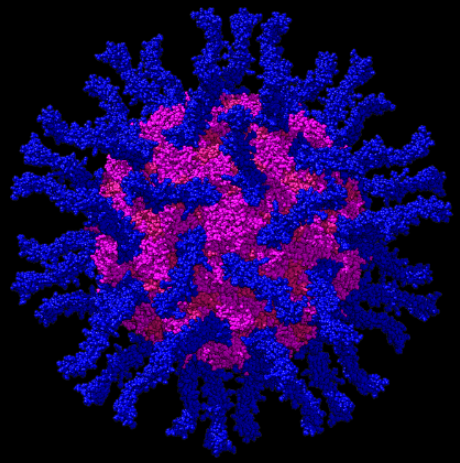


VIROLOGY LIVE

WITH VINCENT RACANIELLO

HIV and AIDS

Session 23

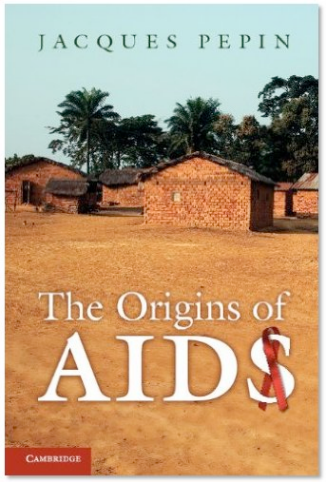
Virology Live

Fall 2021

Nature is not human-hearted
Lao Tzu
Tao Te Ching

This tragedy was facilitated (or even caused) by human interventions: colonization, urbanization, and probably well-intentioned public health campaigns

Pepin, Jacques (2011) *The Origins of AIDS*. Cambridge University Press.



CDC Home | Search | Health Topics A-Z

MMWR Weekly

June 5, 1981 / 30(21);1-3

Epidemiologic Notes and Reports http://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm

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 elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in may 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *p. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/.SMX, but, as of the latest reports, he continues to have a fever each day.

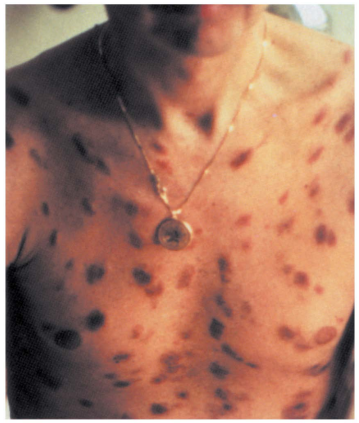
Editorial Note: *Pneumocystis* pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients (1). The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and *Pneumocystis* pneumonia in this population. All 5 patients described in this report had laboratory-confirmed CMV disease or virus shedding within 5 months of the diagnosis of *Pneumocystis* pneumonia. CMV infection has been shown to induce transient abnormalities of *in vitro* cellular-immune function in otherwise healthy human hosts (2,3). Although all 3 patients tested had abnormal cellular-immune function, no definitive conclusion regarding the role of CMV infection in these 5 cases can be reached because of the lack of published data on cellular-immune function in healthy homosexual males with and without CMV antibody. In 1 report, 7 (3.6%) of 194 patients with pneumocystosis also had CMV infection' 40 (21%) of the same group had at least 1 other major concurrent infection (1). A high prevalence of CMV infections among homosexual males was recently reported: 179 (94%) had CMV viruria; rates for 101 controls of similar age who were reported to be exclusively heterosexual were 54% for seropositivity and zero fro viruria (4). In another study of 64 males, 4 (6.3%) had positive tests for CMV in semen, but none had CMV recovered from urine. Two of the 4 reported recent homosexual contacts. These findings suggest not only that virus shedding may be more readily detected in seminal fluid than urine, but also that seminal fluid may be an important vehicle of CMV transmission (5).

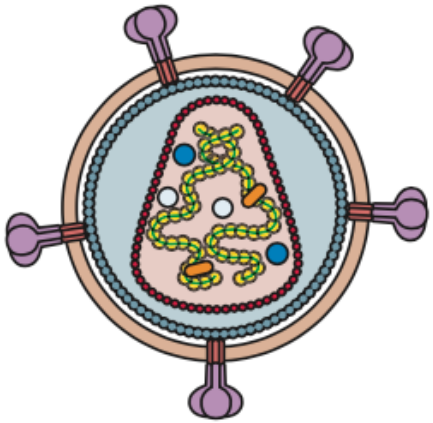
All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia.

December: At Albert Einstein Medical College in New York, pediatric immunologist Dr. Arye Rubinstein treats five black infants who are showing signs of severe immune deficiency, including PCP. At least three are the children of women who use drugs and engage in sex work. He recognizes that the children are showing signs of the same illnesses affecting gay men, but his diagnoses are dismissed by his colleagues.

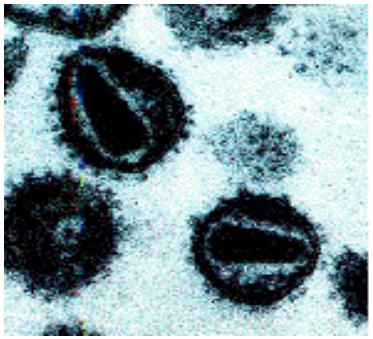
AIDS

- Clusters of PCP and Kaposi's sarcoma observed in other urban centers
- CDC established case definition of KS or opportunistic infections
- 1982 disease was called AIDS (formerly GRID)
- Found transmitted at birth and heterosexually, blood products

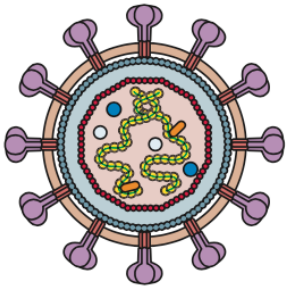




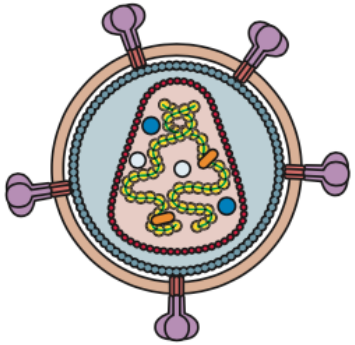
HIV-1 is a lentivirus



- First isolated in 1983 from the lymph node of a patient with lymphadenopathy in Paris; 2008 Nobel to Montagnier & Barré-Sinoussi
- 1984 blood test developed
- Electron microscopy and sequence analysis revealed HIV-1 to be a lentivirus, known group of retroviruses



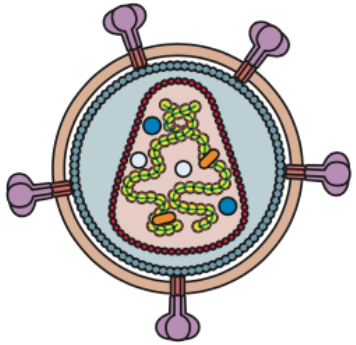
Retroviridae

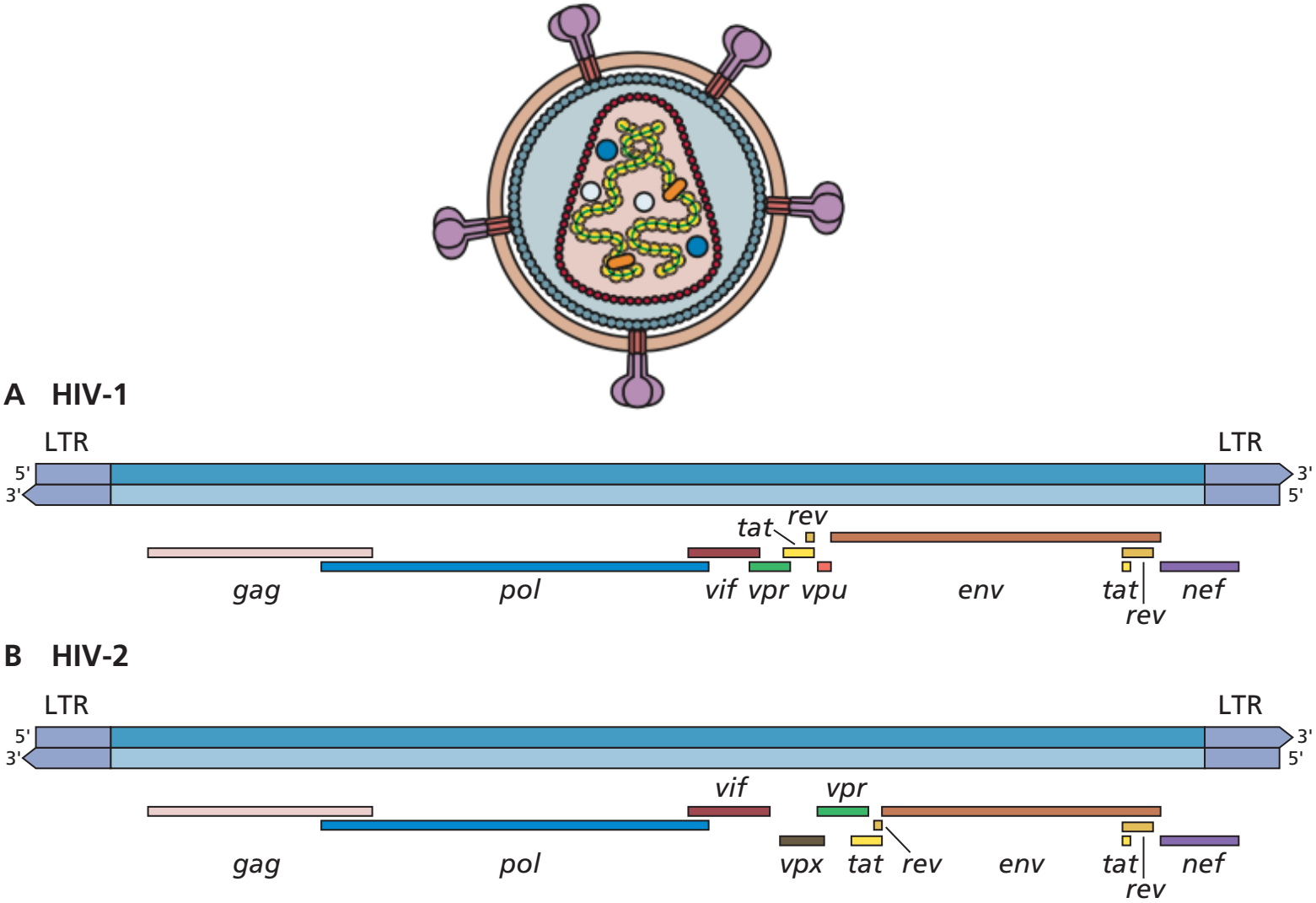


- *Orthoretrovirinae (subfamily)*
  - *Alpharetrovirus (Avian leukosis virus, Rous sarcoma virus)*
  - *Betaretrovirus (Mouse mammary tumor virus)*
  - *Deltaretrovirus (Human T cell lymphotropic virus 1, 2 ,3)*
  - *Epsilonretrovirus (Walleye dermal sarcoma virus)*
  - *Gammaretrovirus (Moloney murine leukemia virus)*
  - *Lentivirus (Human immunodeficiency virus 1, 2)*

Two evolutionarily distinct groups of human retroviruses

- The lymphotropic viruses: HTLV 1, 2, 3, 4
- The immunodeficiency viruses: HIV-1, HIV-2
  - Lentiviruses, not new or unique to humans
  - Equine infectious anemia virus, causes fatal immunodeficiency of horses, isolated early 1900s
  - Bovine, feline, caprine immunodeficiency viruses

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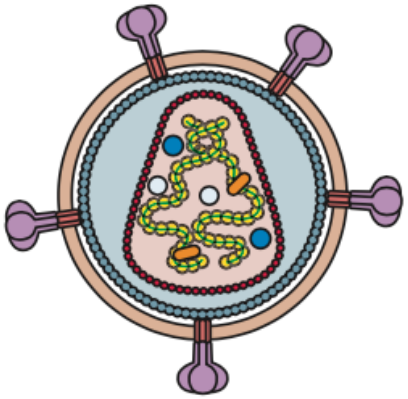
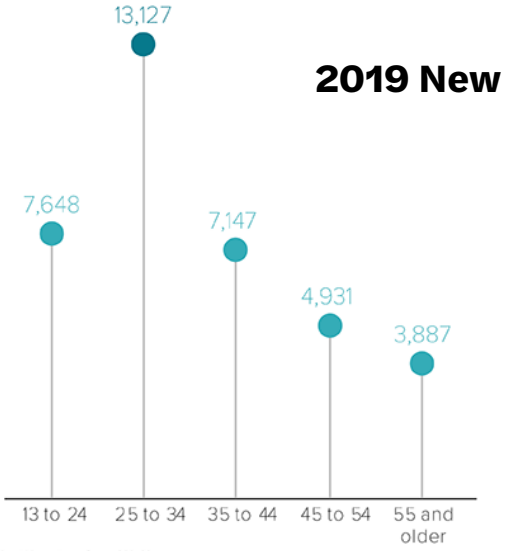
HIV and AIDS: Acquired ImmunoDeficiency Syndrome



