specific CD8+ T cells which coincides with the suppression of viraemia and a recovery in CD4+ T cell numbers. However, CD8+ T cell proliferation is dependent on CD4+ T cell help. Thus, there is a fine balance between virus destroying CD4+ T cells and leaving enough CD4+ T cells to help produce virus-specific activated CD8+ cells. It is suggested that this balance determines the plasma virus load (concentration) at the end of the acute phase, also known as the 'set point'. The set point load appears to be a critical determinant of the rate of progression to AIDS; a low set point load means a longer subclinical period, and a high load means rapid progression to AIDS. However, virus loads ultimately rise again as immune function collapses

With less than 1000 copies/ml of blood, disease will probably occur with a latency period of more than 10 years. With less than 200 copies/ml, disease does not appear to occur at all. Most patients with more than 100,000 copies per ml, lose their CD4+ cells more rapidly and progress to AIDS before 10 years. Most untreated patients have between 10,000 and 100,000 copies per ml in the clinical latency phase.



Limited data exist on HIV-1 and HIV-2 co-infection; in West Africa, up to 15% of individuals have dual infection. HIV-2 does not protect against subsequent HIV-1 acquisition

One study suggested that persons with both HIV-1 and HIV-2 have slower disease progression, with the greatest benefit occurring when HIV-2 precedes HIV-1 infection. Other studies, found no survival benefit

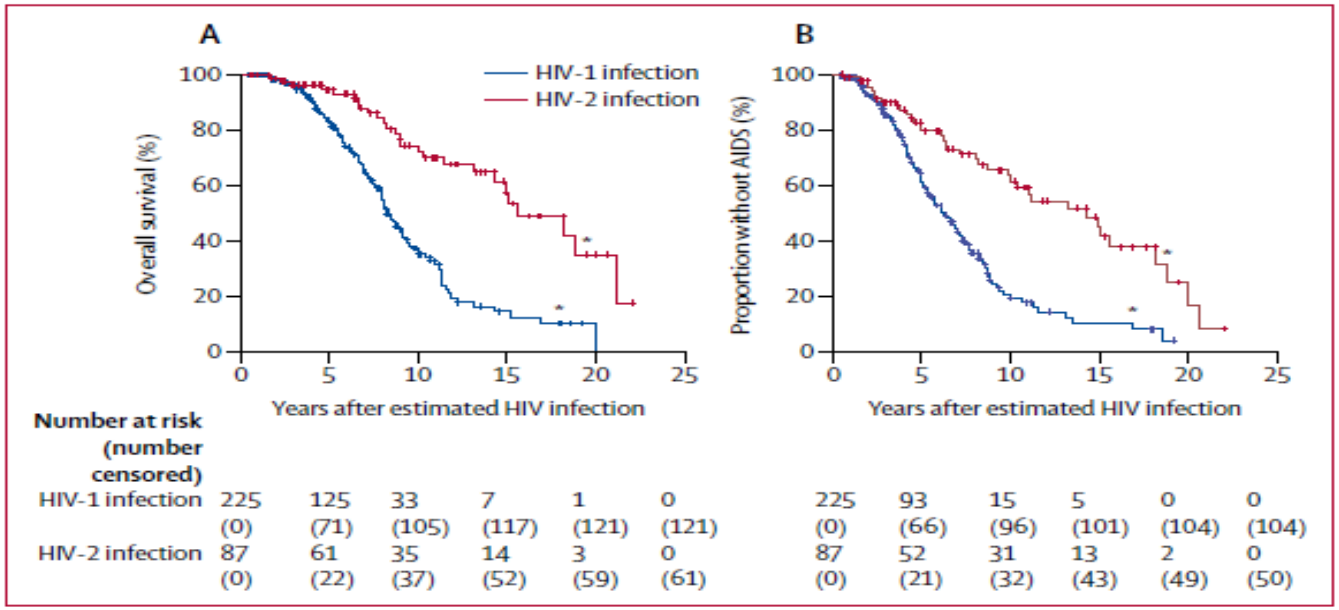
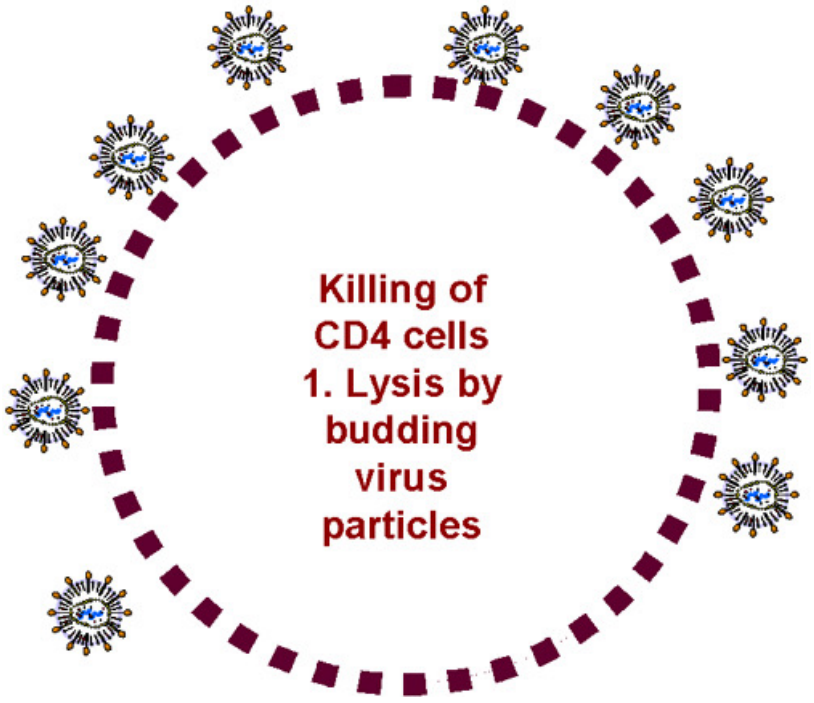


***Figure 1*: Kaplan-Meier curves of survival (A) and AIDS-free time (B) of HIV-1-infected and HIV-2-infected individuals**

Tick marks indicate participants with censored data. HIV-1=HIV type 1. HIV-2=HIV type 2. *The timepoint in each group when five participants are still at mortality risk and risk of developing AIDS.

LOSS OF CD4 CELLS

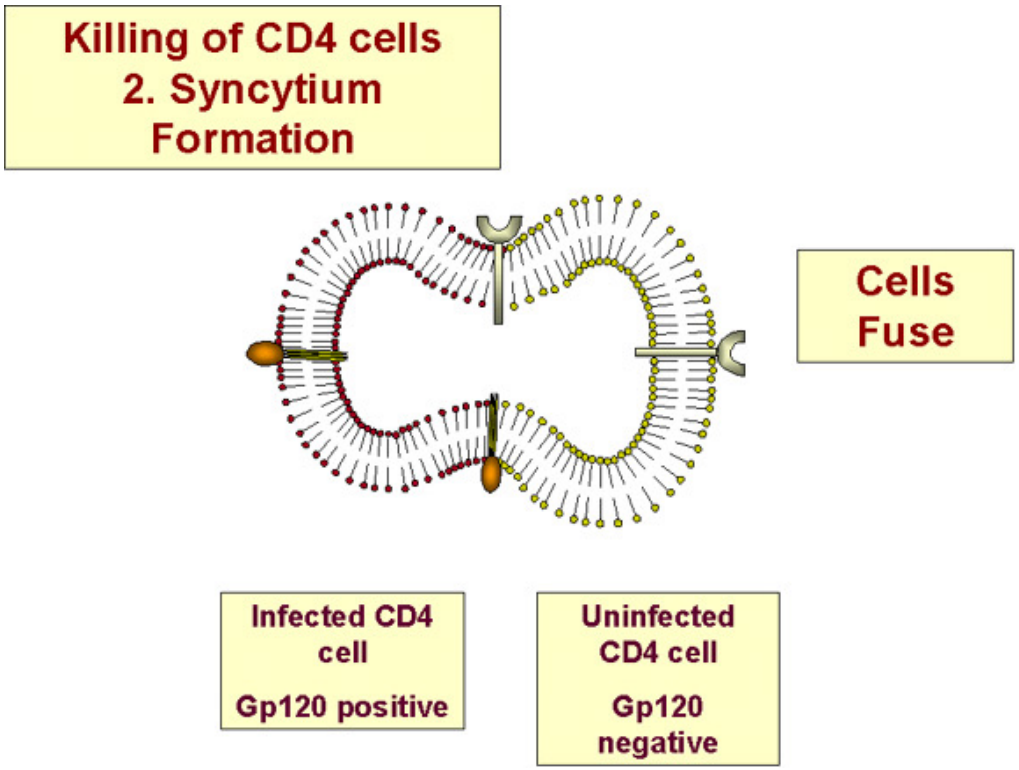
La principale causa della diminuzione dei linfociti T CD4+ nei PLWH è l'effetto diretto esercitato su queste cellule dal virus



La replicazione del virus con produzione della gp41 e la gemmazione dei virioni aumenta la permeabilità della membrana e dunque l'ingresso di concentrazioni letali di ioni Ca++ (apoptosi/lisi osmotica)

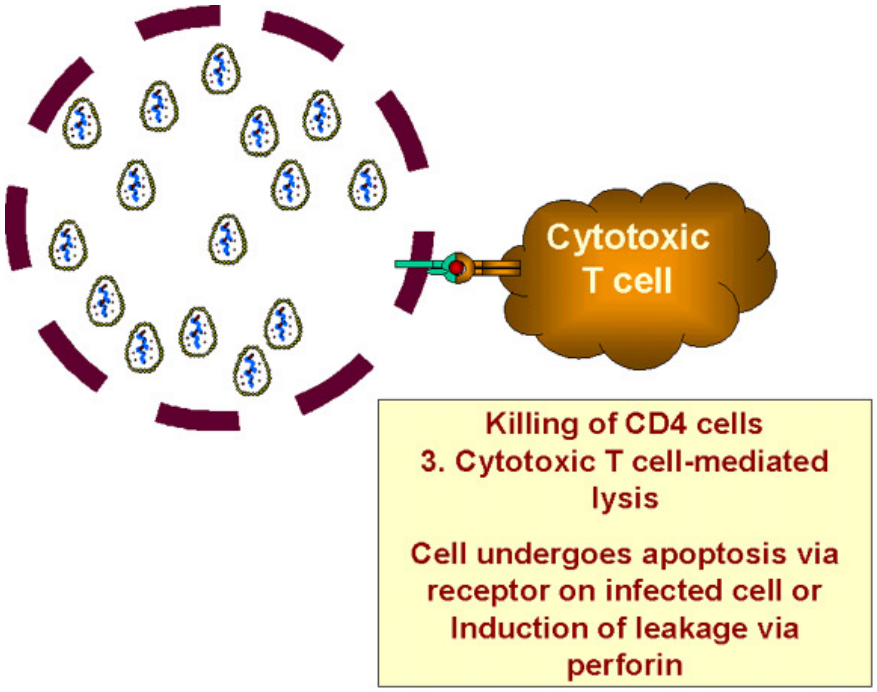
In an activated, infected CD4 cell, huge numbers of virions are synthesized. These bud from the cell and result in punctured membranes.

LOSS OF CD4 CELLS



Since the membrane of HIV fuses with the membrane of the cell to be infected by a pH-independent mechanism, syncytia formation can occur leading syncytium formation

LOSS OF CD4 CELLS



Infected cells that are producing viral proteins (but not those in the latent state) will present those proteins on the cell surface in association with class I MHC histocompatibility antigens. The infected cell, like other virally-infected cells, will be destroyed by cytotoxic T cells. Again this only happens in cells that are infected by HIV.

Gp120 is linked to the Gp41 on the virus surface by non-covalent interactions and is frequently shed from infected cells or from virus particles. This binds to uninfected cells via CD4 antigen. As a result, they appear to be infected and are destroyed by the immune system.

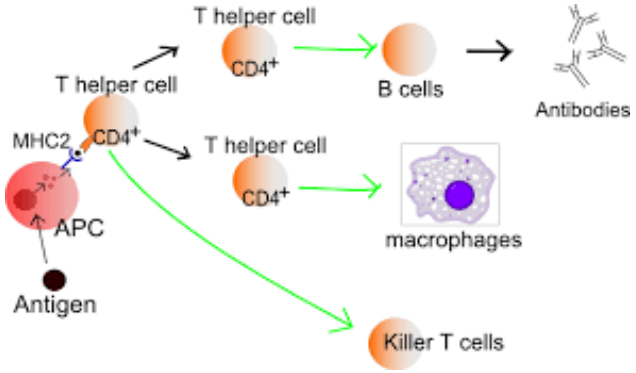
Inoltre la replicazione virale può interferire con la sintesi proteica e portare a morte la cellula

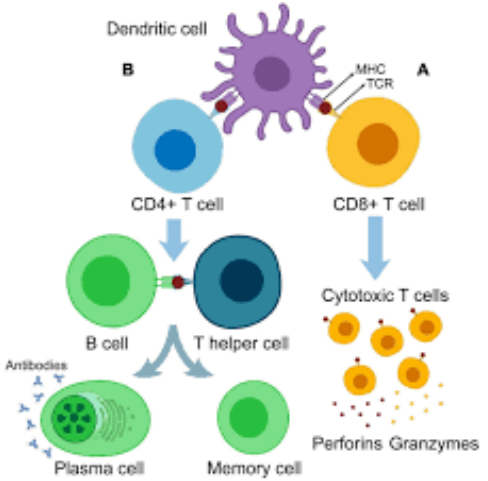
LOSS OF CD4 CELLS and IMMUNODEFICIENCY

La deplezione ed il deficit funzionale dei T CD4+ è anche dovuta a fenomeni indiretti sui linfociti non infetti: Attivazione cronica che predispone all'apoptosi

La perdita di CD4 ha effetti sulle altre funzioni del sistema immune andando ad esempio ad indebolire la risposta anticorpale

I macrofagi, le cellule dendritiche e le cellule dendritiche follicolari sono infettate o danneggiate da HIV con le conseguenti alterazioni che contribuisco all'immunodeficienza





HIV/AIDS Timeline


RARE CANCER SEEN IN 41 HOMOSEXUALS

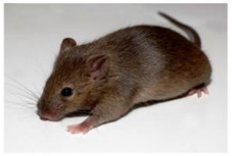
Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