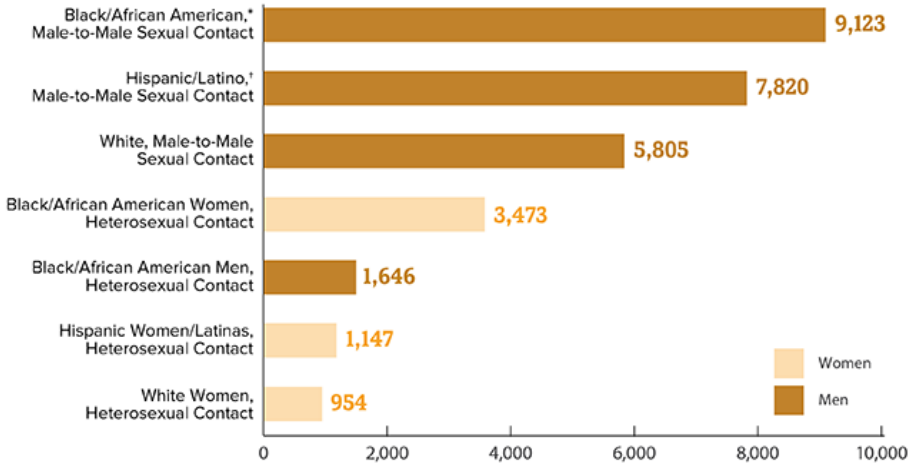
- Syndrome: the occurrence together of a characteristic group or pattern of symptoms
- HIV-1 is the etiological agent of epidemic AIDS
- AIDS denialists: the hypothesis that HIV-1 causes AIDS has been tested by inadvertent infection of people with HIV-1 contaminated blood

HIV/AIDS pandemic in the US

- In the US, HIV-1 has killed over 600,000, exceeding all US combat-related deaths in all wars fought in the 20th century
- 1,140,000 million in the US are living with HIV-1; 1 in 7 don't know it
- 36,801 new infections in 2019; 69% MSM, 23% HS, 7% IVDU



2019 New infections



http://www.cdc.gov/hiv/statistics/overview/ataglance.html

37.7 million

People living with HIV/AIDS worldwide in 2020

680,000

People died of HIV/AIDS worldwide in 2020

Summary of the global HIV epidemic, 2020

	People living with HIV in 2020	People acquiring HIV in 2020	People dying from HIV-related causes in 2020
Total	37.7 million [30.2–45.1 million]	1.5 million [1.0–2.0 million]	680 000 [480 000–1.0 million]
Adults (15+ years)	36.0 million [28.9–43.2 million]	1.3 million [910 000–1.8 million]	580 000 [400 000–850 000]
Women (15+ years)	19.3 million [15.5–23.1 million]	660 000 [450 000–920 000]	240 000 [170 000–360 000]
Men (15+ years)	16.7 million [13.3–20.1 million]	640 000 [460 000–890 000]	340 000 [230 000–490 000]
Children (<15 years)	1.7 million [1.2–2.2 million]	150 000 [100 000–240 000]	99 000 [68 000–160 000]

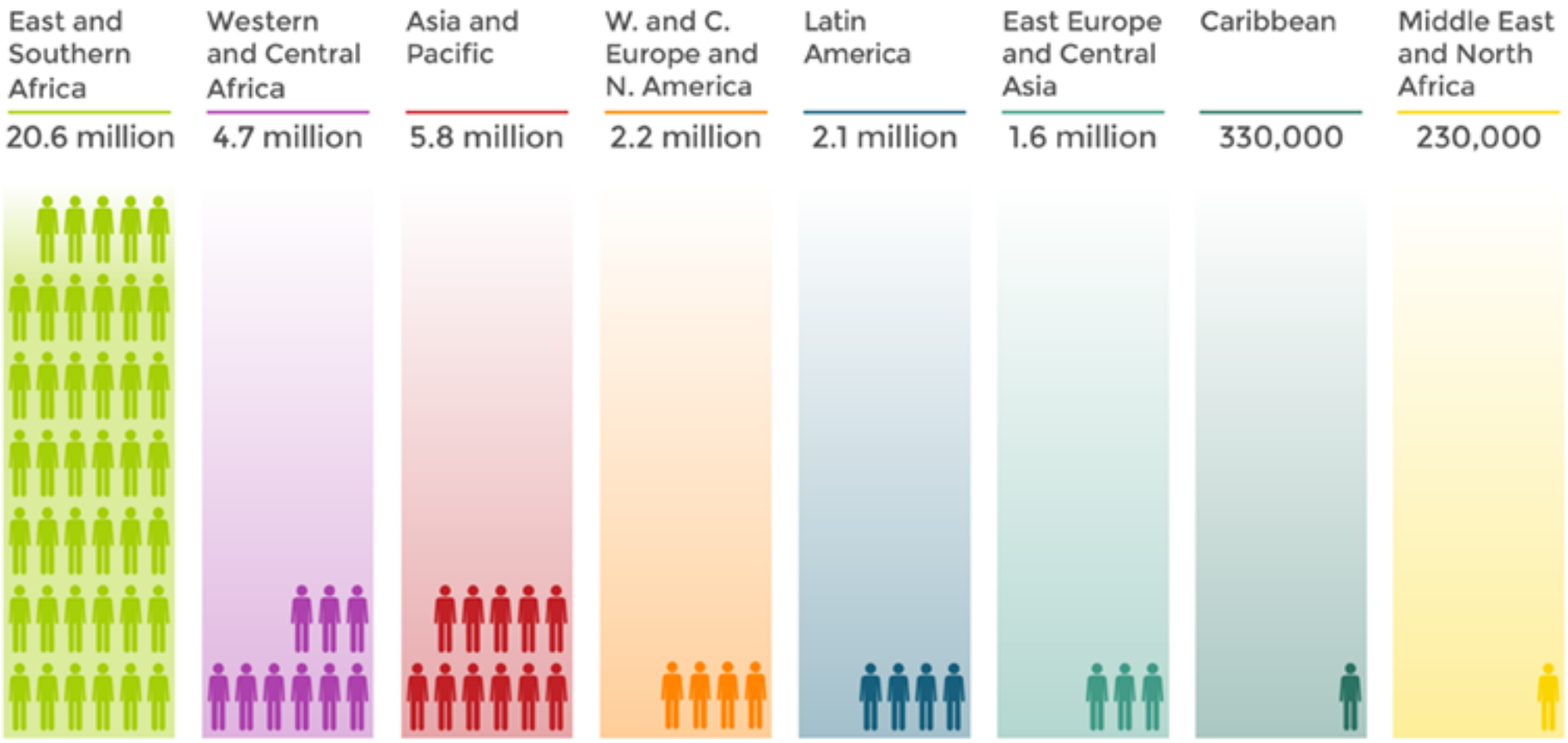
Source: UNAIDS/WHO estimates

Updated: July 2021

World Health Organization

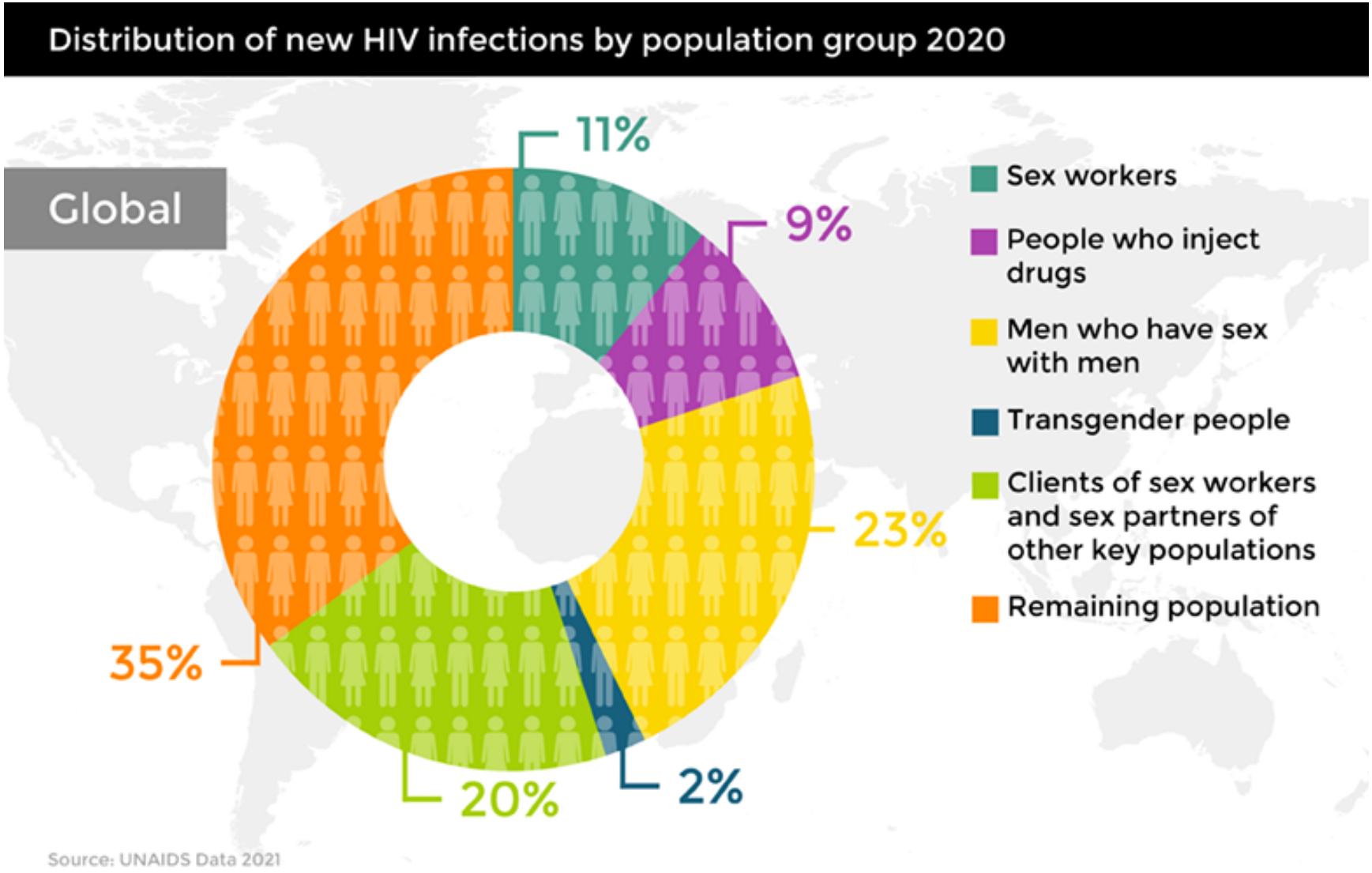
4,600 new HIV infections a day, 190 per hour

Number of people living with HIV in 2020



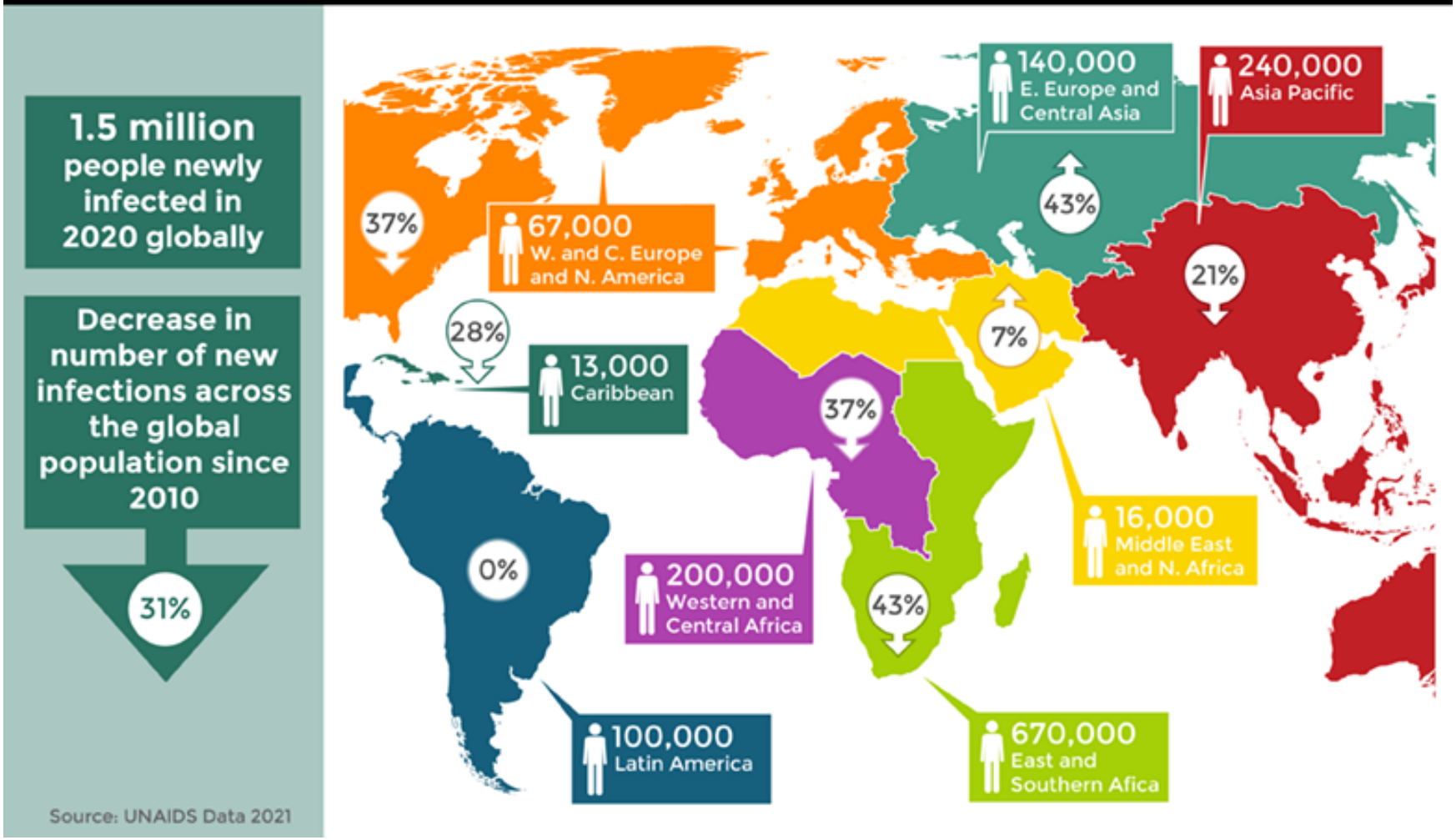
Source: UNAIDS Data 2021

Source: avert.org



Source: avert.org

Number of new HIV infections in 2020 and change since 2010

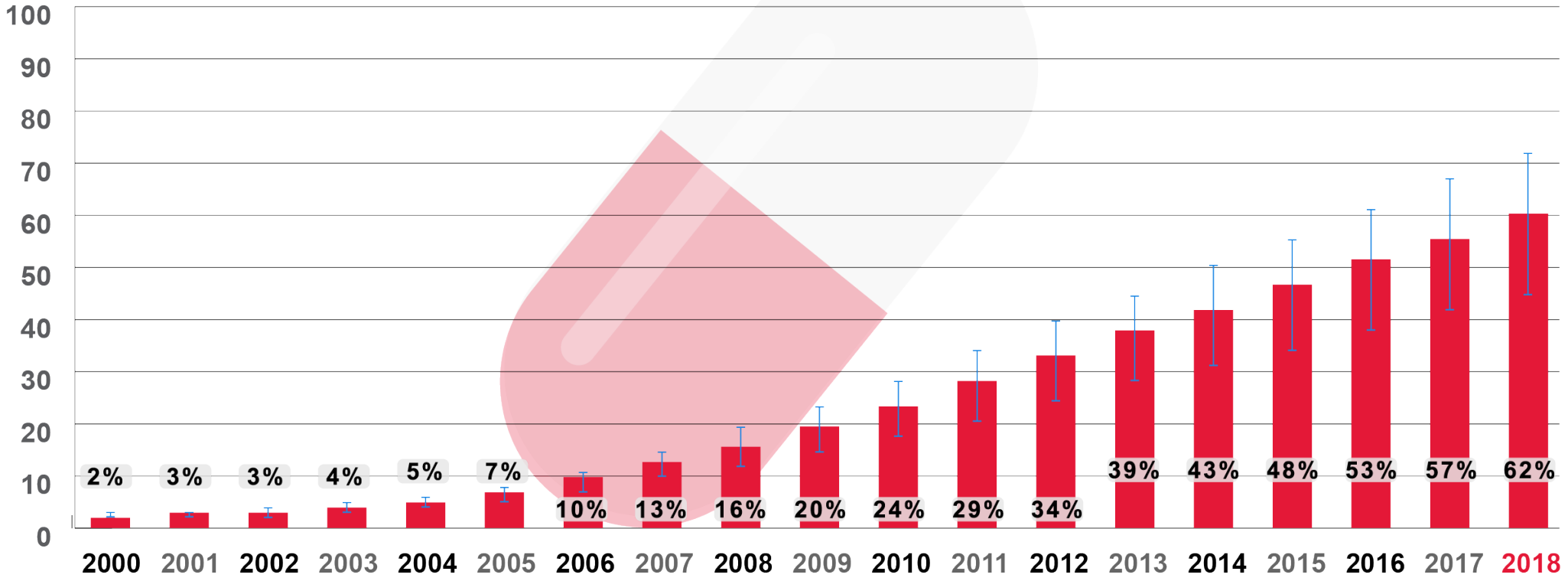


Source: avert.org

Control of AIDS

Triple-drug therapy has slowed the pandemic in countries with money

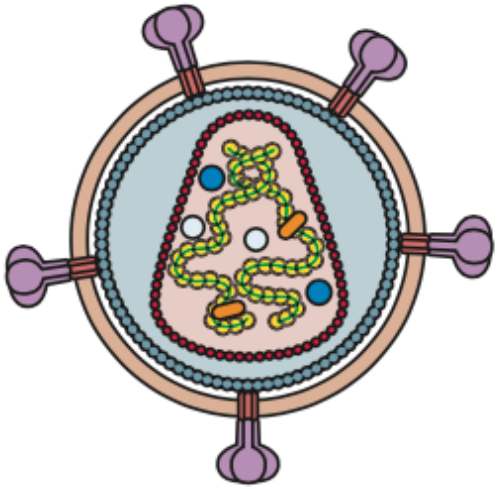
ART coverage over time



Source: UNAIDS/WHO estimates

Question break

But…



- There is as yet no cure
  - Can’t clear virus from an infected individual
- There is no vaccine
  - Can’t block primary infection
- Can’t stop taking antiviral drugs
  - Reservoirs: latently infected hematopoietic progenitor cells
- Drug resistant viruses appear
- Drugs are expensive

Out of Africa

First studies in Africa, in Zaire and Rwanda, showed that AIDS was common in Kinshasa and Kigali, where nearly 90% of sex workers were infected

Out of Africa

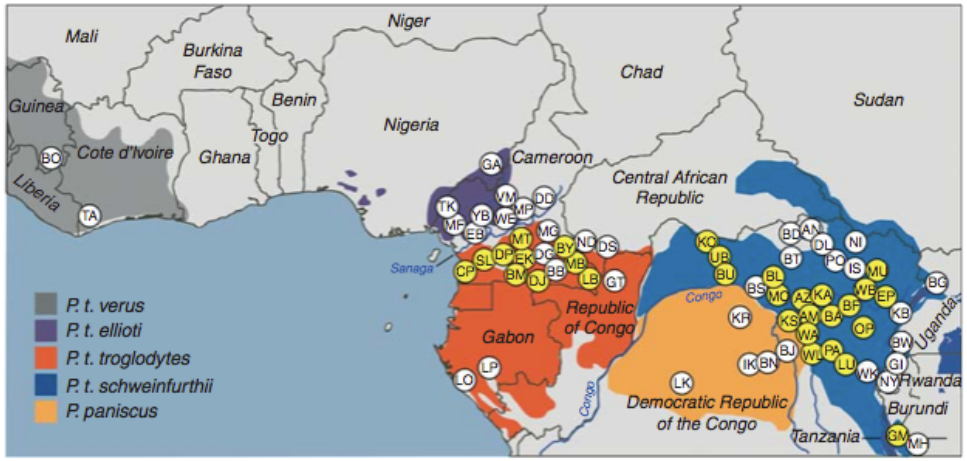
- Testing of archival samples suggested that HIV-1 was present in the 1960s and 1970s in several locations in central Africa but not in West or East Africa
- Serum sample ZR59 from a DRC adult male (1959) found positive for HIV-1 in 1998
- Lymph node sample from DRC adult female (1960)

Out of Africa

- DRC60 and ZR59 differed by about 12%
- No doubt that HIV-1 was present in Léopoldville (Kinshasa today) by 1959–60

What was the source of HIV-1?

- SIV first isolated from chimpanzee in 1989 (SIVcpz)
- Analysis of >7,000 chimpanzee fecal samples from 90 field sites confirmed natural SIVcpz reservoir
- Only *Pan troglodytes troglodytes* and *P. T. schweinfurthii* harbor SIVcpz



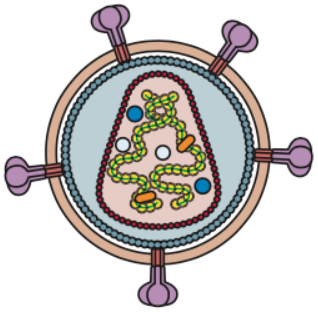
Virology Live 2021 • Vincent Racaniello

Cold Spring Harb Perspect Med 2011;1:a006841

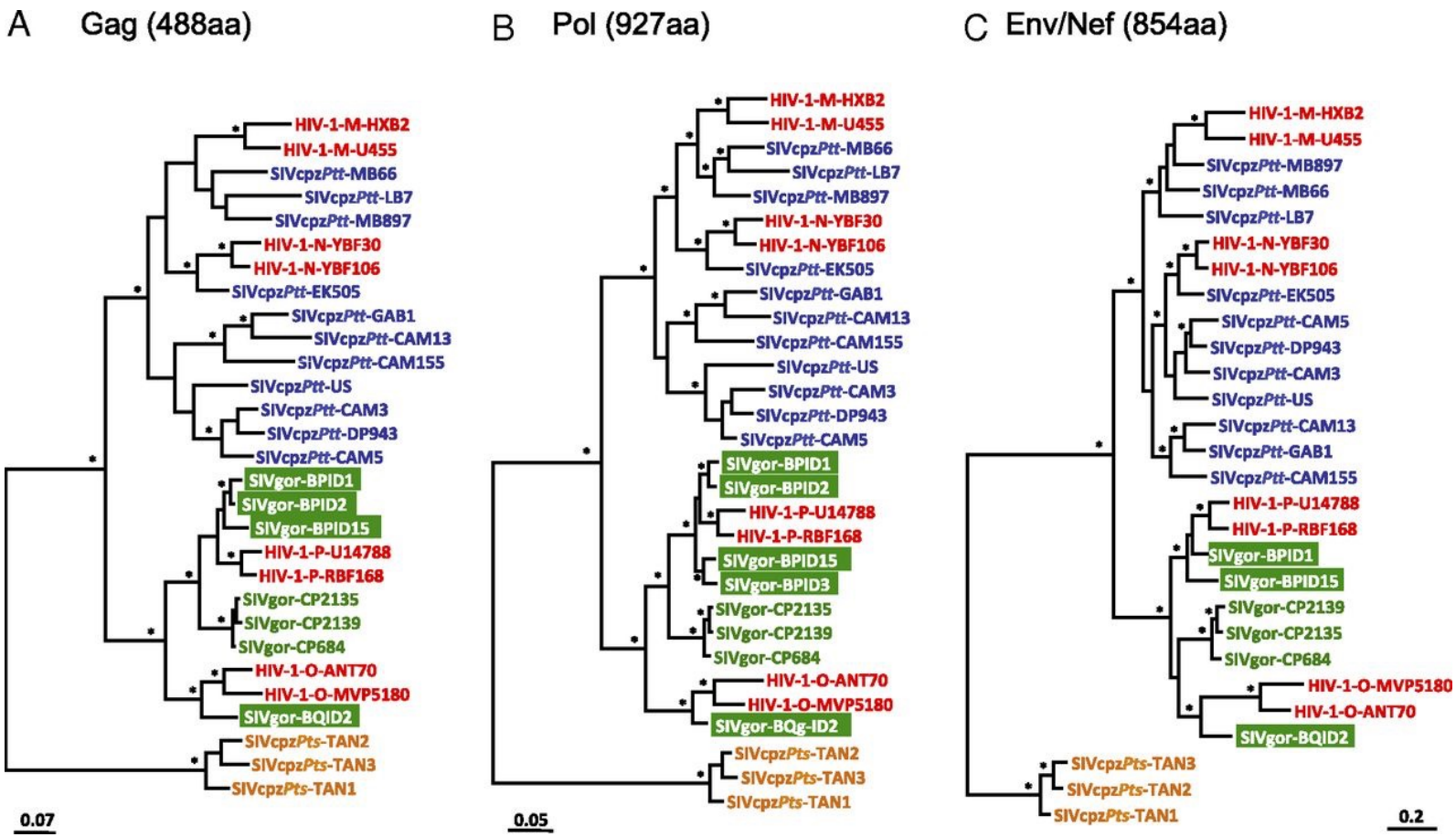
https://bit.ly/3aG7ssz

Beatrice Hahn

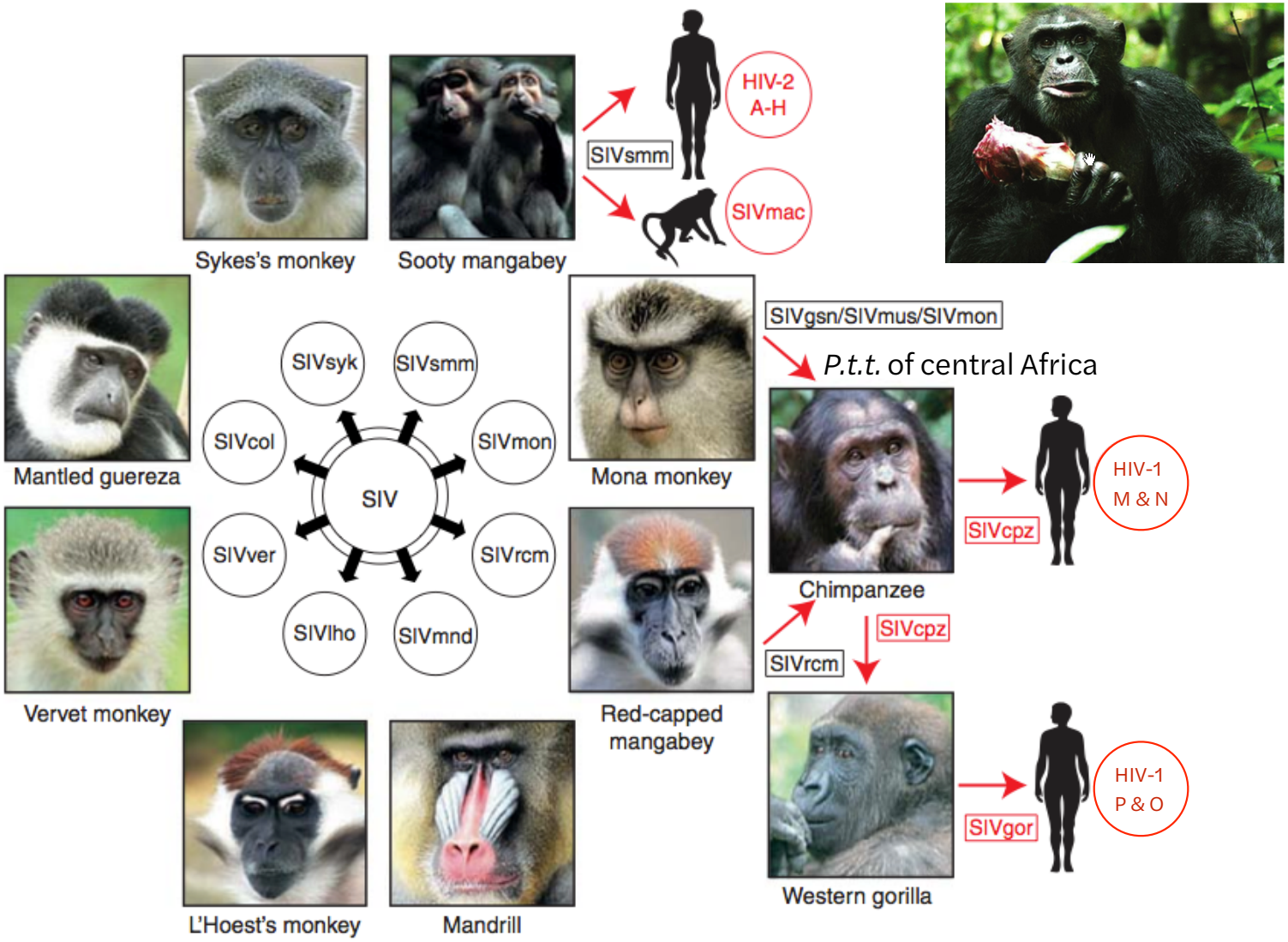
SIVcpz



- Transmitted among chimpanzees by sexual intercourse; mother to child; possibly blood-blood during aggression
- Estimated transmission probability per coital act 0.008 - 0.0015, similar to humans (0.0011)
- SIVcpz is pathogenic in natural host, disease similar to AIDS