1981 The New York Times reports a mysterious illness

1982 The name "AIDS" – Acquired Immune Deficiency Syndrome – is created

1984 Françoise Barré-Sinoussi and Luc Montagnier discover HIV as the cause of AIDS and later win the Nobel Prize

1985 A test for screening blood donations is developed through chimpanzee research



1987 AZT, developed in mice, becomes the first drug approved for treating AIDS

1990 8 million people have HIV

1994 Infant HIV infections begin to fall due to AZT treatment

1996 Combination treatment of antiretrovirals developed

1997 AIDS-related deaths fall in developed countries due to combination treatments

2007 22 million people have HIV

2010 After tests in mice and macaques, Truvada is shown to reduce the risk of HIV infection

2011 33 million people have HIV

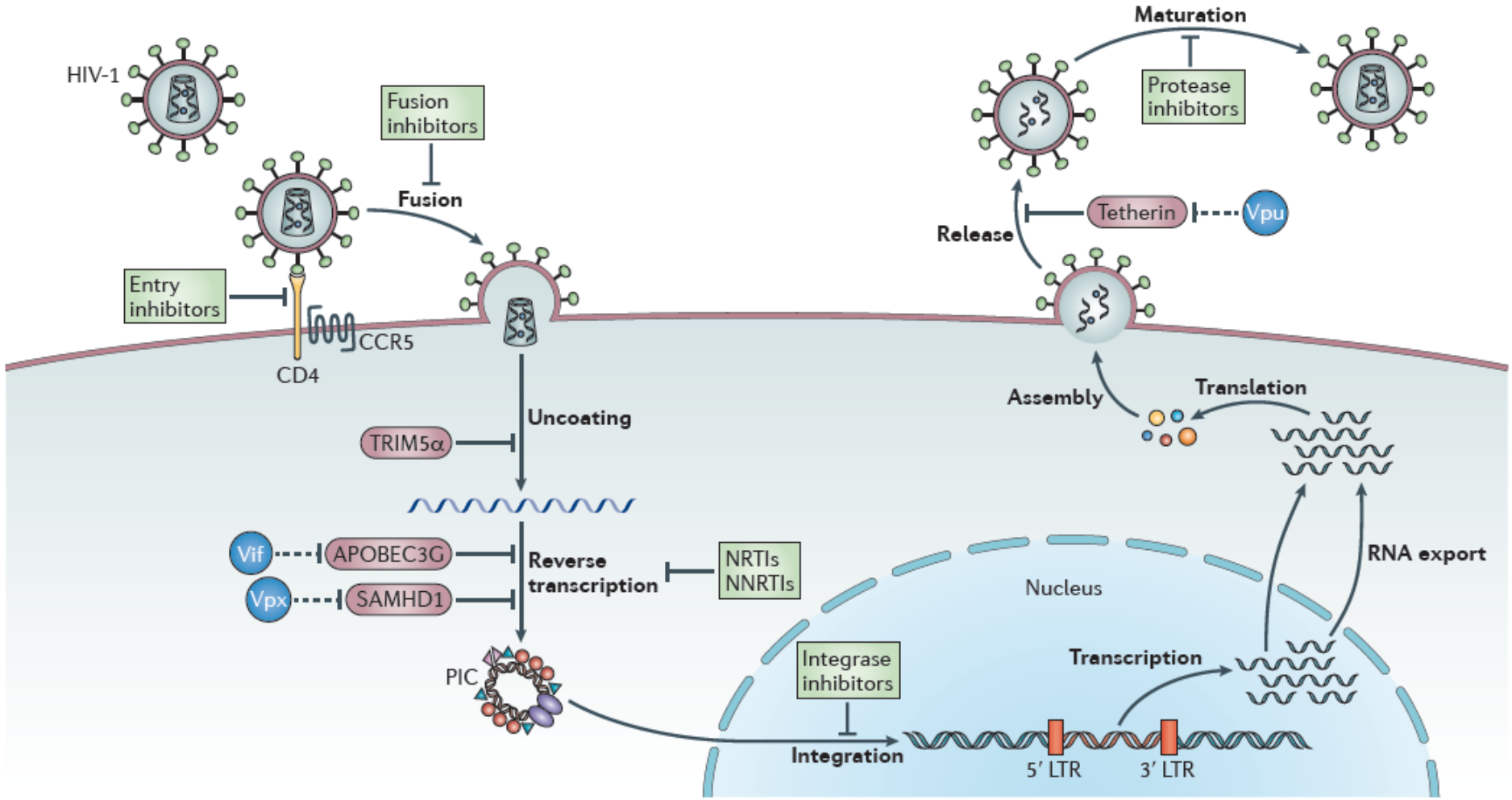
2012 The majority of people worldwide eligible for antiretrovirals are now receiving them

Antiretrovirals are shown to reduce the risk of transmitting HIV by 96%

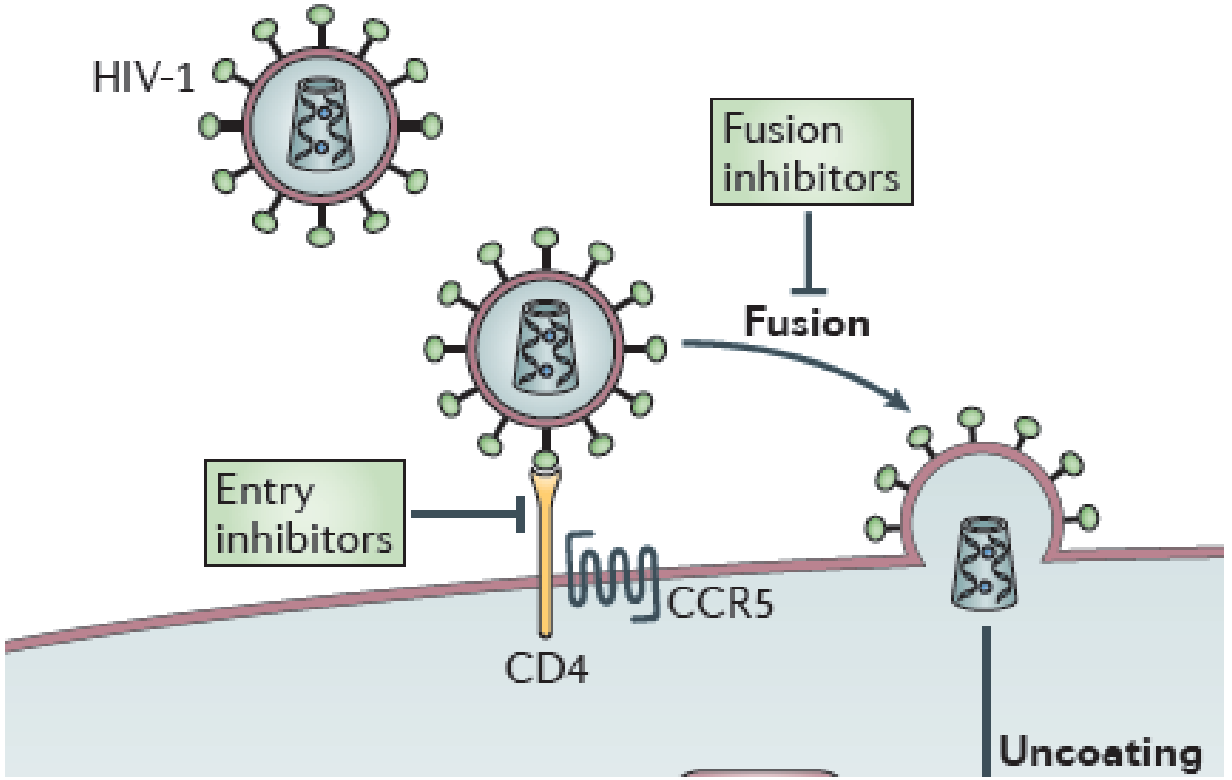
Image credits: Trocaire, Gates Foundation, iStock/LordRunar, Harwell

Understanding ANIMAL RESEARCH

ANTI-HIV CHEMOTHERAPY



ANTI-HIV CHEMOTHERAPY



Agents that block interaction of gp120 with co-receptors

Agents that block fusion by interacting with gp41

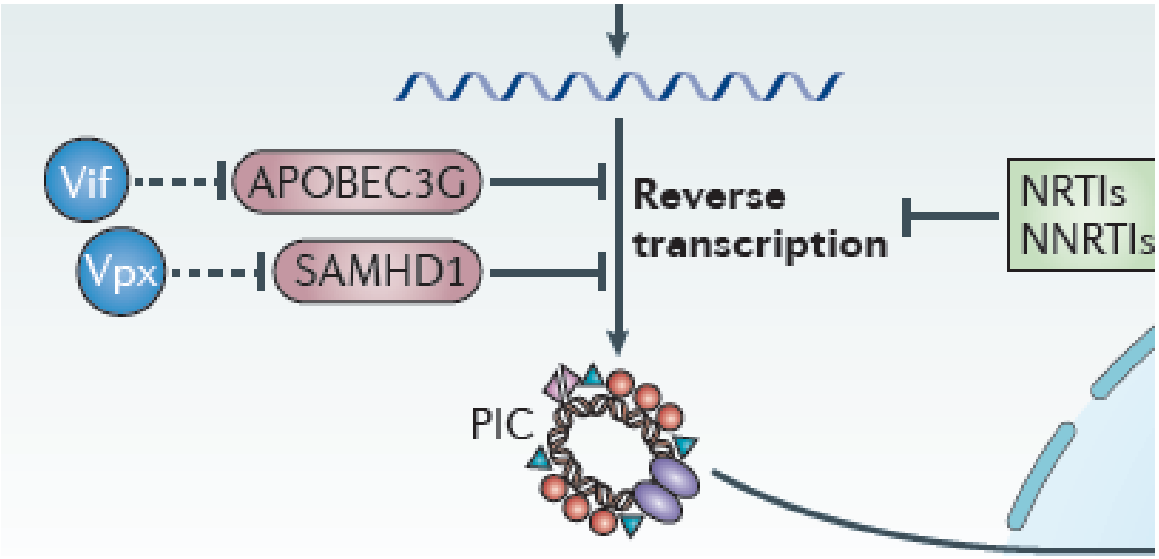
ANTI-HIV CHEMOTHERAPY

Nucleoside-Analog Reverse Transcriptase Inhibitors (NRTI).
They are incorporated into viral DNA, act as chain terminators.

AZT e d4T ⟶ timidina

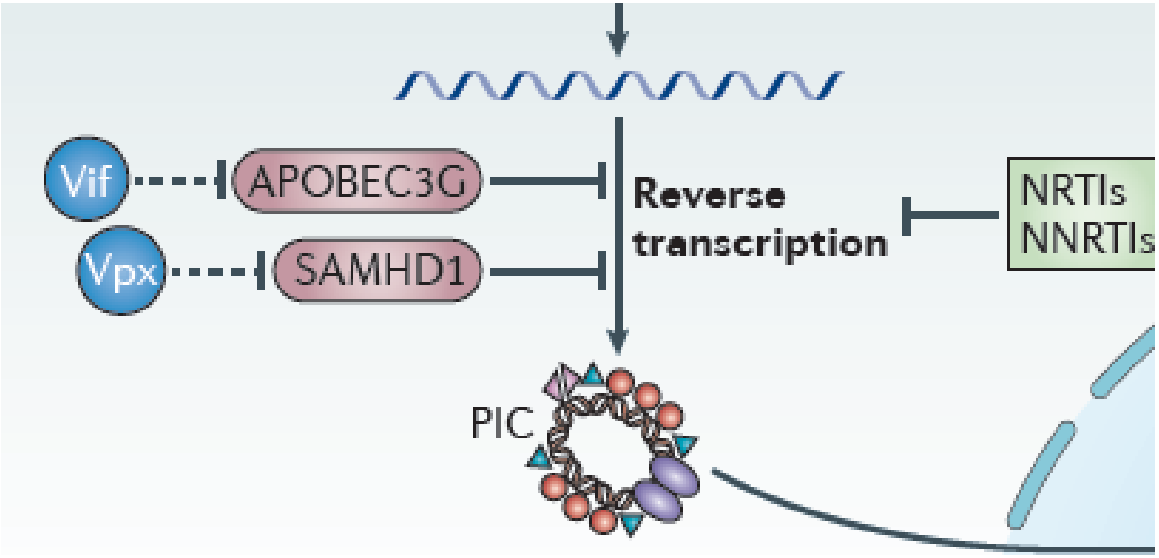
FTC e 3TC ⟶ citidina

Abacavir ⟶ guanosina



They were among the first anti-HIV-1 drugs. However, after long term administration, several side effects have been observed (mainly MITOCHONDRIAL DAMAGE)

ANTI-HIV CHEMOTHERAPY



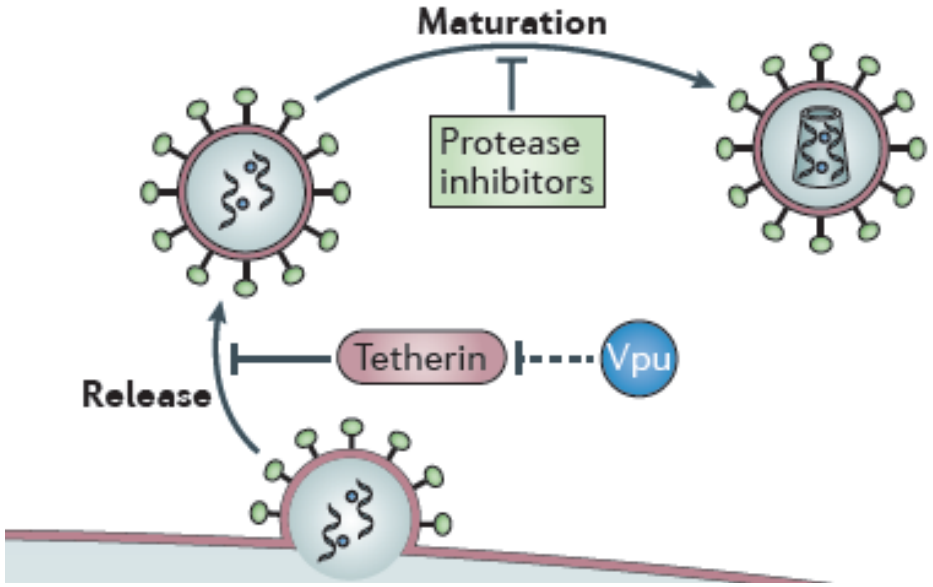
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are small molecule drugs that bind directly to the active site of HIV-1 reverse transcriptase, disrupting its RNA-dependent and DNA-dependent DNA polymerase activities. Unlike nucleoside analogs, they have minimal toxicity in tests with cultured cells. There is some toxicity when used in humans, mainly gastrointestinal problems or elevated liver enzymes

Nevirapine – Delaviridine - Efavirenz

ANTI-HIV CHEMOTHERAPY

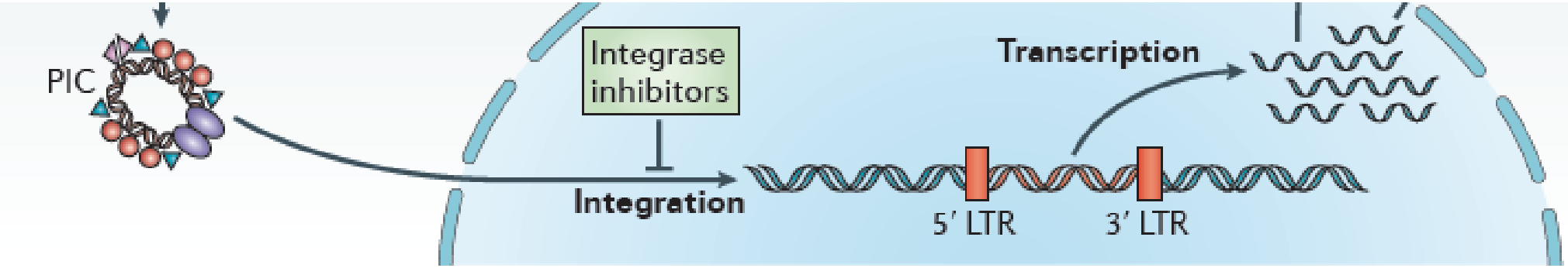
Protease Inhibitors. They are all substrate analogs, that is they mimic a peptide that can bind to the active site of the viral protease.