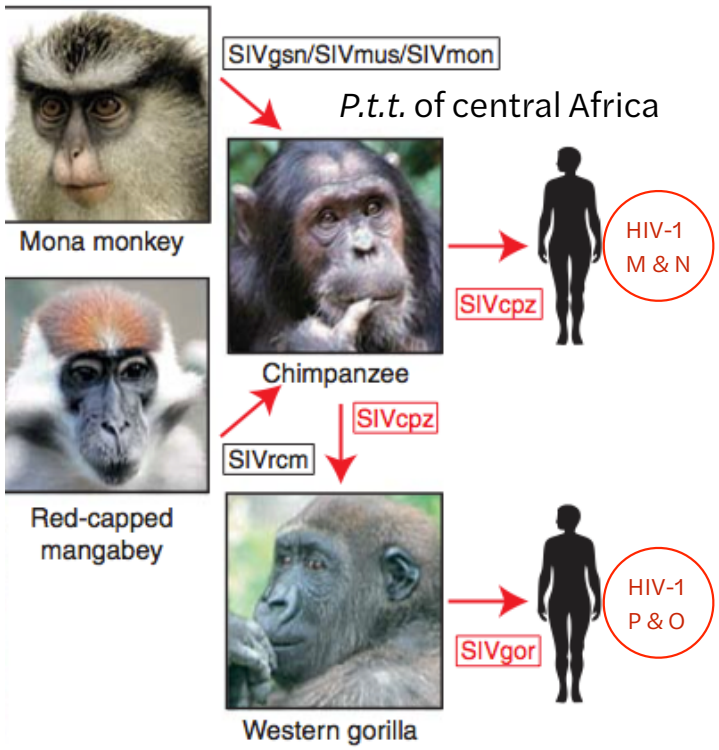
PNAS 112(2015) doi: 10.1073/pnas.1502022112



Cold Spring Harb Perspect Med 2011;1:a006841

When did SIV infect humans?

- Four separate crossover events
- M, O: First three decades of 20th century
- N, P: more recently but not enough data

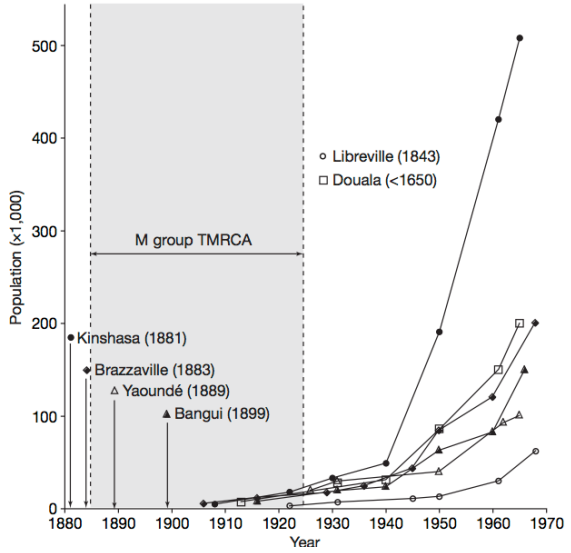


Cold Spring Harb Perspect Med 2011;1:a006841

How did SIVcpz infect humans?

- The cut hunter: bushmeat hunting
- Cutaneous or mucous membrane exposure to infected chimpanzee blood, body fluids
- Calculations suggest that in 1921 number of people infected with SIVcpz was <10, but probably only one spread and multiplied
- Such cross-species infections probably have occurred many times previously
- Why did this one spread?

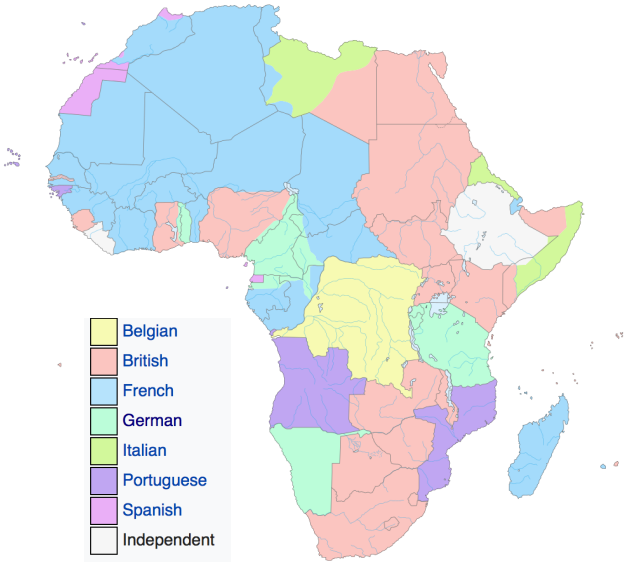
Spread of HIV-1



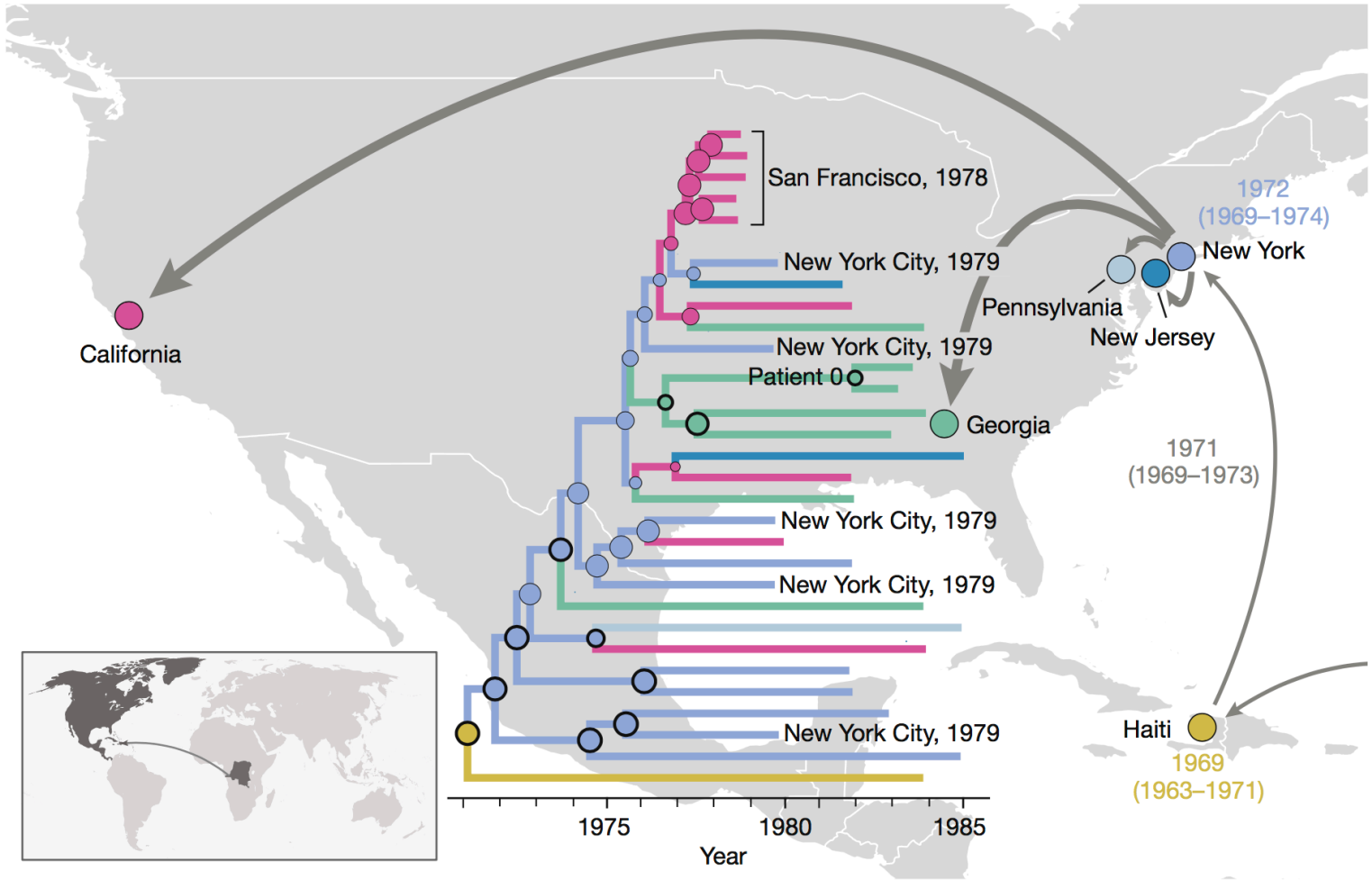
- Leopoldville (Kinshasa) was the most dynamic city in the region, attracted large numbers of migrants and traders
- The cut hunter might have traveled there, visited a brothel, then a STD clinic
- Then amplification by non-sterile syringes, sex (some women had 1,000 clients/yr)
- Haiti and the Belgian Congo

Why did HIV-1 spread?

- European colonization of Africa beginning end of 19th century
- Establishment of large population centers, movement of adult males for labor - large scale prostitution
- Introduction of health care - colonial medicine - injections and transmission of viruses
- Egypt at turn of 20th century - well intentioned treatment for schistosomiasis spread HCV to millions
- Large scale amplification of HIV-1



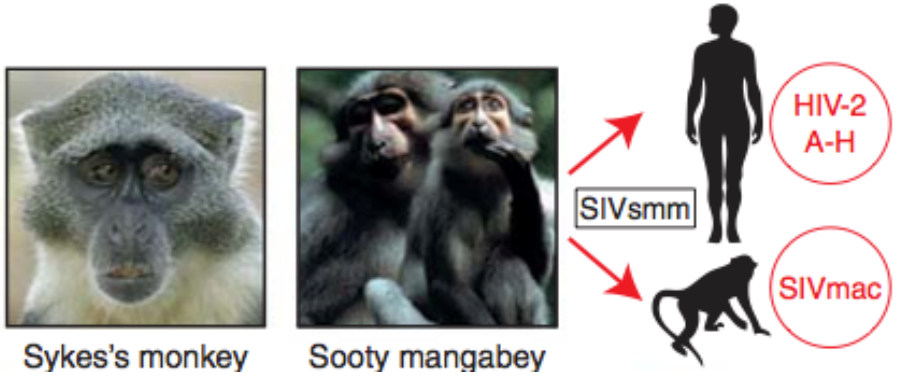
Early HIV/AIDS in North America



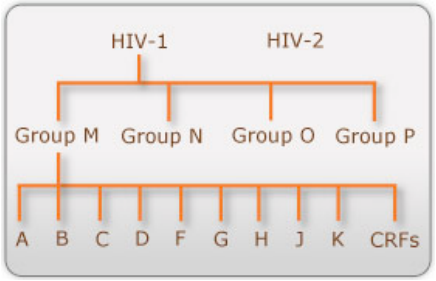
doi:10.1038/nature19827

HIV-2

- First isolated Guinea-Bissau, 30-40% identity HIV-1
- Restricted primarily to populations in West Africa
- Less virulent (most infections do not progress to AIDS), transmissible than HIV-1, no mother-infant spread
- Crossover from sooty mangabey
- 8 distinct lineages, each arose from separate infection

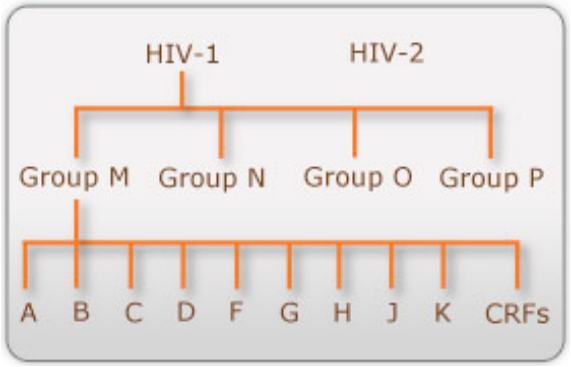


HIV-1 diversity

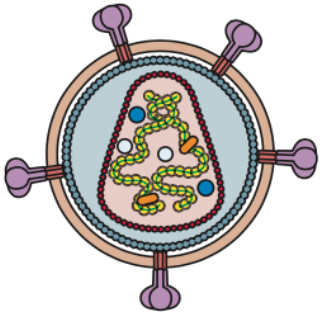


- Four groups based on sequence alignment
- Group M (main): 99% of all HIV-1 infections
- Group O (outlier): <1% of infections, limited to Cameroon, Gabon, neighboring countries
- Group N: Only 13 cases, Cameroon
- Group P: Only 2 cases, Cameroon
- *Each from an independent transmission event of SIV to humans*

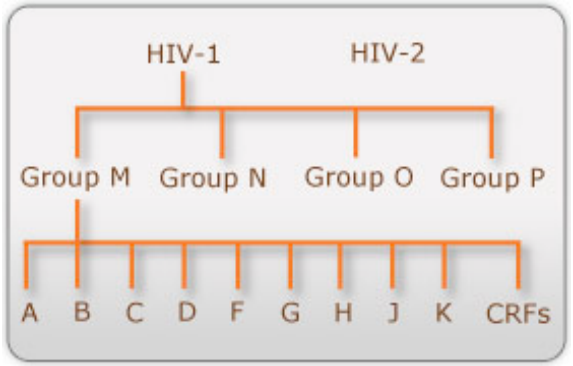
HIV-1 diversity



- HIV-1 group M further divided into 9 subtypes
- High-risk individuals multiply infected, recombinants emerge (CRFs) 48 so far
- No clear cut difference between subtypes in propensity to cause AIDS, except that those infected with D die faster
- Shedding of subtype C in female genital tract is higher, perhaps higher female to male transmission, extensive spread in Africa

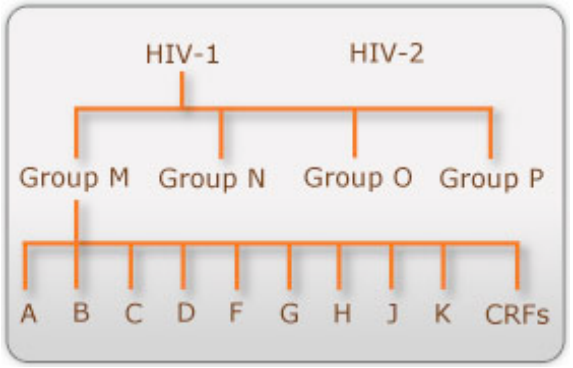


HIV-1 subtypes



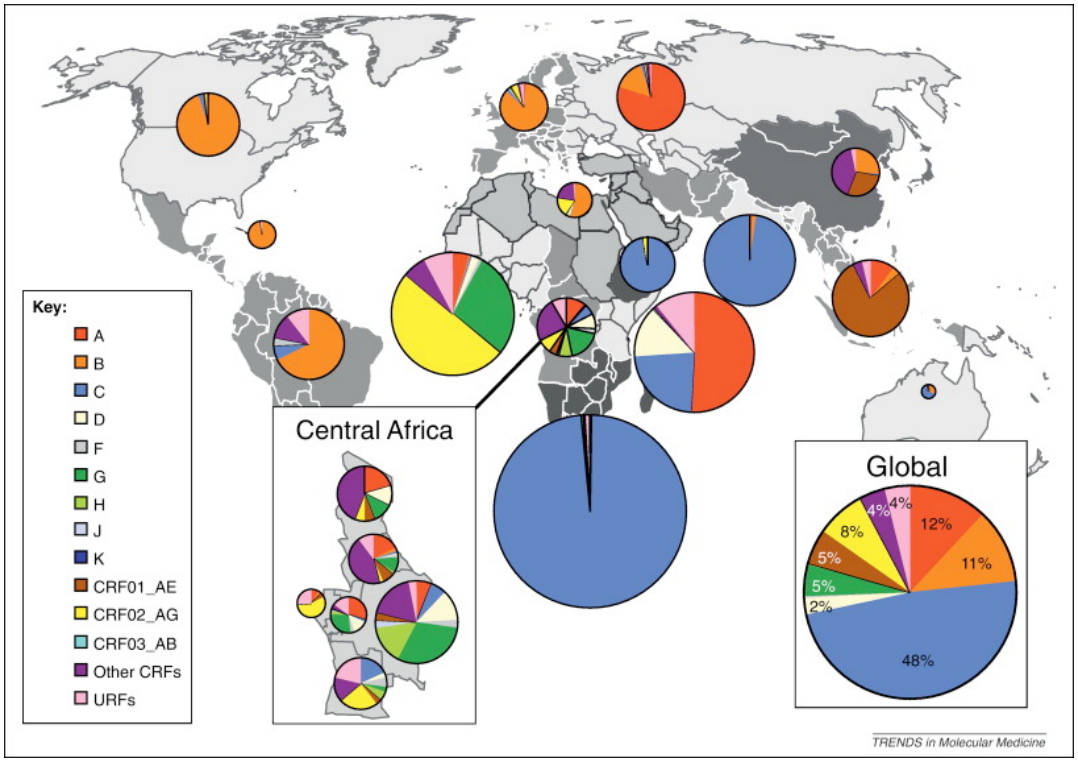
- HIV-1 evolves in one direction to numerous subtypes and recombinants
- Therefore can reconstruct sequence of progress in region or country by examining local distribution of subtypes
- Facilitated in 1990s by new tools enabling examination of nucleotide sequences from large number of isolates
- Extreme diversity of HIV-1 in central Africa, clearly the origin as had more time to diversify

HIV-1 subtypes



- Some subtypes associated in specific locations with modes of transmission
- Founder effect: subtype will *predominate* in at-risk group
- Example: subtype B found in 96% of white homosexuals in South Africa (imported from US); subtype C accounts for 81% of infections of black heterosexuals

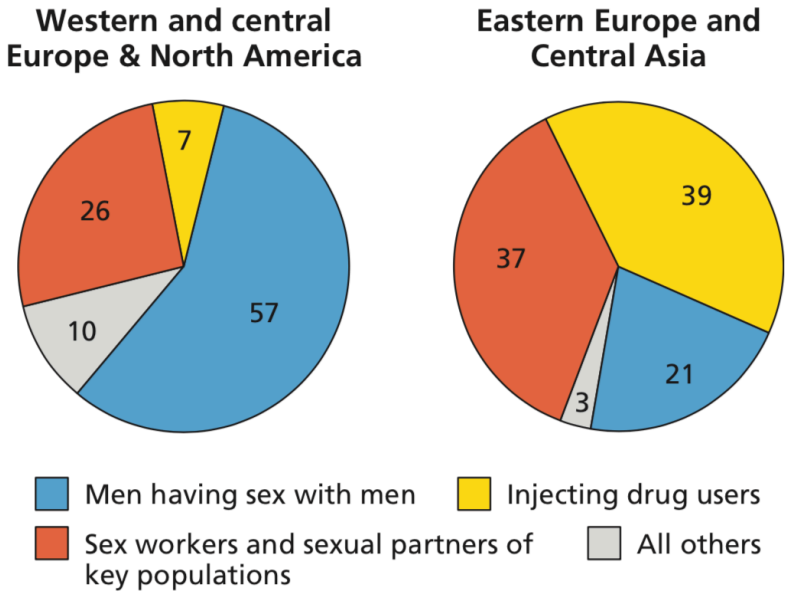
- Subtype C (50%), B and A (10-12%), G (6%), CRF02_AG (5%), CRF01_AE (5%), D (2.5%) of all HIV-1 infections
- Subtypes F, H, J, K limited transmission (<1%)



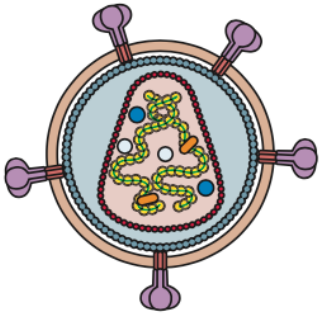
Question break

Transmission

- Transmitted by sex, intravenous drug use, at birth (R_0 2-5)
- Not spread by respiratory, alimentary, or vector routes



Mother to child at birth, ~5%



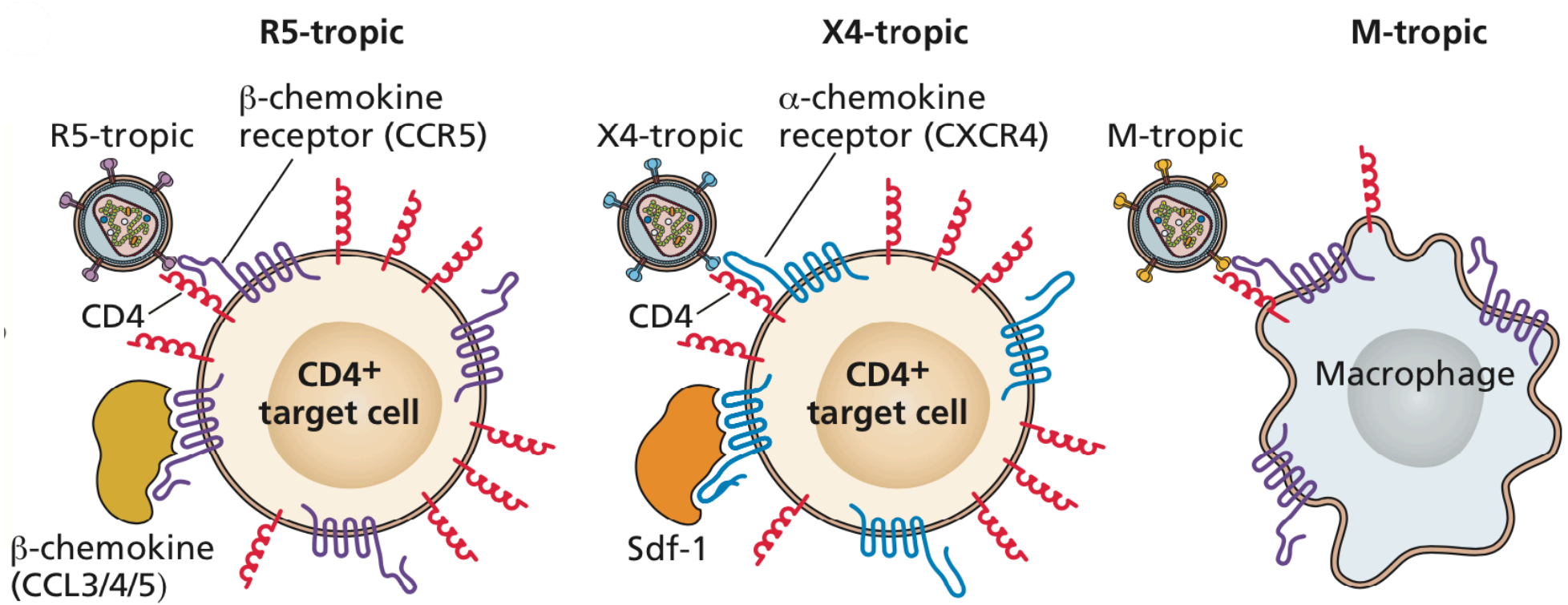
Transmission

- HIV-1 infectivity reduced by air drying (99%/24 hr)
- By heating (56°C/30 min)
- By 10% bleach or 70% alcohol
- By pH extremes (<6 or >10)
- Sex/IVDU bypass these!

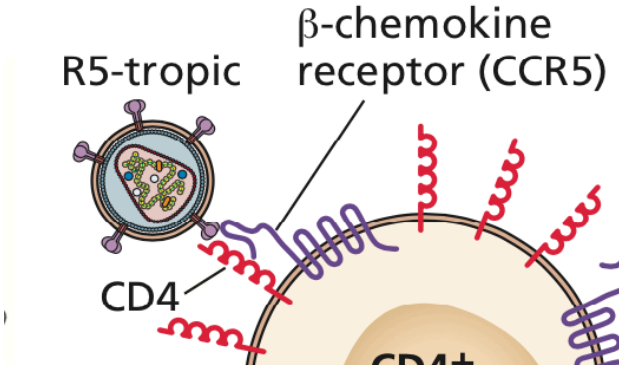
Risk of transmission of HIV-1

Mode	Infection risk per 10,000 exposures
Sexual transmission	
Receptive anal sex	138
Insertive anal sex	11
Reeptive penile-vaginal sex	8
Insertive penile-vaginal sex	4
Parenteral	
Transfusion of infected blood	9250
Needle sharing	63
Needle stick	23
Needle stick /AZT PEP	1
Mother to infant	
Without AZT	2260
With AZT	<1000

Co-receptors



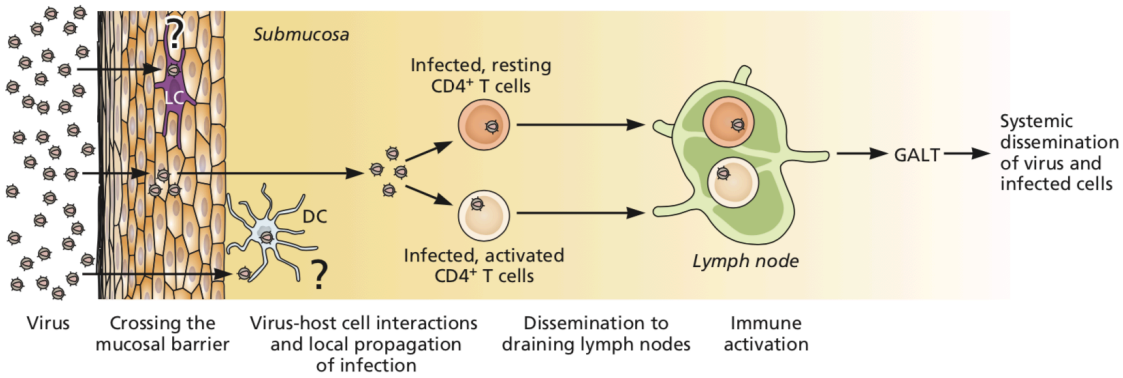
Host genes that determine susceptibility