Indinavir – Ritonavir - Saquinavir



There have a few side effects in patients. These are mild: nausea, diarrhea, upset stomach, and heartburn.

Drugs that inhibit integrase (IN) activity



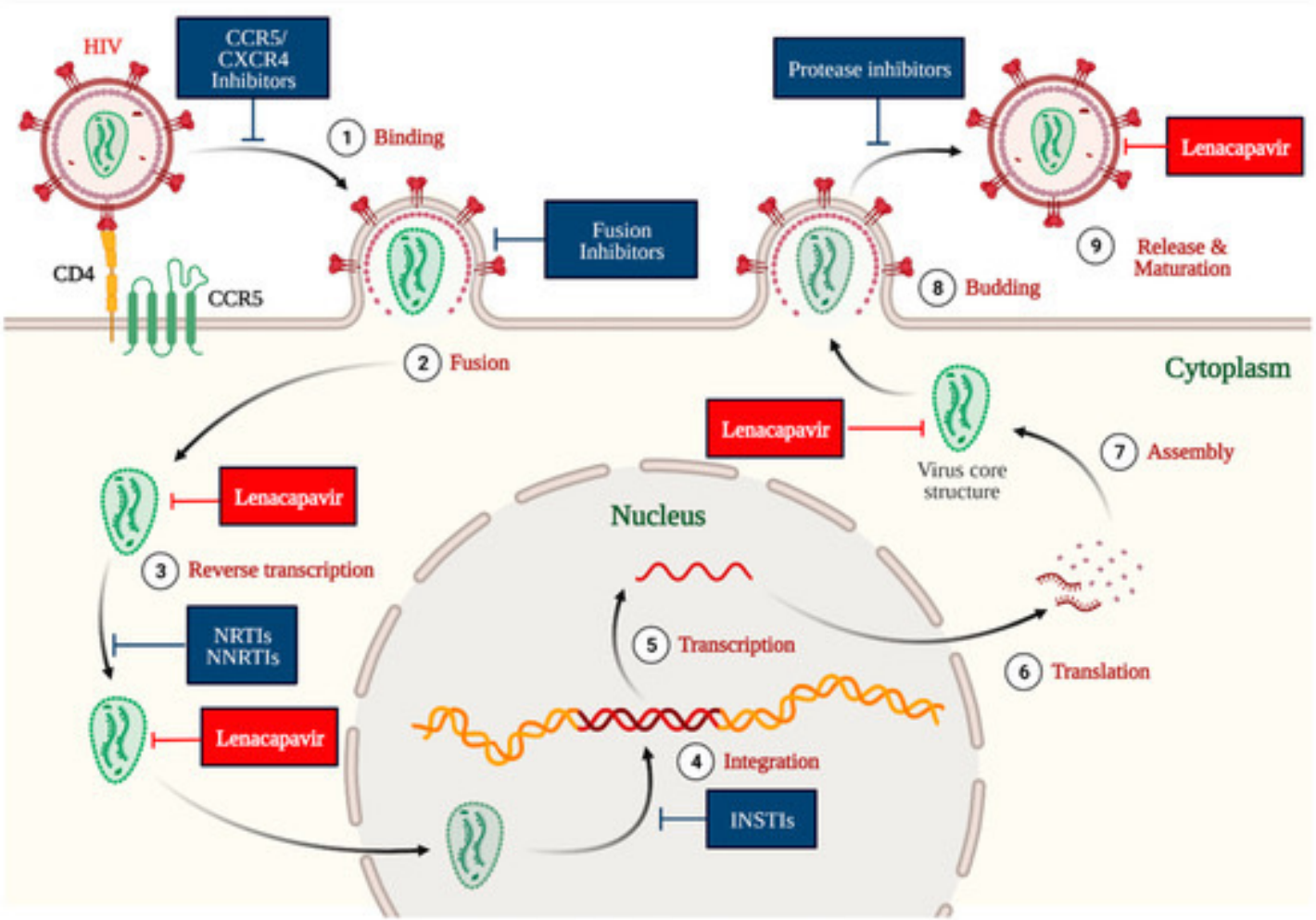
Viral DNA integration requires several steps. These can be targeted by different IN inhibitors:

IN associates with the viral DNA in the cytoplasm to form the pre-integration complex (PIC).

In a first catalytic step IN cuts a dinucleotide from both ends of the viral DNA to produce hydroxylated 3’ ends in the PIC

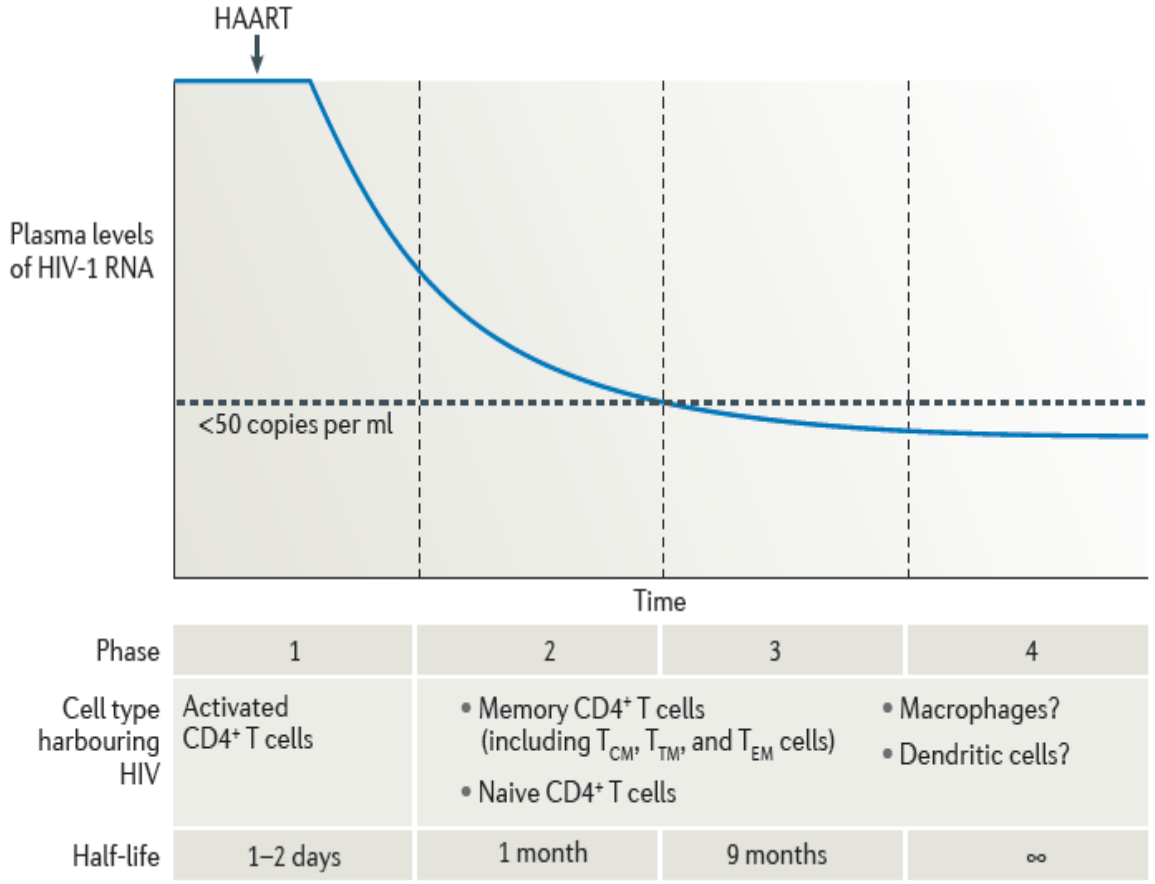
In the nucleus IN binds the host DNA to allow annealing of hydroxylated ends of the proviral DNA to the host DNA

Inhibition of capsid: Lenacapavir



By targeting HIV capsid, lenacapavir interferes with multiple early- to late-stage processes of the viral life cycle: nuclear transport, virus assembly and release, and capsid assembly. Lenacapavir binds directly to HIV capsid in a pocket between capsid protein subunits in hexamers. In early stages of the virus life cycle, lenacapavir interferes with capsid-mediated nuclear import of HIV-1 proviral DNA, as it targets the same capsid binding site utilized by host factors that aid in viral nuclear import and integration. In late stages of the HIV life cycle, lenacapavir interferes with the functioning of Gag/Gag-Pol and reduces capsid protein subunit production. Additionally, lenacapavir increases the rate of HIV capsid assembly, resulting in abnormalities in capsid structure

The impact of antiretroviral therapy on HIV reservoirs.



Most patients who adhere to antiretroviral therapy have dramatic and rapid decreases in plasma levels of HIV RNA. Persistent viraemia largely reflects the release of the virus from stable cellular reservoirs. The source of the virus during effective antiretroviral therapy is primarily defined by the half-life of the cells that were infected before therapy was initiated. After several years of therapy, long-lived populations of resting CD4+ central memory T (T_{CM}) cells become the dominant source of HIV persistence. HAART, highly active antiretroviral therapy; T_{EM}, effector memory T; T_{TM}, transitional memory T.

NATURE REVIEWS | IMMUNOLOGY

HIV - Life History

Latency – Cellular – The problem of memory T4 cells

Only activated T4 cells can replicate virus

Most infected T4 cells are rapidly lyzed but are replaced

Some T4 cells revert to resting state as memory cells which are long-lived

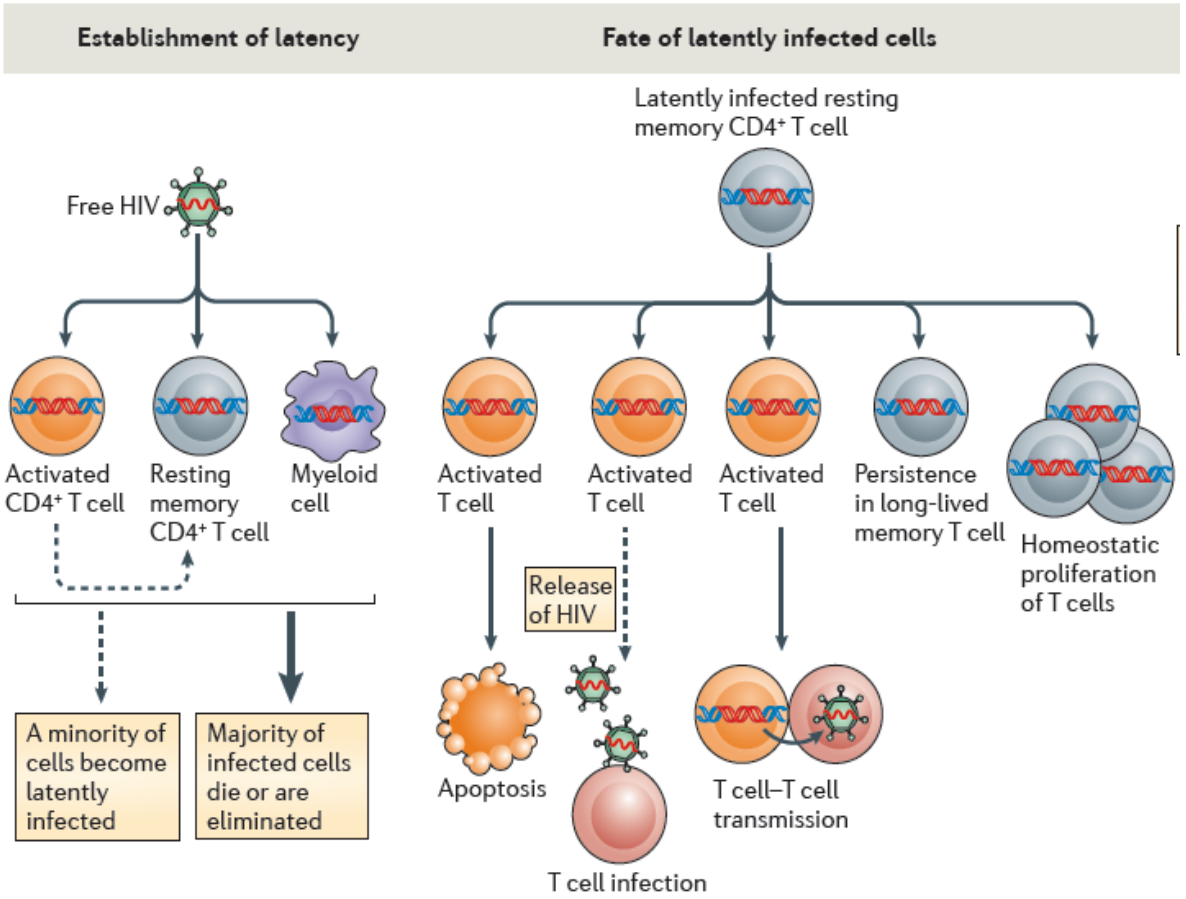
Memory T4 cells cannot replicate the virus unless they become activated

Clinical Latency

HIV infection is not manifested as disease for years

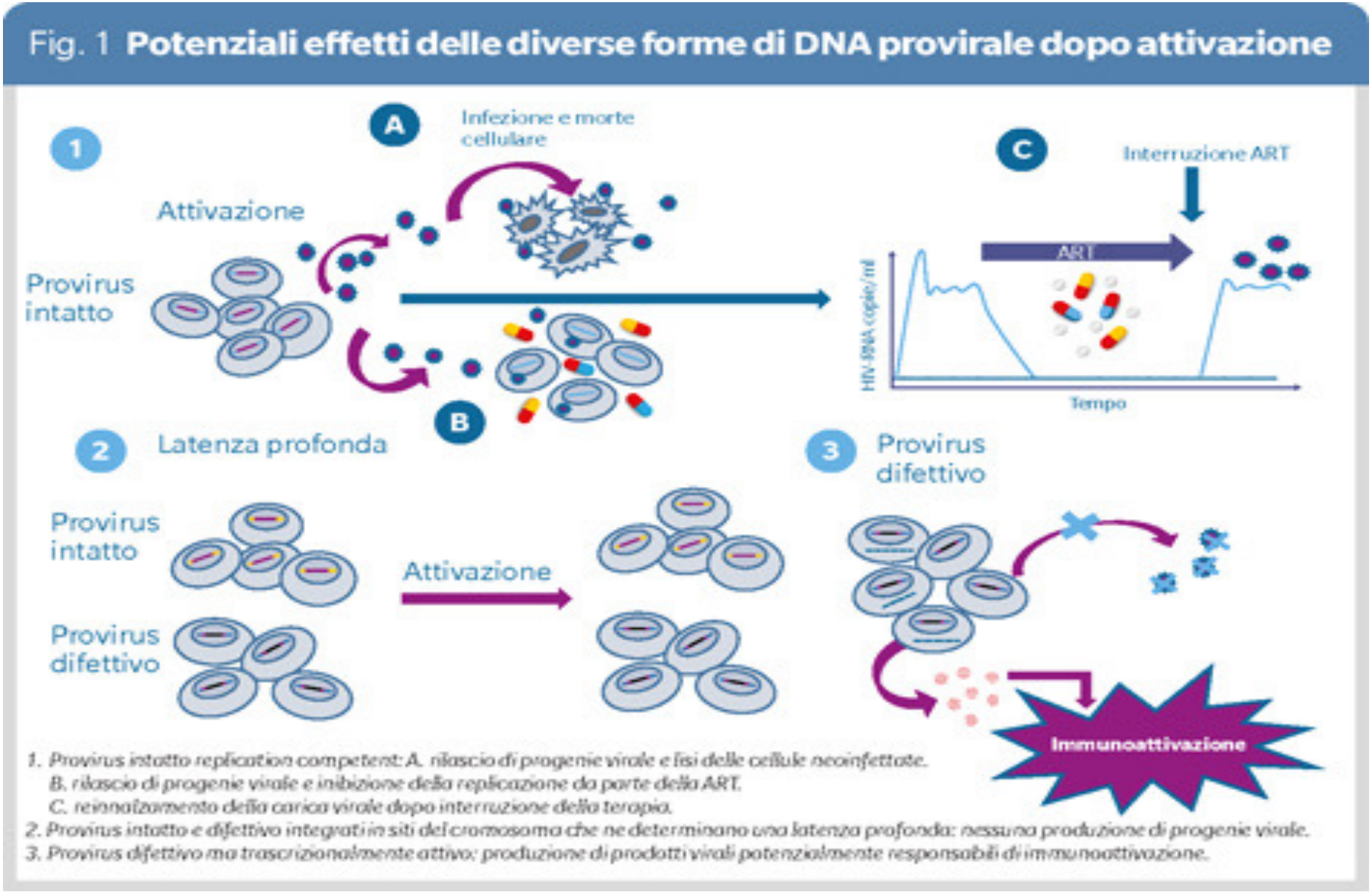
During apparent clinical latency, virus is being replicated and cleared

Mechanisms of HIV persistence during antiretroviral therapy



The left panel illustrates how latent HIV infection can be established in T cell and myeloid cell reservoirs. The primary mechanism is probably infection of activated memory CD4+ T cells. Most of these cells die, but a minority revert to a resting state. The right panel illustrates the fate of these now resting 'latently infected' memory CD4+ T cells. These cells either die slowly, become a source of new infections, persist as long-lived cells or expand through homeostatic mechanisms.

NATURE REVIEWS | IMMUNOLOGY



Sebbene le cellule T CD4+ della memoria siano da sempre considerate il principale sito di persistenza virale, anche altre cellule, come i macrofagi e le cellule dendritiche, sembrano avere un ruolo importante nella persistenza virale

https://www.readfiles.it/ n3 2024 G Antonelli O Turriziani

FDA Approval of HIV Medicines

1981: First AIDS cases are reported in the United States.

1985-89	1990-94	1995-99	2000-04	2005-09	2010-14	2015-19	2020-24
1987 Zidovudine (NRTI)	**1991** Didanosine* (NRTI) **1992** Zalcitabine* (NRTI) **1994** Stavudine* (NRTI)	**1995** Lamivudine (NRTI) Saquinavir Mesylate* (PI) **1996** Indinavir* (PI) Nevirapine (NNRTI) Ritonavir (PI) **1997** Combivir* (FDC) Delavirdine* (NNRTI) Nelfinavir* (PI) Saquinavir* (PI) **1998** Abacavir (NRTI) Efavirenz (NNRTI) **1999** Amprenavir* (PI)	**2000** Didanosine EC* (NRTI) Kaletra (FDC) Trizivir* (FDC) **2001** Tenofovir DF (NRTI) **2002** Stavudine XR* (NRTI) **2003** Atazanavir (PI) Emtricitabine (NRTI) Enfuvirtide (FI) Fosamprenavir* (PI) **2004** Epzicom* (FDC) Truvada (FDC)	**2005** Tipranavir* (PI) **2006** Atripla* (FDC) Darunavir (PI) **2007** Maraviroc (CA) Raltegravir (INSTI) **2008** Etravirine (NNRTI)	**2011** Complera (FDC) Nevirapine XR (NNRTI) Rilpivirine (NNRTI) **2012** Stribild (FDC) Truvada (PrEP) **2013** Dolutegravir (INSTI) **2014** Cobicistat (PE) Elvitegravir* (INSTI) Triumeq (FDC)	**2015** Evotaz (FDC) Genvoya (FDC) Prezcobix (FDC) **2016** Descovy (FDC) Odefsey (FDC) **2017** Juluca (FDC) Raltegravir HD (INSTI) **2018** Biktarvy (FDC) Cimduo (FDC) Delstrigo (FDC) Doravirine (NNRTI) Ibalizumab-uiyk (PAI) Symfi (FDC) Symfi Lo (FDC) Symtuza (FDC) Temixys* (FDC) **2019** Dovato (FDC) Descovy (PrEP)	**2020** Fostemsavir* (AI) Tivicay PD (INSTI) **2021** Cabenuva (FDC) Cabotegravir (INSTI) Cabotegravir (PrEP) **2022** Triumeq PD (FDC) Lenacapavir (CI) **2024** Rilpivirine PED (NNRTI)

Drug Class Abbreviations:
AI: Attachment Inhibitor; **CA:** CCR5 Antagonist; **CI:** Capsid Inhibitors; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor; **PAI:** Post-Attachment Inhibitor; **PrEP:** Pre-exposure prophylaxis

***Note:** Approvals are for HIV treatment, unless otherwise indicated. Drugs in gray are no longer available and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations. Fixed-dose combination brand products in gray may be available as generics.

For more information, visit HIVinfo.NIH.gov.

HIVinfo.NIH.gov

DRUGS THAT FIGHT HIV

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs block reverse transcriptase, an enzyme HIV needs to make copies of itself.

Abacavir (ABC)*

trade name: ZIAGEN

300 mg Ziagen tablet

20 mg/mL Ziagen oral solution

Tenofovir alafenamide (TAF or Tenofovir AF)*

For the treatment of HIV, TAF is only available in coformulated tablets. However, it is available as a single 25 mg tablet (Vemlidy) for the treatment of Hepatitis B.

Emtricitabine (FTC)*

trade name: EMTRIVA

200 mg Emtriva capsule

10 mg/mL Emtriva oral solution

Tenofovir disoproxil fumarate (TDF or Tenofovir DF)*

trade name: VIREAD

150 mg Viread tablet

200 mg Viread tablet

250 mg Viread tablet

40 mg/g Viread oral powder

300 mg Viread tablet

Lamivudine (3TC)*

trade name: EPIVIR

150 mg Epivir tablet

300 mg Epivir tablet

10 mg/mL Epivir oral solution

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs bind to and alter reverse transcriptase, an enzyme HIV needs to make copies of itself.

Doravirine (DOR)*

trade name: PIFELTRO

100 mg Pifeltro tablet

Efavirenz (EFV)*

trade name: SUSTIVA

50 mg Sustiva capsule

200 mg Sustiva capsule

600 mg efavirenz generic tablet

Etravirine (ETR)

trade name: INTELENCE

100 mg Intelence tablet

200 mg Intelence tablet

25 mg Intelence tablet

Rilpivirine (RPV)*

Intramuscular rilpivirine is available as part of the copackaged product, Cabenuva.

trade name: EDURANT

25 mg Edurant tablet

Integrase Strand Transfer Inhibitors (INSTIs)

INSTIs block HIV integrase, an enzyme HIV needs to make copies of itself.

Bictegravir (BIC)*

Bictegravir is only available as part of a coformulated tablet.

Cabotegravir (CAB)

Oral tablet (Vocabria) is only available for combination therapy with oral rilpivirine. Intramuscular cabotegravir is only available for the treatment of HIV as a component of the copackaged product Cabenuva. However, it is available as a single agent (Apretude) for HIV prevention.

trade name: VOCABRIA

30 mg Vocabria tablet

Dolutegravir (DTG)*

trade name: TIVICAY

5 mg Tivicay PD soluble tablet

10 mg Tivicay tablet

50 mg Tivicay tablet

25 mg Tivicay tablet

Elvitegravir (EVG)*

Elvitegravir is only available as part of coformulated tablets.

Raltegravir (RAL)

trade name: ISENTRESS

400 mg Isentress tablet

25 mg chewable Isentress tablet

100 mg chewable Isentress tablet

Isentress HD 600 mg Isentress HD tablet

100 mg packet Isentress for oral suspension

Protease Inhibitors (PIs)

PIs block HIV protease, an enzyme HIV needs to make copies of itself.

Atazanavir (ATV)*

trade name: REYATAZ

150 mg Reyataz capsule

200 mg Reyataz capsule

50 mg packet Reyataz oral powder

300 mg Reyataz capsule

Darunavir (DRV)*

trade name: PREZISTA

75 mg Prezista tablet

600 mg Prezista tablet

150 mg Prezista tablet

800 mg Prezista tablet

100 mg/mL Prezista oral suspension

Lopinavir (LPV)*

Lopinavir is only available as part of a coformulated tablet.

Pharmacokinetic (PK) Enhancers

These are pharmacokinetic boosters for some antiretroviral medications.

Cobicistat (COBI or c)*

trade name: TYBOST

150 mg Tybost tablet

Ritonavir (RTV)*

Ritonavir is an HIV protease inhibitor. At the doses currently used in clinical practice, it primarily serves as a PK enhancer.

trade name: NORVIR

80 mg/mL Norvir oral solution

100 mg Norvir tablet

100 mg packet Norvir oral powder

gp120 Attachment Inhibitor

This drug binds to HIV to block the virus from entering the CD4 cells of the immune system.

Fostemsavir (FTR)

trade name: RUKOBIA

600 mg Rukobia tablet

Post-Attachment Inhibitor (PAI)

Monoclonal antibody that binds to CD4 receptors to block HIV from entering the CD4 cells of the immune system.

Ibalizumab-uiyk (IBA)

(intravenous infusion or intravenous push administered every 2 weeks)

trade name: TROGARZO

150 mg/mL Trogarzo vial

Fusion Inhibitor

Fusion inhibitors block HIV from entering the CD4 cells of the immune system.

Enfuvirtide [T-20]

(subcutaneous injection self-administered twice daily)

trade name: FUZEON

90 mg Fuzeon vial

* These drugs are also available as part of coformulated medications and images are on the last page.

= Image not available

CCR5 Antagonists

CCR5 antagonists block CCR5, a protein on the CD4 cells that a certain type of HIV needs to enter the cell.

Maraviroc (MVC)

trade names: SELZENTRY

150 mg Selzentry tablet

300 mg Selzentry tablet

25 mg Selzentry tablet

75 mg Selzentry tablet

20 mg/mL Selzentry oral solution

Capsid Inhibitor

This drug inhibits HIV replication by interfering with multiple steps of the viral life cycle.