- Ccr5-delta32 mutation protects vs HIV-1 infection
- Present in 4-16% of European descent
- Stem cell therapy cured German and London AIDS patients

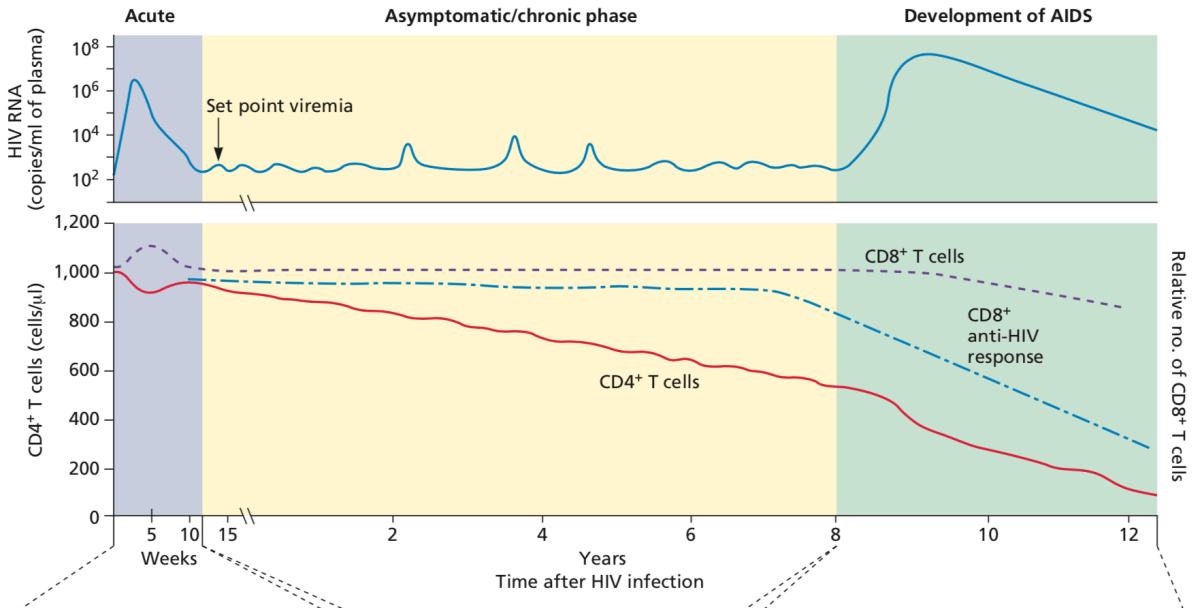
  http://www.virology.ws/2019/03/13/the-london-patient/
- Disrupting *ccr5* with Crispr/cas9
- Recent reports of spontaneous cures

Primary HIV Infection



- Virus-dendritic cell interaction (no activation)
  - Infection typically with CCR5 binding strains
  - Importance of DC-SIGN (dendritic cell-specific, Icam-3 grabbing nonintegrin)
- Delivery of virus to lymph nodes
- Active replication in lymphoid tissue
- High levels of viremia and dissemination
- Down-regulation of virus replication by immune response
- Viral set point reached after ~6 months

Progression of HIV Infection



Acute phase

Symptoms
Swollen lymph nodes (Lymphadenopathy)
Fever
Diarrhea

At cellular level
$CD4^+$ T cells decline temporarily
$CD8^+$ T cells increase temporarily (homeostasis) & anti-HIV-1 CTLs increase temporarily
B cells: anti-HIV-1 antibodies appear

Chronic phase

Symptoms
Usually: no symptoms
Sporadically: fatigue, mild weight loss, generalized lymphadenopathy, rash, shingles

At cellular level
$CD4^+$ T cells gradually decline
$CD8^+$ T cells: levels largely unaffected and CTL responses evolve
B cells: co-evolution of anti-viral antibodies and viral antigens
Acquisition of macrophage tropism
Infection of central nervous system (in some patients)

Symptomatic phase

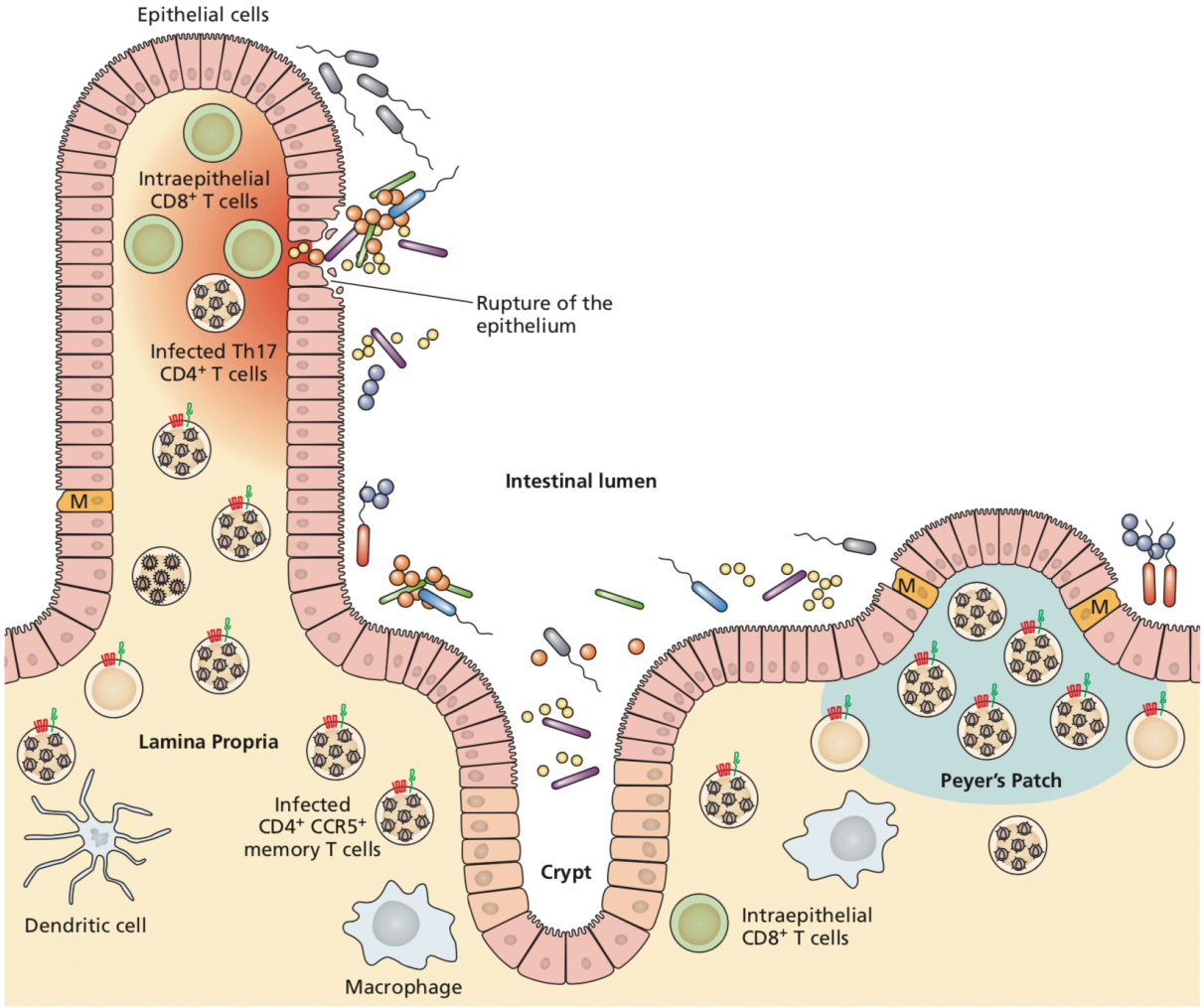
Symptoms
200-500 $CD4^+$ T cells/ml
Oral/skin lesions
Genital warts
Development of Kaposis's sarcoma
Reactivation of latent Mycobacterium tuberculosis

<200 CD4+ T cells/ml
Opportunistic infections by protozoa/bacteria/fungi/viruses
Weight loss
Malignancies
Neurological symptoms

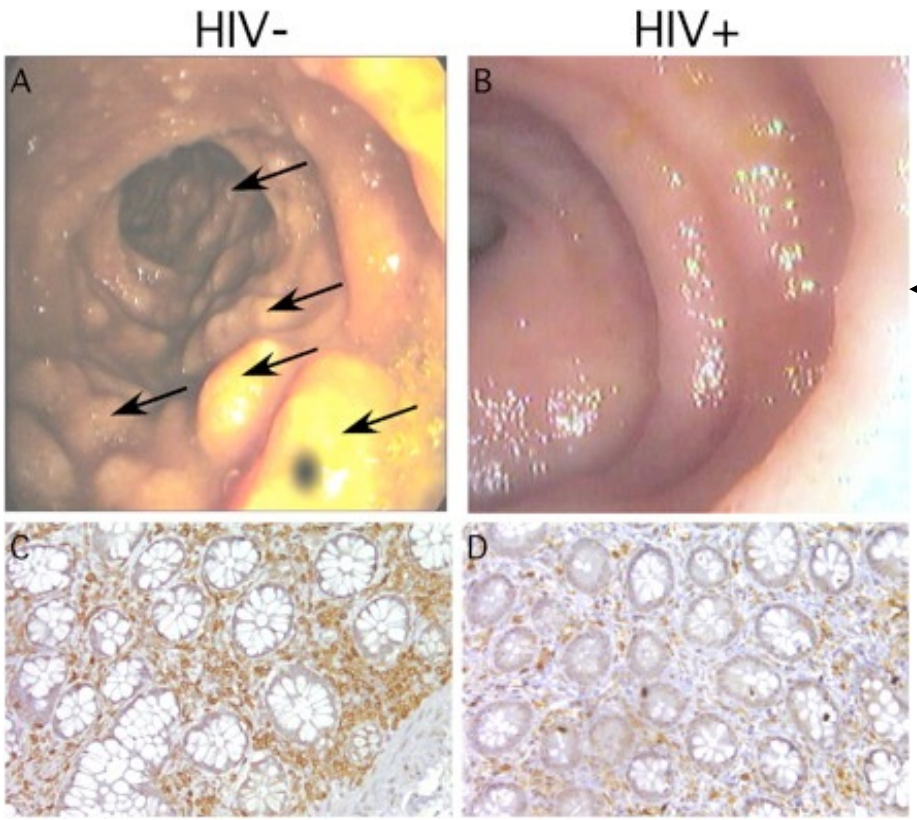
At cellular level
$CD4^+$ T cell depletion, loss of helper function
HIV-1-specific $CD4^+/CD8^+$ T cell exhaustion
B cells: decrease/dysregulation
natural killer (NK) cells: impairment of function

Principles of Virology, ASM Press

Effects of HIV-1 infection on intestinal mucosa

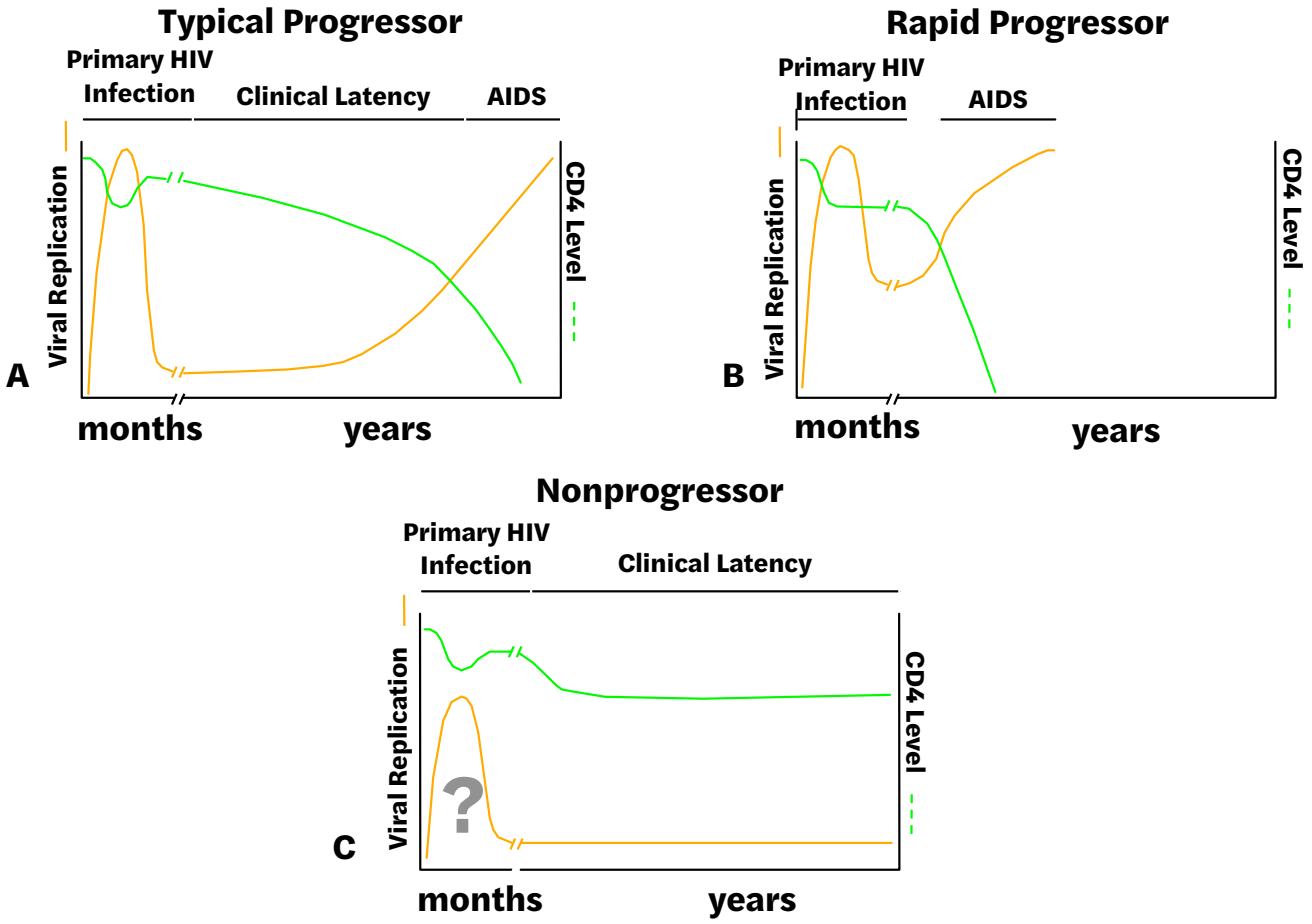


GI associated lymphoid tissue following acute infection



Absence of lymphoid cell aggregates in terminal Ileum

The variable course of HIV-1 infection



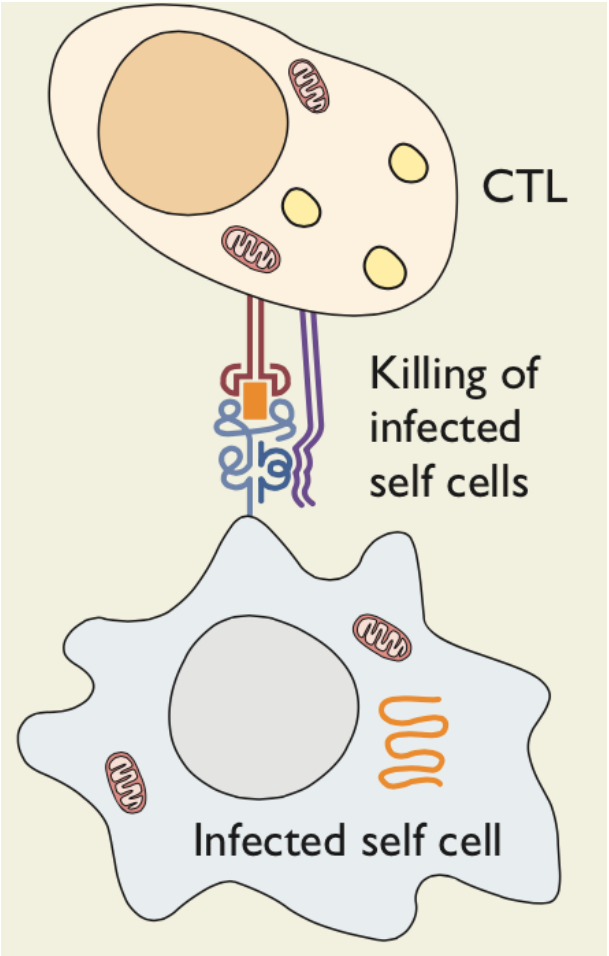
Elite HIV Controllers

- Individuals who maintain normal CD4 counts and undetectable viral loads (1-30 copies HIV RNA/ml of plasma) for >10 years in the absence of antiretroviral therapy

  - Estimated at 1/300 infected persons

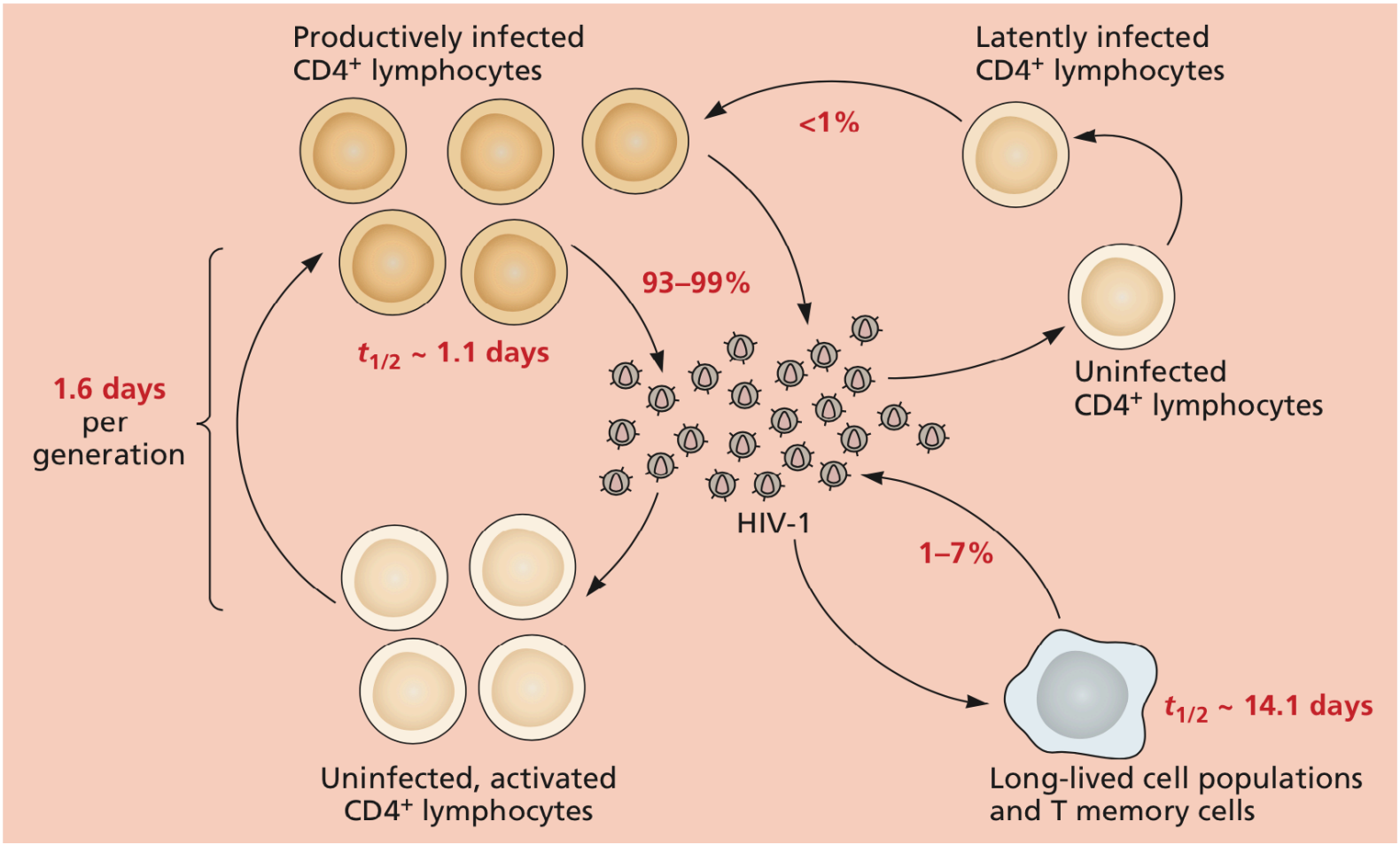
- 20% are associated with favorable HLA (MHC) types (esp HLA B57 and B27) and T-cell responses (CD4 and CD8) to Gag

- Not associated with attenuated viruses

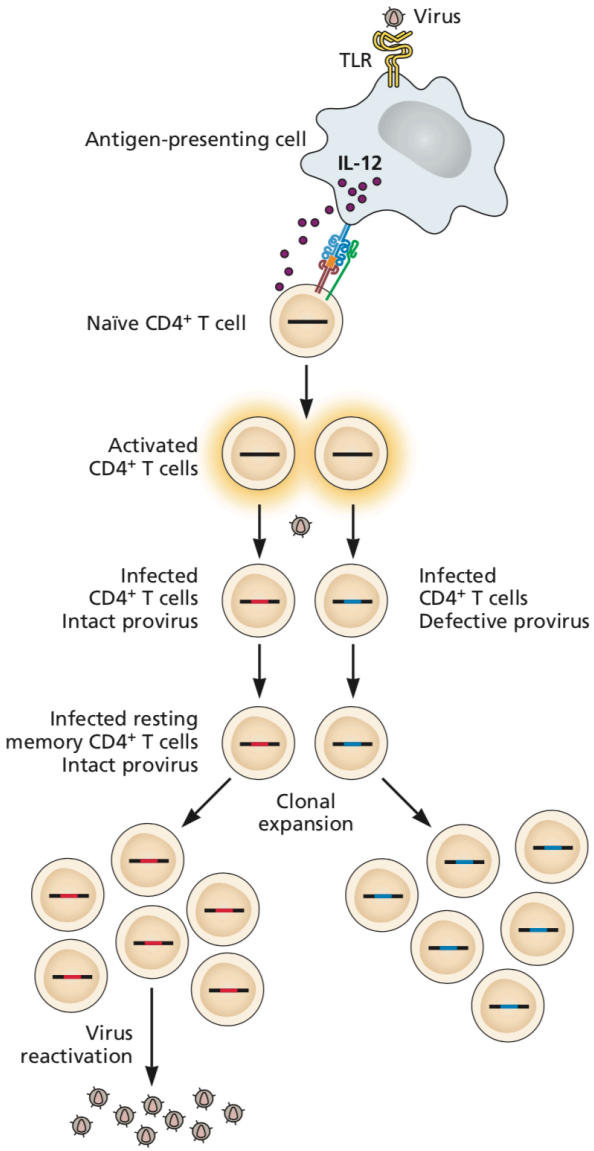


Principles of Virology, ASM Press

HIV-1 dynamics

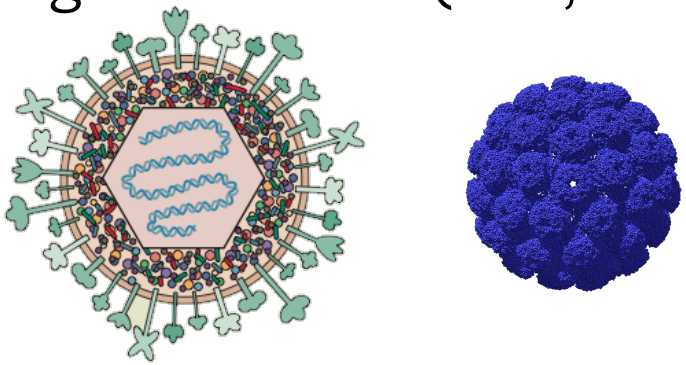


HIV-1 latency

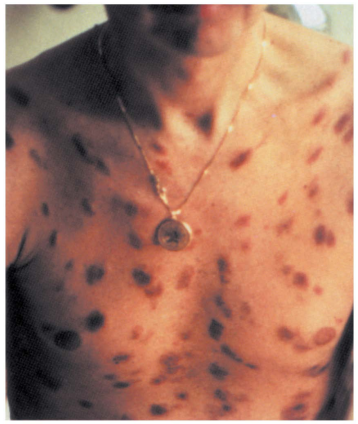


HIV and cancer

- HIV-1 infection leads to increased incidence of malignancy: 40% of infected individuals
- An indirect effect of dysregulation of the immune system
  - Absence of proper immune surveillance
  - High levels of cytokines leads to inappropriate cell proliferation, replication of oncogenic viruses (EBV, HHV8, HPV), angiogenesis