Lenacapavir (LEN)

(oral tablets and subcutaneous injections are used during treatment initiation; this is followed by maintenance dosing with subcutaneous injections every 6 months)

trade names: SUNLENCA

300 mg Sunlenca tablet

463.5mg/1.5 mL Sunlenca vial

Extended-release Intramuscular Suspension

This complete regimen is administered intramuscularly every 1-2 months.

trade names: CABENUVA

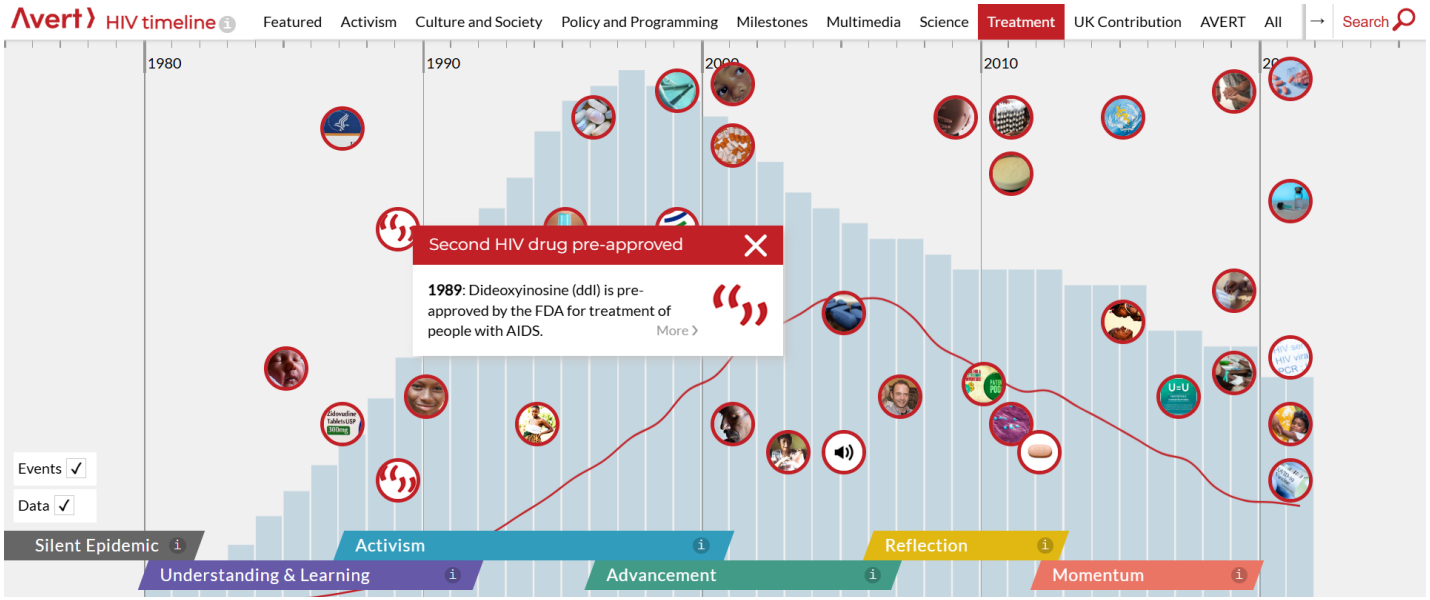
600 mg/3mL cabotegravir/ 900 mg/3mL rilpivirine dosing kits

400 mg/2mL cabotegravir/ 600 mg/2mL rilpivirine dosing kits

March 1987

Approval of AZT is fast-tracked by the FDA after a small-scale trial finds that rates of opportunistic infections and deaths are lower for those on the drug.

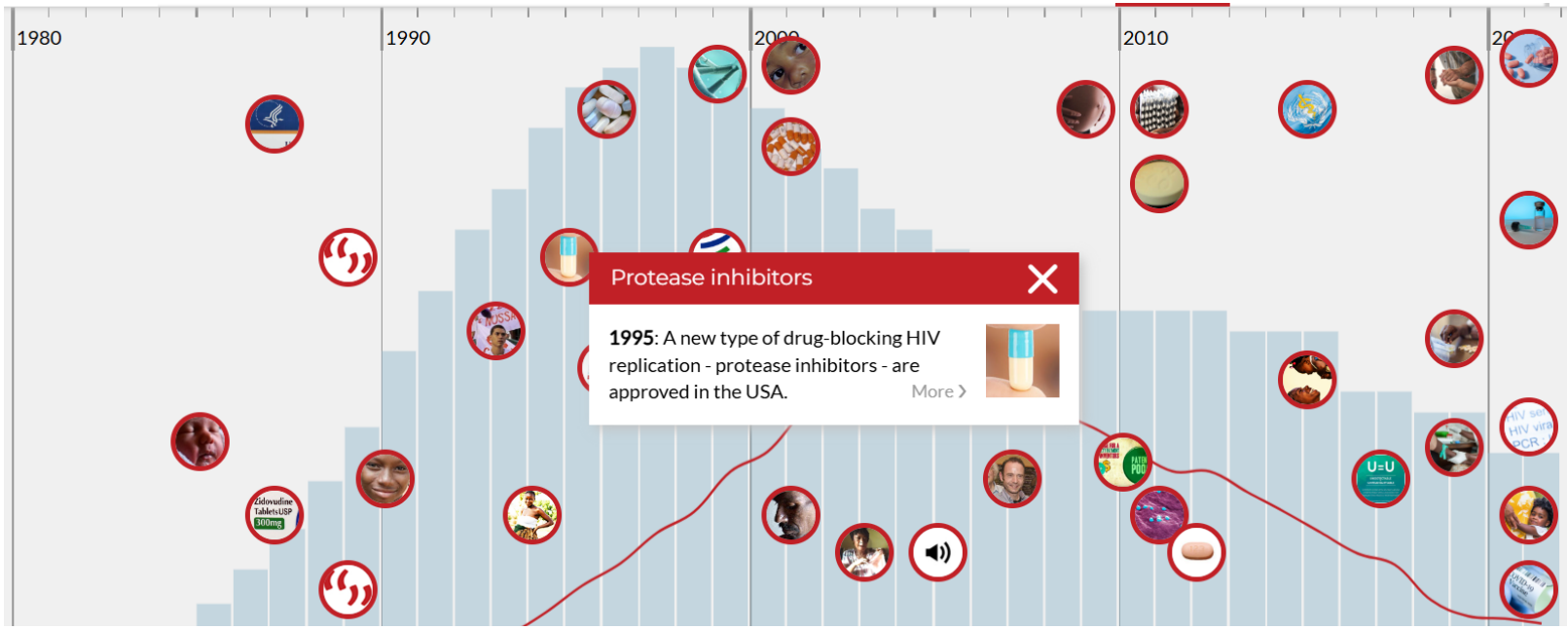
The drug is highly toxic, difficult to produce and leaves many with concerns about the long-term effects on people living with HIV. But at this point it is the only hope in the armoury of defeating HIV, and it becomes the most expensive drug on the market.



NRTIs

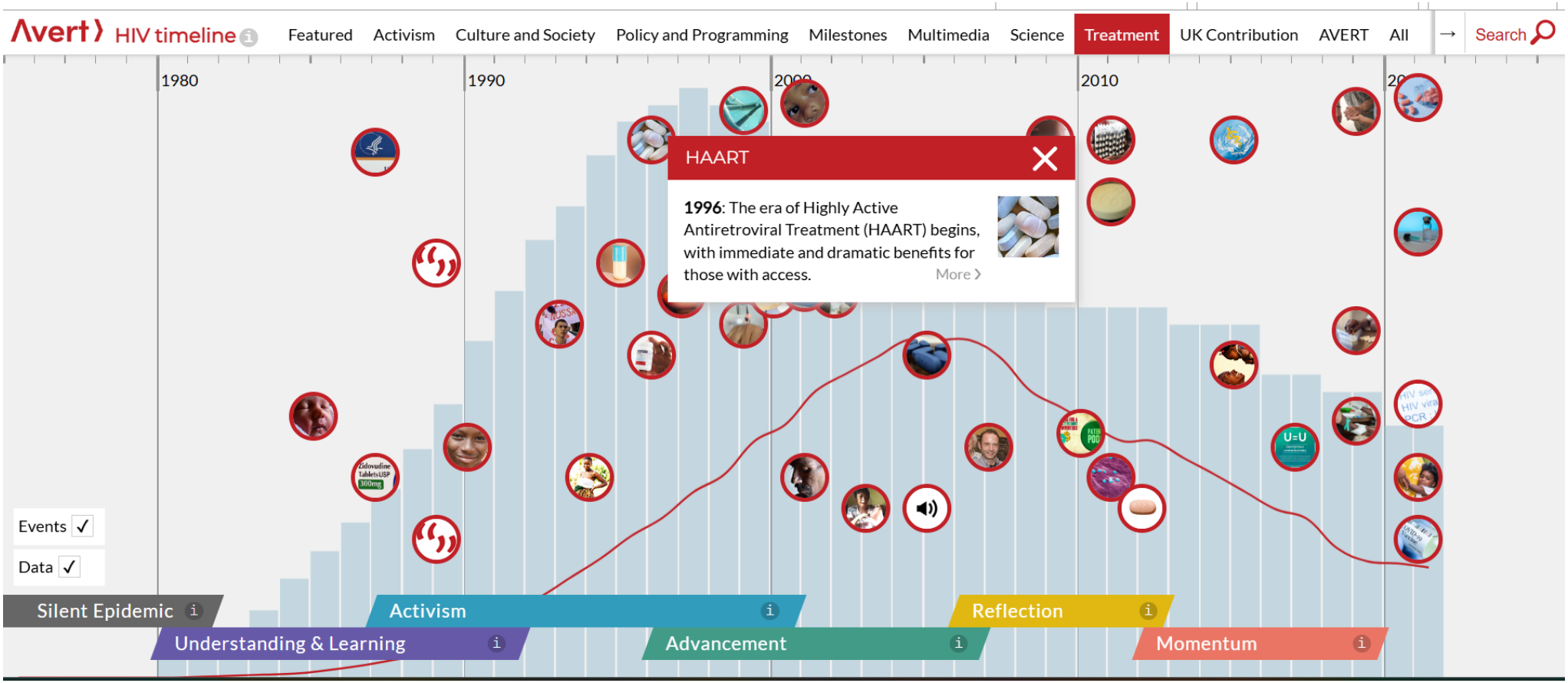
1989 ddI The second drug available for the treatment of HIV and AIDS is made available by the USA Food and Drug Administration (FDA) on compassionate access grounds for people who fail treatment using zidovudine (AZT).

1995 **A revolutionary development in HIV treatment, protease inhibitor drugs** provide a new way to block HIV replicating and multiplying in the human body.



1996

NNRTIs inhibit reverse transcriptase They are an important component of Highly Active Antiretroviral Therapy (HAART). In 1999, a study in Uganda finds that a single dose of nevirapine given to both mother and child reduced the rate of HIV transmission by almost 50% compared with a very short course of zidovudine (AZT). The World Health Organization subsequently endorses nevirapine as a cost-effective way of reducing mother-to-child transmission in developing countries.

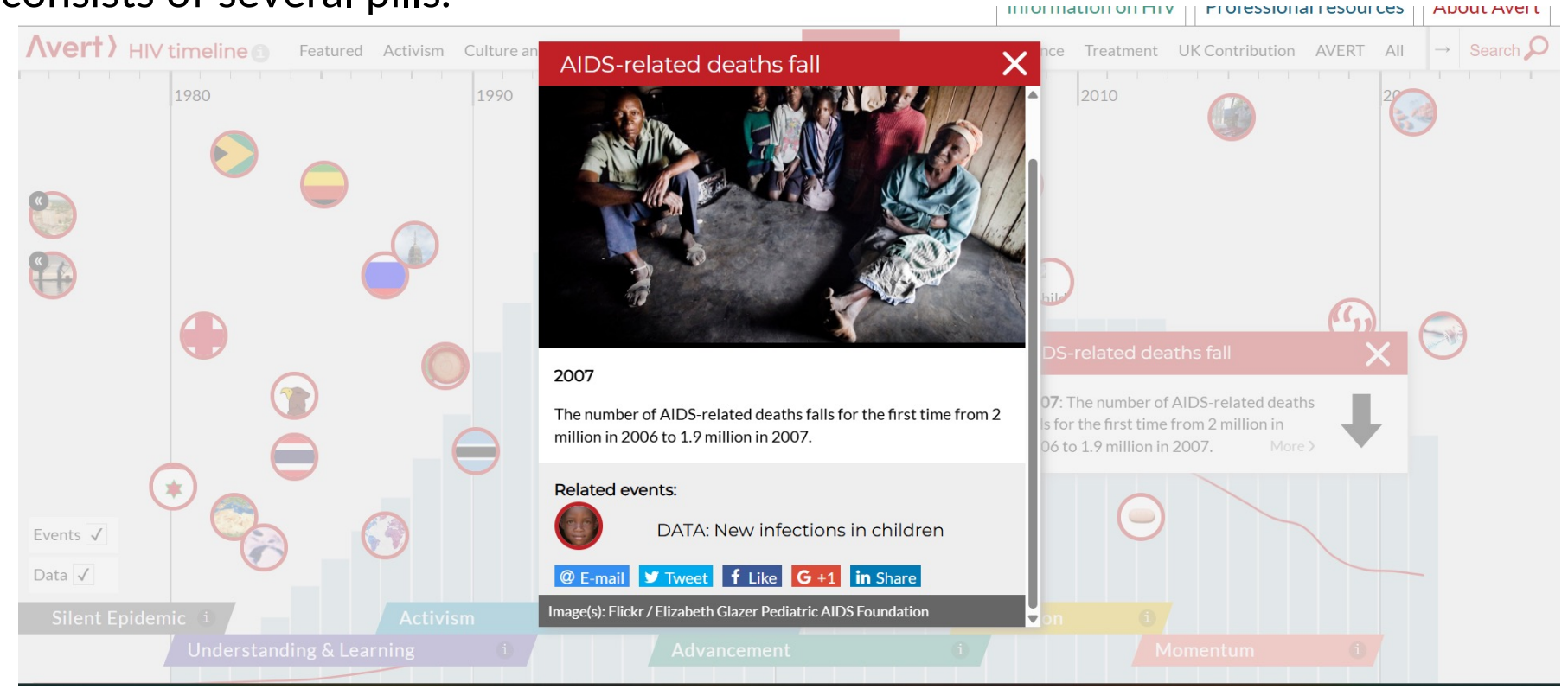


1996

Following a number of breakthrough trials and new drugs, it becomes clear during 1996 that **combining a number of drug types could have a dramatic effect on keeping HIV under control. Highly Active Antiretroviral Therapy (combining at least three drug types) is quickly incorporated into clinical practice** in rich nations, **with an immediate decline of between 60% and 80% in rates of AIDS-related deaths and hospitalisation**. However, in low-income countries, even ten years later, less than 5% of those in need have access to this treatment.

September 1997

Combivir is the first fixed dose combination (FDC) antiretroviral pill. It is made up of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Prior to this, HIV treatment consists of several pills.

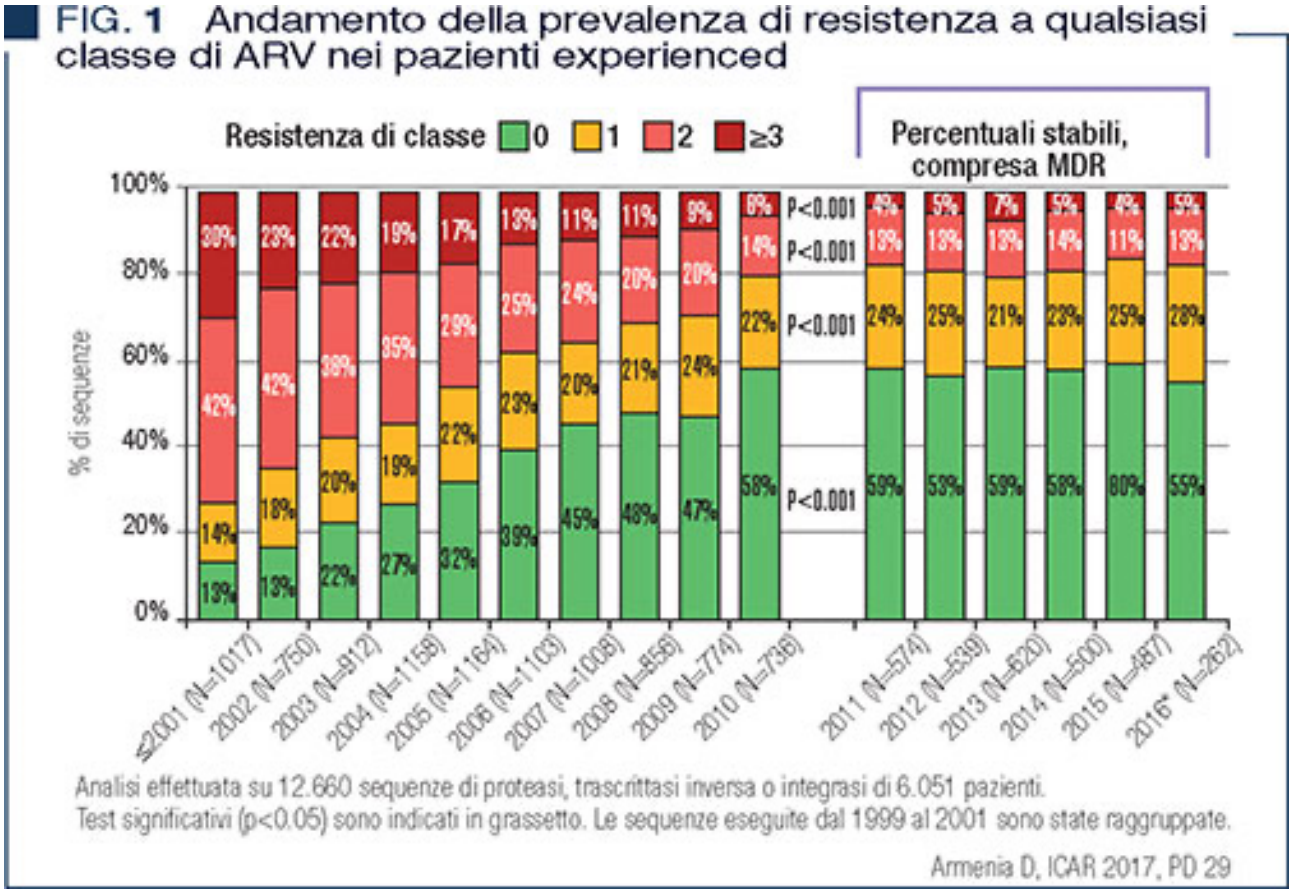


2011

The United States Food and Drugs Administration approves a new HIV treatment, known as Complera (2NRTI+1NNRTI), designed to be taken as a single daily tablet (STR single tablet regimen). Only needing to take a single tablet once a day, rather than multiple pills, makes maintaining adherence easier. Complera goes on to become one of the most widely-prescribed ARV regimens for HIV in the USA.

2019 The World Health Organization (WHO) publishes its **HIV drug resistance** report 2019, shining a light on the emerging threat of HIV drug resistance (HIVDR) to the global scale-up of treatment access, particularly in sub-Saharan Africa and other low- and middle-income countries.

In response, the WHO recommends that countries use dolutegravir, where HIVDR is already prevalent, as the preferred drug for HIV treatment because of its effectiveness and high barrier to resistance.



2022

Sunlenca® (lenacapavir) Receives FDA Approval as a First-in-Class, Twice-Yearly Treatment Option for People Living With Multi-Drug-Resistant HIV

2DR

Two-drug regimens for HIV treatment

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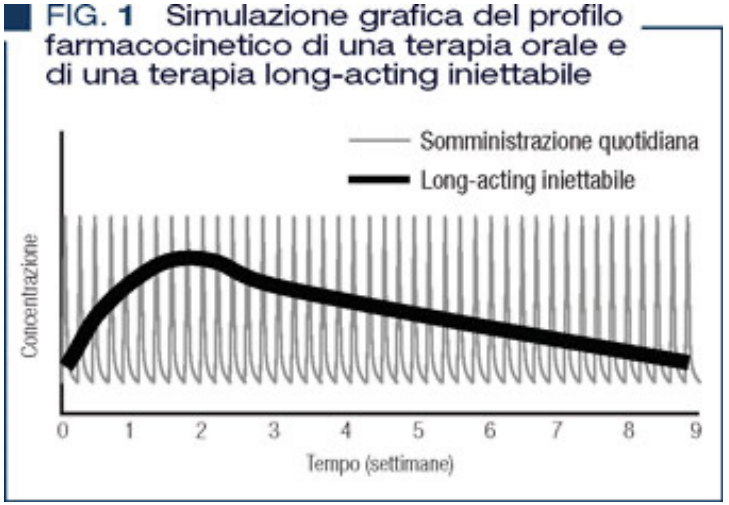
Combination therapy with three antiretroviral agents has been integral to successful HIV-1 treatment since 1996. Although the efficacy, adverse effects, and toxicities of contemporary three-drug regimens have improved, even the newest therapies have potential adverse effects. The use of two-drug regimens is one way to reduce lifetime exposure to antiretroviral drugs while maintaining the benefits of viral suppression. Multiple large, randomised trials have shown the virological non-inferiority of certain two-drug regimens versus three-drug comparators, including adverse effect differences that reflect known profiles of the antiretroviral drugs in the respective regimens. Two-drug combinations are now recommended in treatment guidelines and include the first long-acting antiretroviral regimen for the treatment of HIV-1. Recommended two-drug regimens differ in their risks for, and factors associated with, virological failure and emergent resistance. The tolerability, safety, metabolic profiles, and drug interactions of two-drug regimens also vary by the constituent drugs. No current two-drug regimen is recommended for people with chronic hepatitis B virus as none include tenofovir. Two-drug regimens have increased options for individualised care.

Long Acting therapy

2021

HIV treatment that can be injected every one or two months is approved for use in some countries after trials prove they work as effectively as daily tablets.



2011

The results of the groundbreaking HPTN 052 trial show that people living with HIV and taking antiretroviral drugs were 96% less likely to transmit the virus to their partners. This was the first step in establishing treatment as prevention.

The journal Science names the study the most important scientific breakthrough of 2011.

2014

The PARTNER study finds no transmissions within couples where one person is HIV positive and the other not, when the viral load is undetectable. The study covers an estimated 16,400 occasions of sex between gay men and 28,000 in heterosexuals.

2017 HIV organisations around the world endorse the "Undetectable = Untransmittable" stating that those who take antiretroviral treatment regularly, and have achieved an undetectable viral load as a result, cannot pass on the virus to others. The message helps to tackle the stigma towards those living with HIV, and provides many people living with HIV with the reassurance that they are not a threat to their partners. However, in lower resource settings, the message has less resonance, as individuals often face more difficulty in accessing HIV services, including viral load testing. As such these issues need to be addressed before U=U can have an impact on people living with HIV in these countries.

2018 New evidence from phase 2 of the PARTNER study extends U=U (undetectable=untransmittable) message to gay men. It confirms that HIV cannot be passed on in (any) couple where one partner has an undetectable viral load. The study of nearly 1,000 gay male couples who had sex without using condoms, where one partner was HIV positive and on effective treatment and the other was HIV negative, reports no cases of within-couple HIV transmission over eight years.

April 2005

The CDC approves the use of Post Exposure Prophylaxis (PEP) for the general public for the first time. The drug can be used to prevent HIV infection up to 72 hours after exposure. The side effects of PEP, however, mean that it cannot be taken regularly and is only authorised for use when someone is known to have been exposed to HIV. Ronald Valdiserri, a spokesperson from the CDC comments that because “Too many Americans are affected each year. The severity of this epidemic dictates we utilize all available tools to reduce new infections".

2010

iPrEx (Pre-exposure Prophylaxis Initiative) is the first randomised controlled trial of PrEP. The trial proves that taking PrEP provides protection against HIV. In the trial, gay men at high risk of HIV were either given a daily pill containing HIV drugs or a placebo. The HIV infection rate was 44% lower in the group given PrEP. Moreover, for those men who managed to take the pill daily, the infection rate was 73% lower. These results pave the way for PrEP as an HIV prevention method.

2012

PrEP is a course of drugs designed for people who are not HIV-positive but are at high risk of being exposed to the virus – for example, if they have an HIV-positive partner or regularly inject drugs. By 2012, the evidence is clear that, when taken daily, PrEP reduces the chance of acquiring HIV by more than 90%. The US is the first country to approve its use as a method of HIV prevention. PrEP offers an extra option for protection that could be combined with condoms and other prevention methods.

PrEP vs. PEP

When you take steps to protect yourself against a disease, like HIV, it's called prophylaxis. PrEP and PEP are for protecting people who are HIV negative.

PrEP		PEP
PrEP stands for pre-exposure prophylaxis.	**What's it called?**	PEP stands for post-exposure prophylaxis.
Before HIV exposure. PrEP is taken before sex, drug use, or other HIV exposure.	**When is it taken?**	**After HIV exposure.** In emergency situations, PEP is started within 72 hours after possible exposure, and taken for a month thereafter.
PrEP is for people who don't have HIV and: • are at risk of getting HIV from sex • are at risk of getting HIV from injection drug use	**Who's it for?**	PEP is for people who don't have HIV but may have been exposed: • during sex • during a sexual assault • at work through a needlestick or other injury • by sharing injection drug equipment
Consistent use of PrEP can reduce the risk of getting HIV from sex by about 99% and from injection drug use by at least 74%.	**How effective is it?**	PEP can prevent HIV when taken correctly, but it is not always effective. Start PEP as soon as possible to give it the best chance of working.
Ask your health care provider about a prescription for PrEP, or use PrEPlocator.org to find a health care provider in your area who can prescribe PrEP.	**How do you get it?**	Within 72 hours after potential exposure to HIV, get a PEP prescription from your health care provider, urgent care, or an emergency room.

For more information, visit HIVinfo.NIH.gov.

HIVinfo.NIH.gov

BBC

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Timothy Ray Brown, also known as the Berlin patient, pictured in 2012

The Berlin patient

CCR5 Δ32 is a 32-base-pair deletion that introduces a premature stop codon into the CCR5 receptor locus, resulting in a nonfunctional receptor

2007

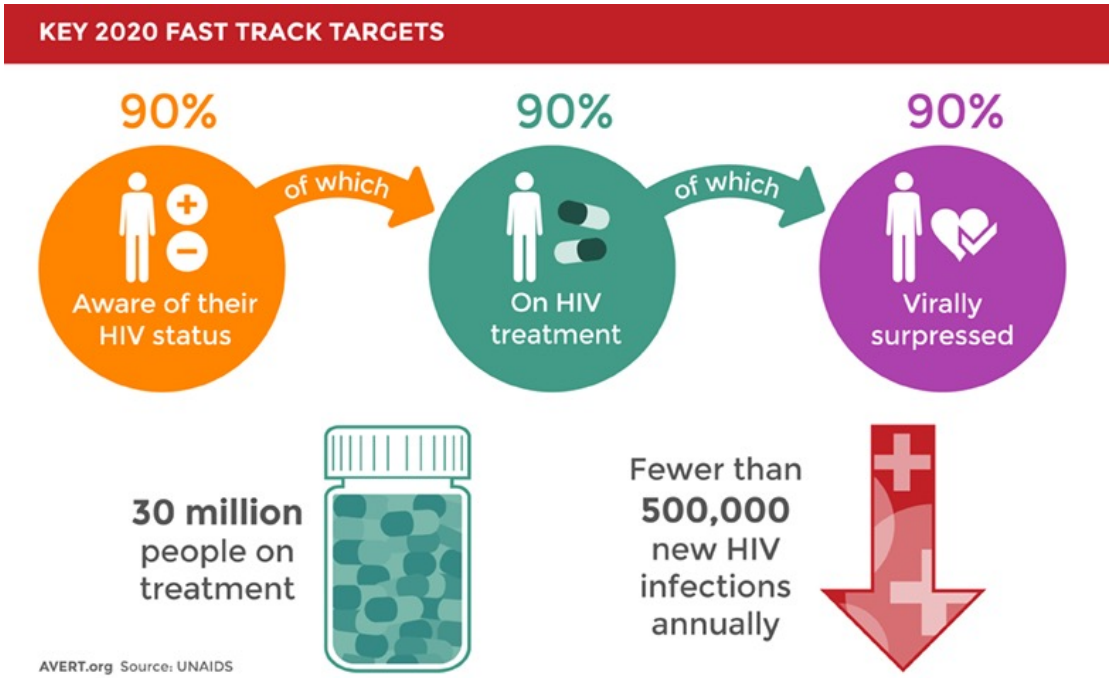
American Timothy Ray Brown had been living with HIV for 11 years, taking antiretroviral medication to suppress the virus, when he developed leukemia (unrelated to his HIV infection). His doctor in Berlin, where he was living, used a bone marrow donor with a known genetic mutation which gives resistance to HIV infection by blocking attachment of HIV to cells (CCR5 Δ32). Despite discontinuing his antiretroviral therapy, levels of HIV in his blood rapidly fell to undetectable levels, his CD4 count increased, and researchers have not detected HIV in his blood or in various biopsies since. It's thought that a combination of chemotherapy destroying his own immune system, a transplant using a naturally resistant donor, and his new immune system attacking the remnants of his old one all helped rid his body of HIV. Brown is the only individual who is considered to have a 'sterilizing cure', meaning he no longer harbours the HIV virus within his body, as opposed to a functional cure when someone still harbours the virus within their bodies but does not need to take antiretroviral treatment..