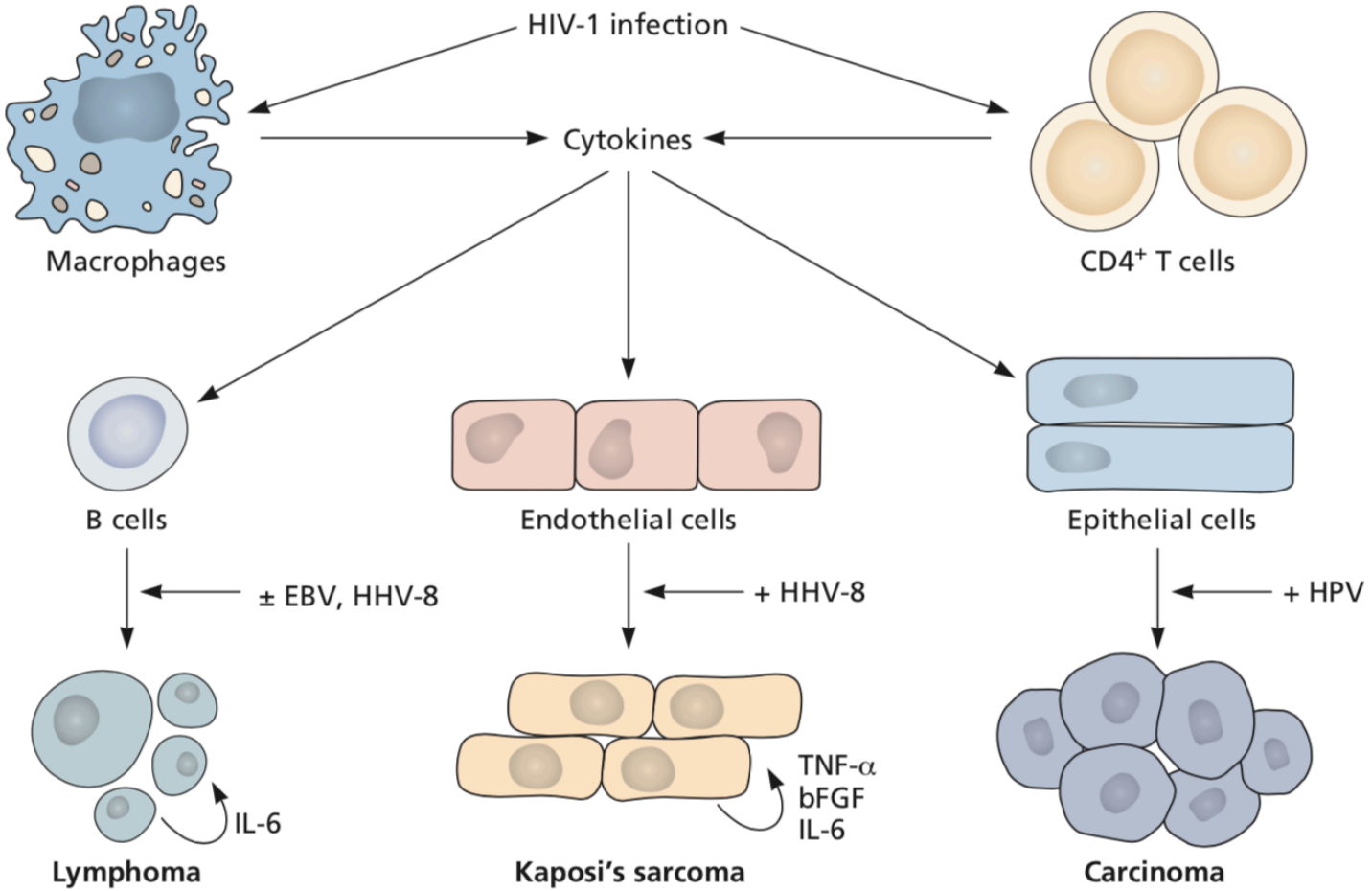


Kaposi's sarcoma



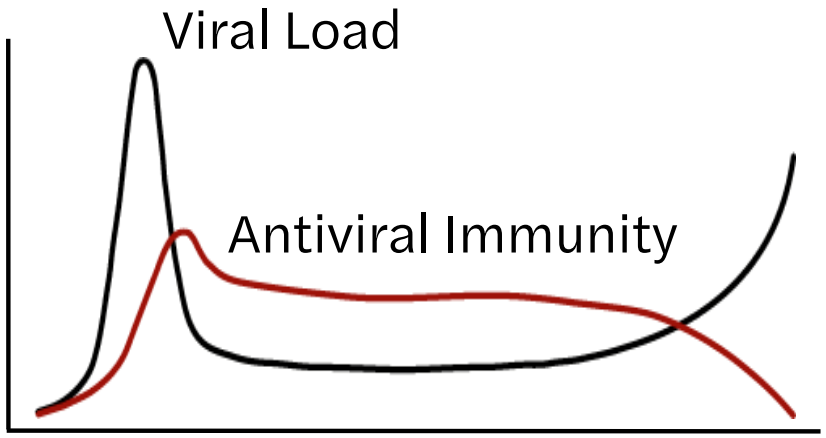
- Described 1872 by Hungarian physician
- Pre-AIDS: mainly in older Mediterranean men
- Occurs in 20% of HIV-1 infected homosexual men, 2% of HIV-1 infected women, transfusion recipients
- Infection with human herpesvirus 8 is necessary for development of KS

Induction of cancers in HIV-1 infected patients



Question break

Is an HIV-1 vaccine possible?

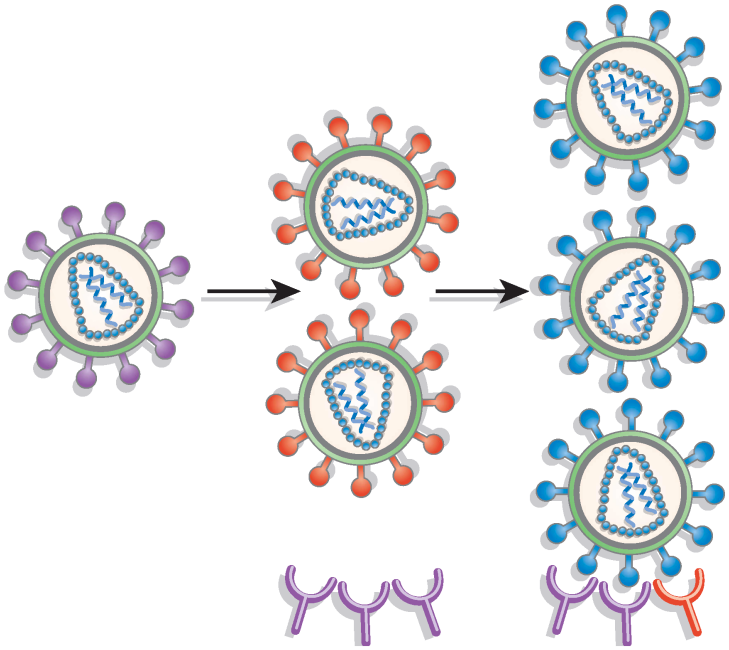


How does HIV-1 persist despite effective anti-viral immunity?

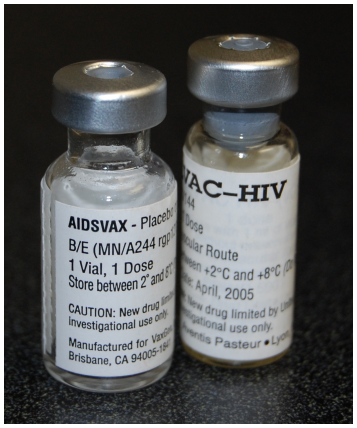
How does it eventually outstrip immune control?

HIV-1 superinfection occurs less frequently than initial infection

HIV-1 escape from neutralizing antibody



RV144

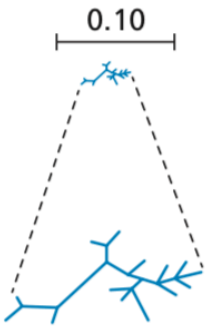


- Prime-boost: ALVAC-HIV (gag, pol, env in canarypox vector) and AIDSVAX B/E (recombinant gp120 protein)
- 16,000 adult volunteers in Thailand
- 6 prime, 6 boost injections
- Lowered rate of HIV-1 infection by 31.2% compared with placebo
- n=51 vs n=74

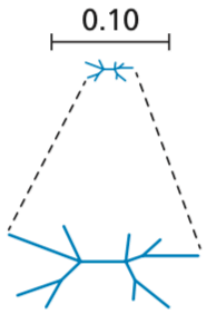
http://www.nejm.org/doi/full/10.1056/NEJMoa0908492

HIV-1 envelope and influenza virus HA diversity

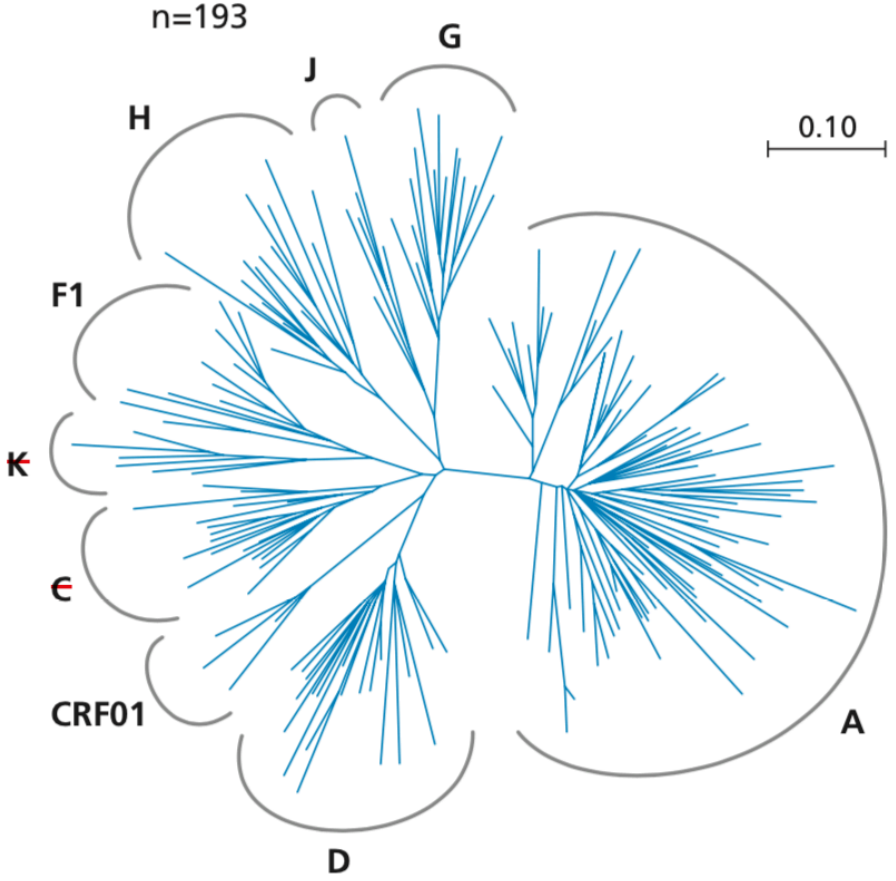
A **1996 Influenza sequence**
Hemagglutinin (H3)
n=96



B **HIV-1 Single Individual**
Subtype B
n=9

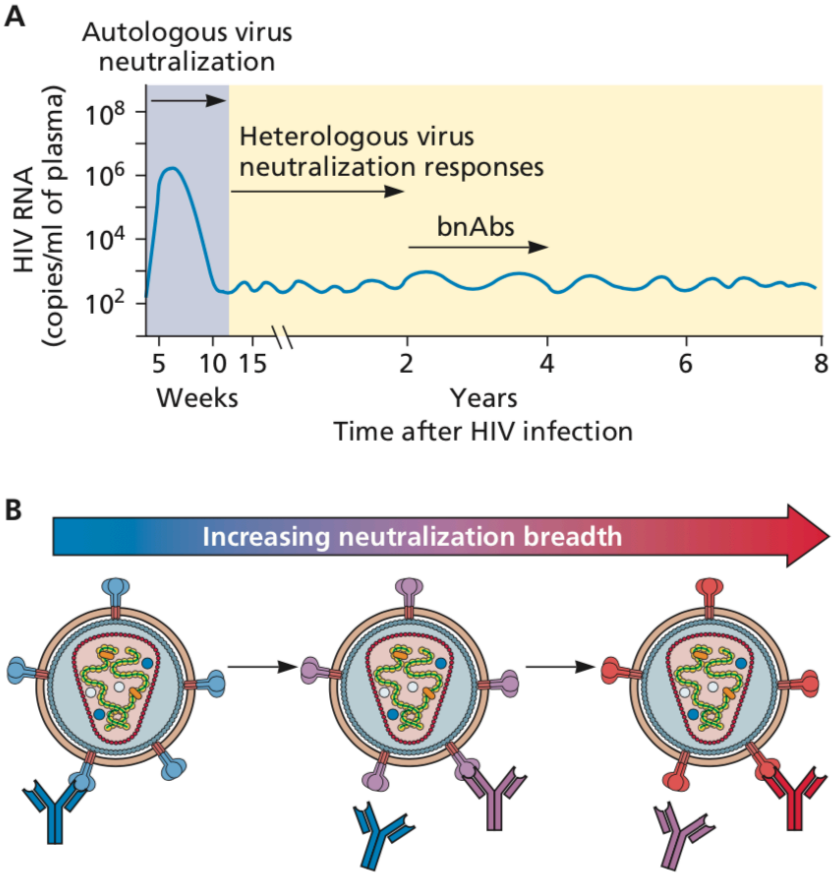


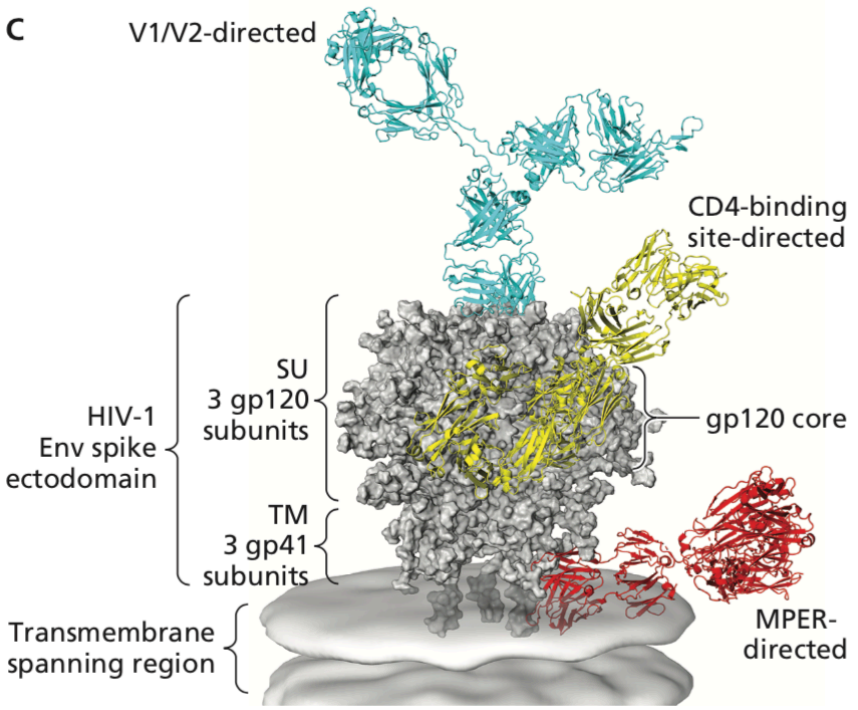
C **Democratic Republic of the Congo**
1997
n=193



Principles of Virology, ASM Press

Broadly neutralizing antibodies





Confronting persistence and latency

- Eradicating all HIV-1 is challenging due to long-lived latent reservoir
- Intense drug therapy + broadly nAb failed
- Shock and kill: Induce provirus expression, treat with antiviral drugs
- Block and lock: Complete and irreversible inhibition of genome transcription

SIV

~1921: Patient zero

HIV-1

75,000,000 infections

32,000,000 deaths

Next time: Unusual infectious agents