FACT SHEET 2024

Global HIV statistics

- **39.9 million** [36.1 million–44.6 million] people globally were living with HIV in 2023.
- **1.3 million** [1 million–1.7 million] people became newly infected with HIV in 2023.
- **630 000** [500 000–820 000] people died from AIDS-related illnesses in 2023.
- **30.7 million** people [27–31.9 million] were accessing antiretroviral therapy in 2023.
- **88.4 million** [71.3 million–112.8 million] people have become infected with HIV since the start of the epidemic.
- **42.3 million** [35.7 million–51.1 million] people have died from AIDS-related illnesses since the start of the epidemic.

The UNAIDS Fast-Track strategy, launched in 2014, aims to greatly step up the HIV response in low- and middle-income countries to end the epidemic by 2020
The Fast-Track treatment targets are known as the 90-90-90 targets:



accanto a questi obiettivi era stato proposto di affiancare un "quarto 90" che in sintesi consisteva nel fare in modo che almeno il 90% delle persone con HIV avesse una buona qualità della vita correlata alla salute.

In September 2016 Sweden became the first country to achieve these targets.

Taking this action would mean that in 2020, there would be:
•fewer than 500,000 people newly infected with HIV
•fewer than 500,000 people dying from AIDS-related illnesses
•elimination of HIV-related discrimination.

The 90-90-90 targets refer to the pathway by which a person is tested, linked and retained in HIV care, and initiates and adheres to antiretroviral drugs (ARVs).
See more at: http://www.avert.org/professionals/hiv-around-world/global-response/

The UNAIDS Fast-Track strategy by 2030
The Fast-Track treatment targets are known as the 95-95-95 targets:

Achieving the 95–95–95 targets translates to 95–90–86 when expressed as a cascade. These targets should be achieved in ALL sub-populations, age groups and geographic settings.

Testing, treatment and viral load suppression cascades among all people living with HIV

By 2025, 95% of people living with HIV should know their HIV status (first 95)
•In 2023, 86% [69–>98%] of people living with HIV knew their status.

To reach the first 95–95–95 target, an additional 3.4 million people living with HIV need to be made aware of their HIV status.

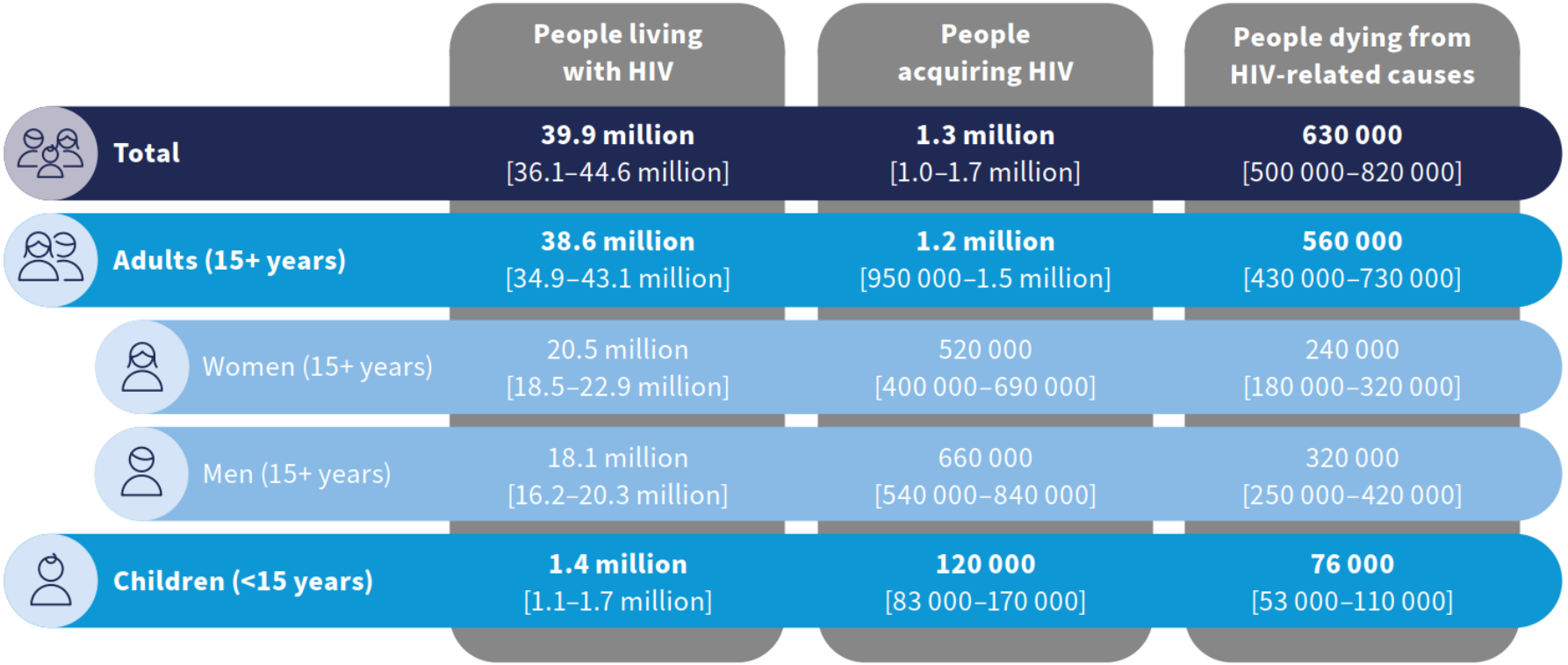
People living with HIV receiving antiretroviral therapy (second 90)
•In 2023, 77% [61–89%] of people living with HIV were receiving antiretroviral therapy.

To reach the second 95–90–86 testing, treatment and viral load suppression cascade target, an additional 5.4 million people living with HIV need to know their status and access antiretroviral therapy.

People living with HIV with suppressed viral loads (third 86)
•In 2023, 72% [65–80%] of people living with HIV had suppressed viral loads.

To reach the third 95–90–86 testing, treatment and viral load suppression cascade target, an additional 5.6 million people living with HIV need to know their status, access antiretroviral therapy, and have viral load suppression.

Summary of the global HIV epidemic, 2023



Source: UNAIDS/WHO estimates, 2024.

Global HIV epidemic – incidence and mortality since 2010

2023
Globally

39.9 million

People living with HIV

– 39%

New HIV infections
annually compared with 2010

– 51%

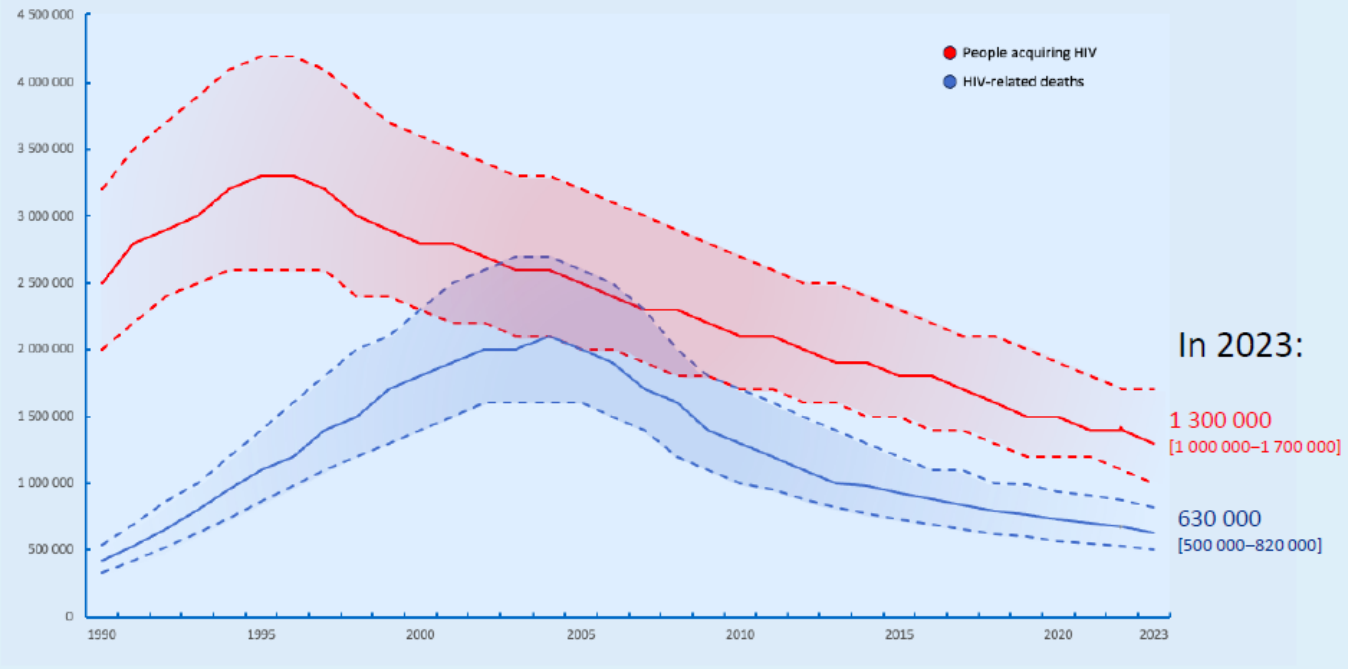
HIV-related deaths
annually compared with 2010

World Health Organization

Source: UNAIDS/WHO estimates, 2024.

Updated: July 2024

Decline in number of people acquiring HIV and HIV-related deaths, globally over time



World Health Organization

Source: UNAIDS/WHO estimates, 2024.

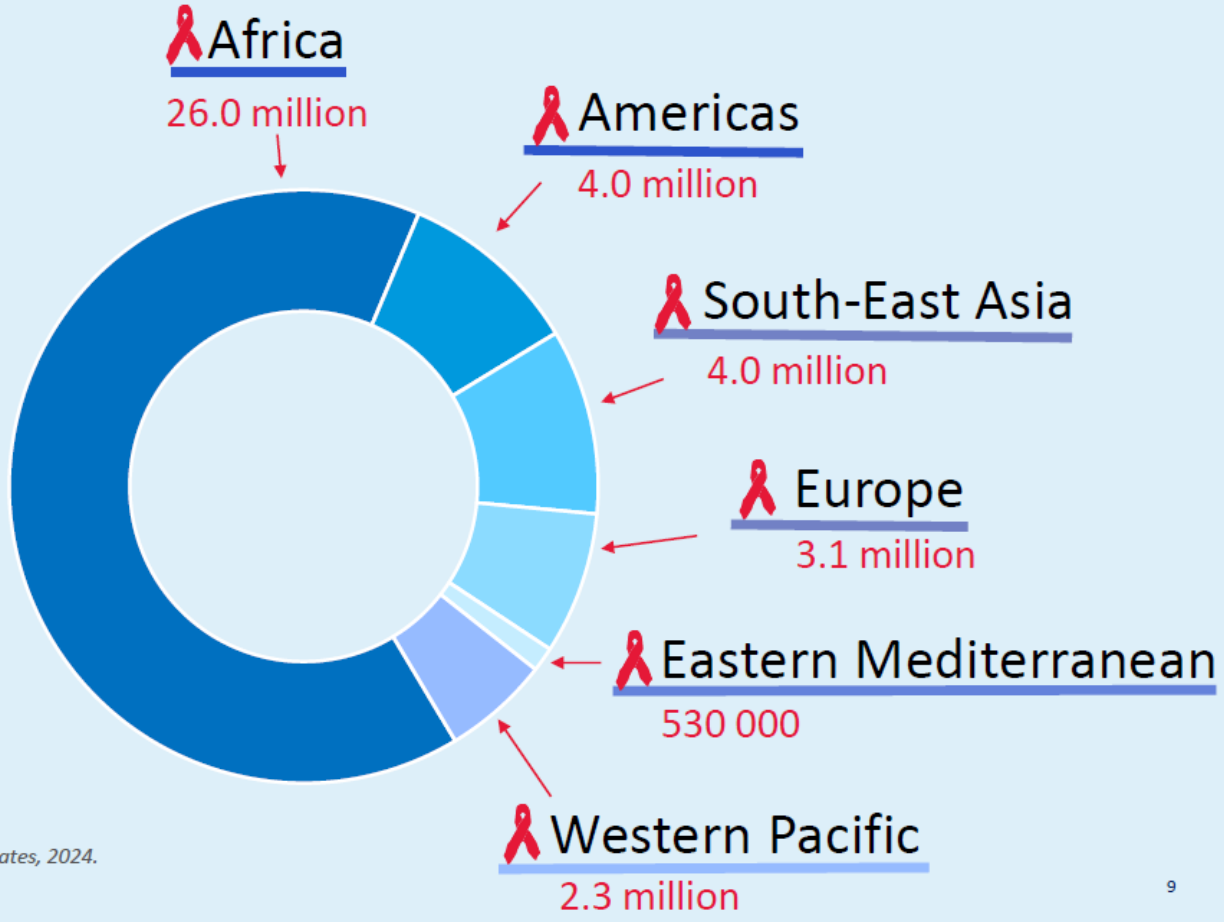
8

Updated: July 2024

Despite a reduction in incidence over the last few decades due to improved treatment and prevention efforts, this decline in infections has slowed over the past 5 years—especially in key populations: sex workers and their clients, men who have sex with men (MSM), people who inject drugs (PWIDs), transgender individuals, and prison inmate

People living with HIV by WHO region, 2023

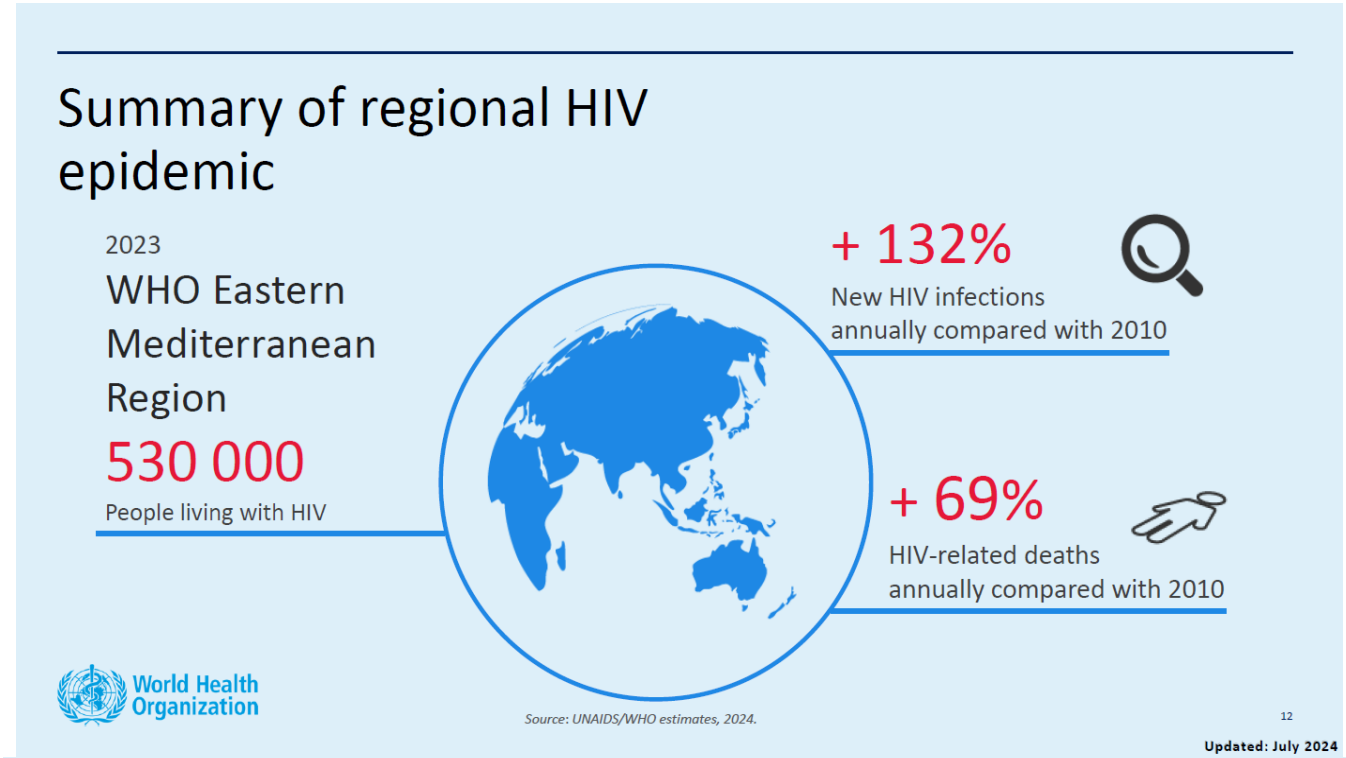
39.9 million
people living with HIV globally



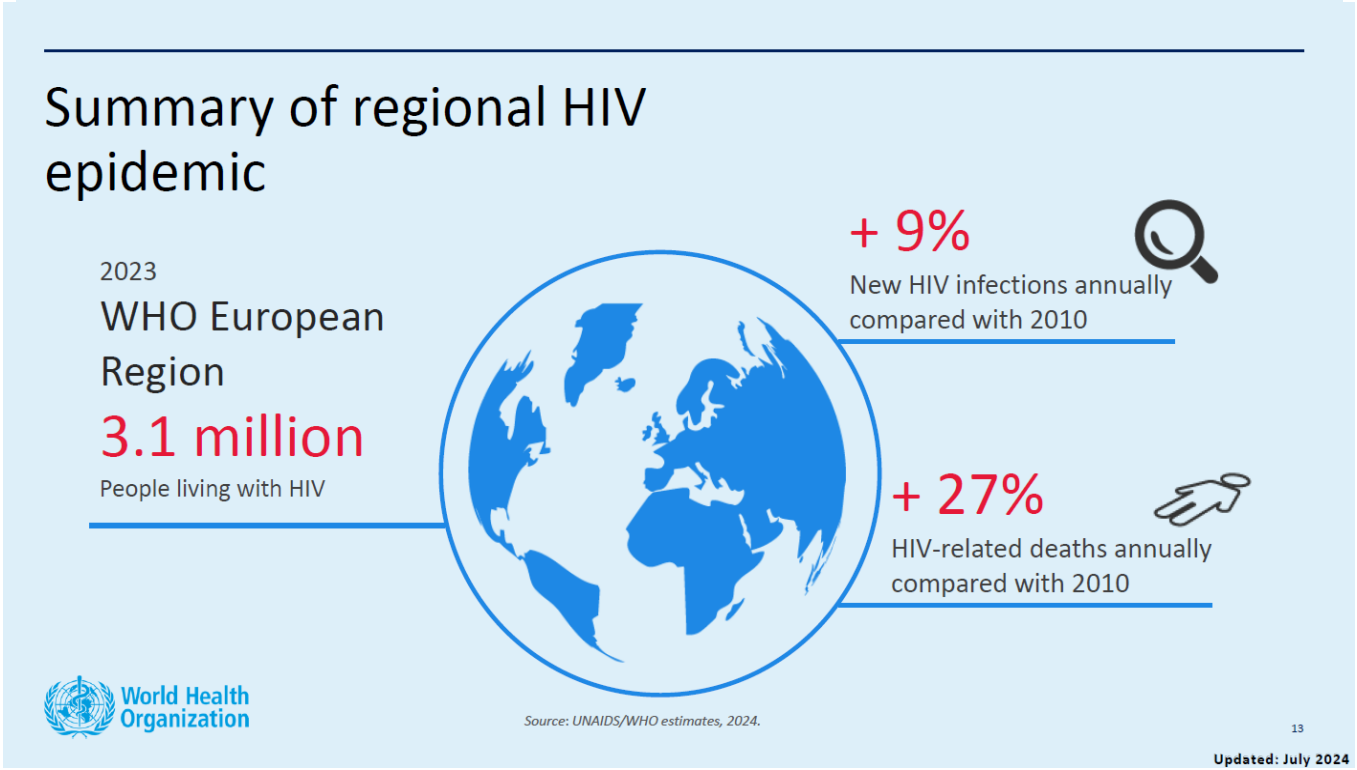
World Health Organization

Source: UNAIDS/WHO estimates, 2024.

Updated: July 2024



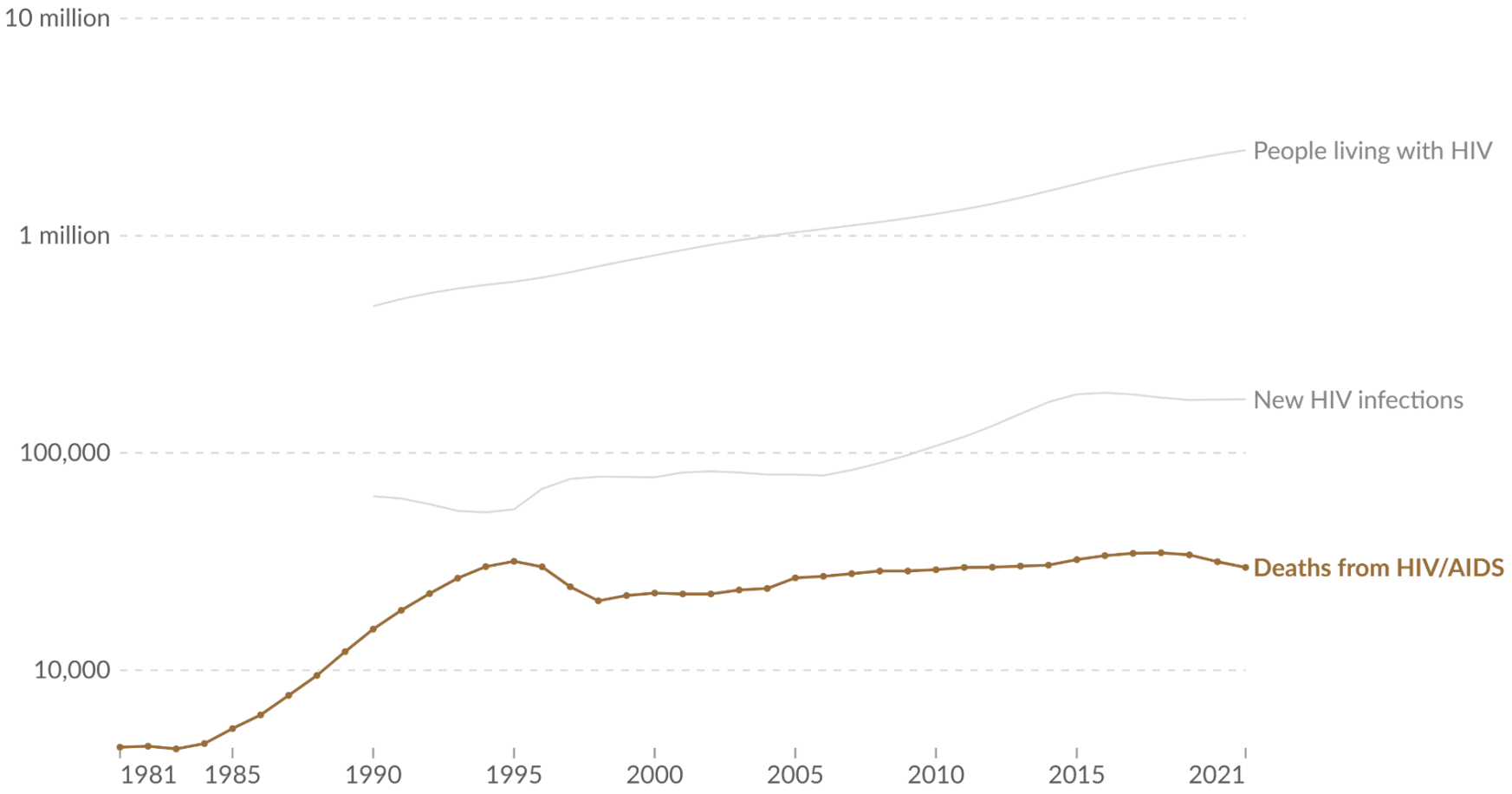
The increase in HIV diagnoses in 2023 can be attributed to various factors across different subregions. In the east of the WHO European Region, countries reported a rebound in HIV testing and case detection since the COVID-19 pandemic subsided, focusing on increasing case detection and introducing new testing policies to close the gap on undiagnosed individuals.



In the EU/EEA and the west of the Region, the increase may be a result of increased diagnoses among migrants, particularly from high-prevalence countries, and expanded HIV testing services. In contrast, the number of HIV diagnoses in the centre of the Region decreased in 2023 compared to 2022, mainly due to a reduction in previous positive diagnoses. However, six out of 15 countries in the centre still reported an increase in 2023 compared to 2022.

https://www.ecdc.europa.eu/sites/default/files/documents/HIV_Surveillance_Report_2024.pdf

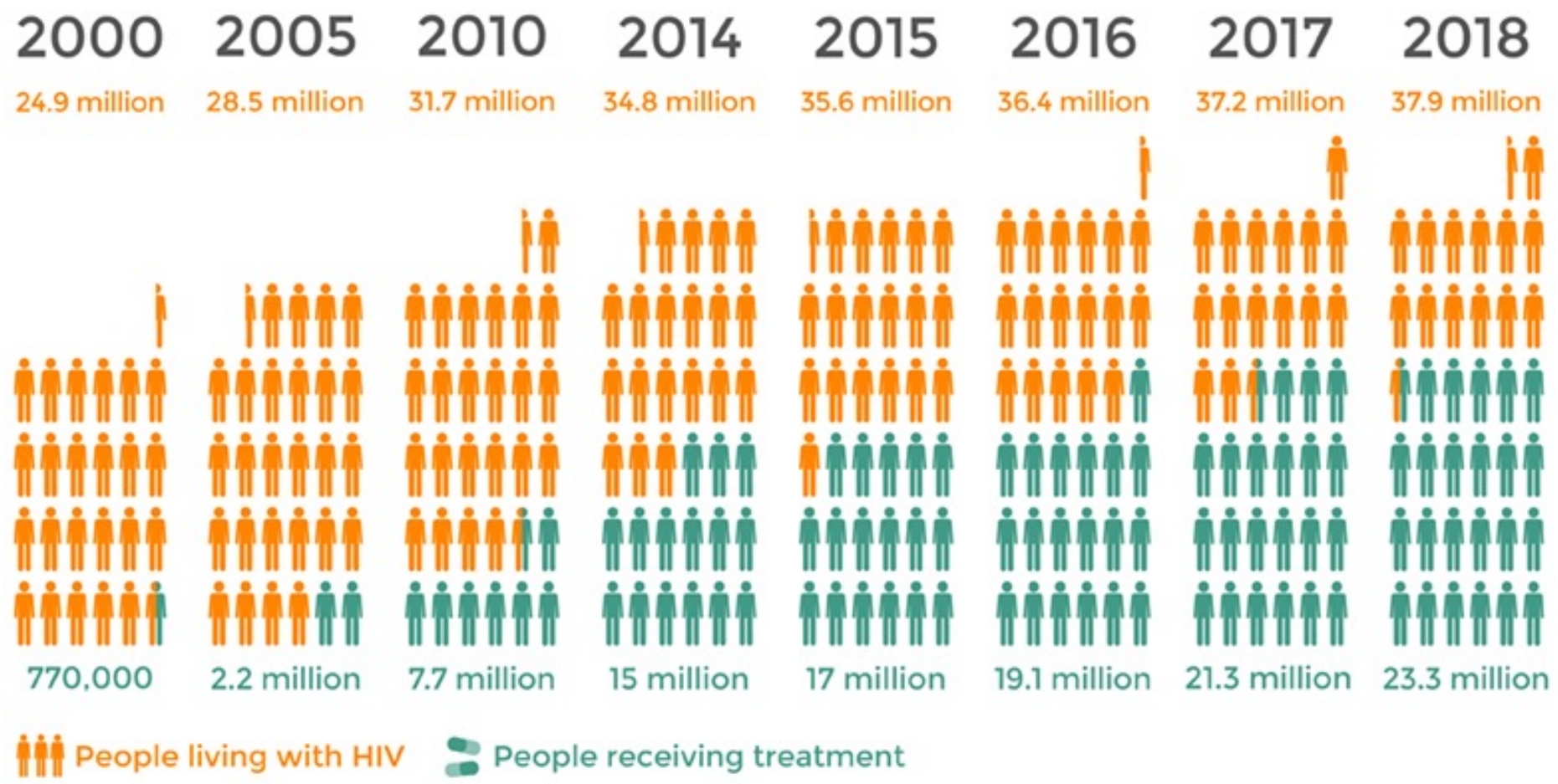
New cases, deaths, and people living with HIV/AIDS, Europe



Data source: IHME, Global Burden of Disease (2024)

OurWorldinData.org/eradication-of-diseases | CC BY

Number of people living with HIV and accessing treatment globally



Source: UNAIDS Data 2019


IGNORANCE = FEAR
SILENCE = DEATH
FIGHT AIDS
ACT UP