

# **HIV and AIDS**

Lecture 24

Biology W3310/W4310

Virology

Spring 2016

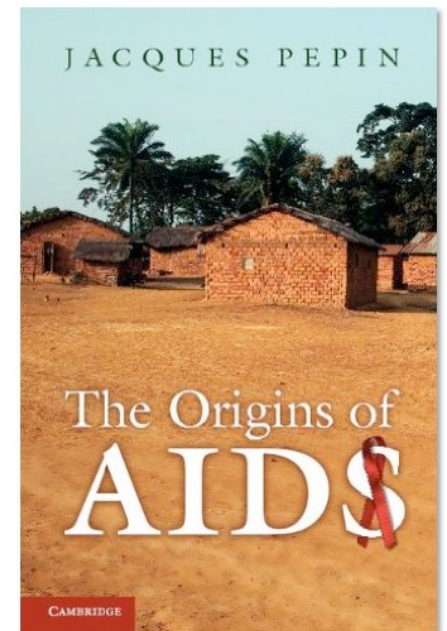
*Nature is not human-hearted*

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.



### Epidemiologic Notes and Reports

[http://www.cdc.gov/mmwr/preview/mmwrhtml/june\\_5.htm](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 viremia. 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 viremia, 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.

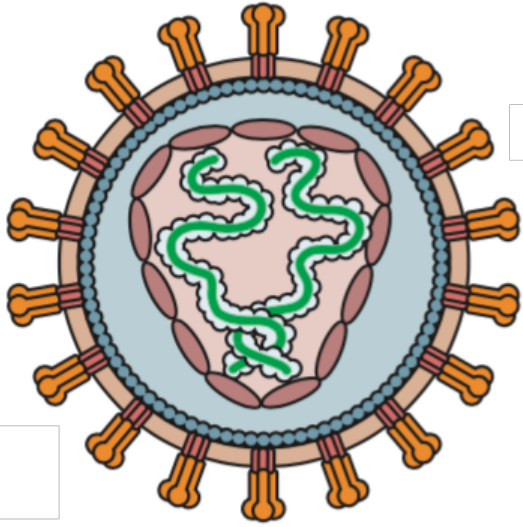
**Editorial Note:** *Pneumocystis pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients* (1). The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these 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 viremia; rates for 101 controls of similar age who were reported to be exclusively heterosexual were 54% for seropositivity and zero for viremia (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.

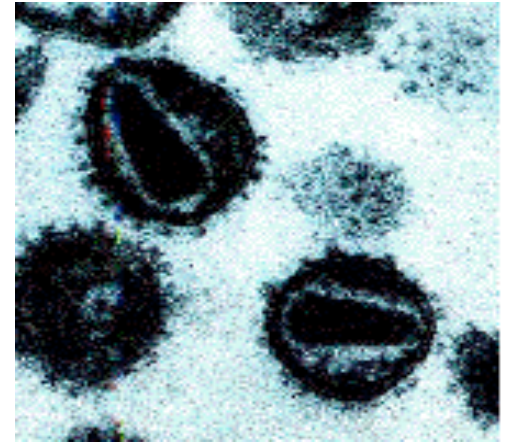
# AIDS

- 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



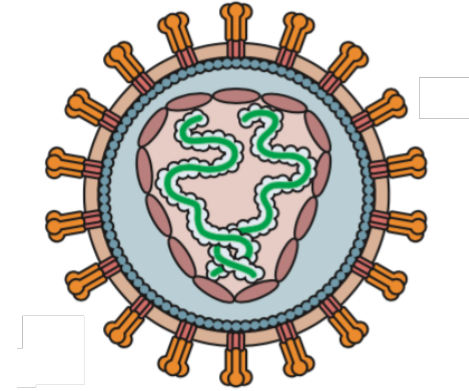


# HIV is a lentivirus



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

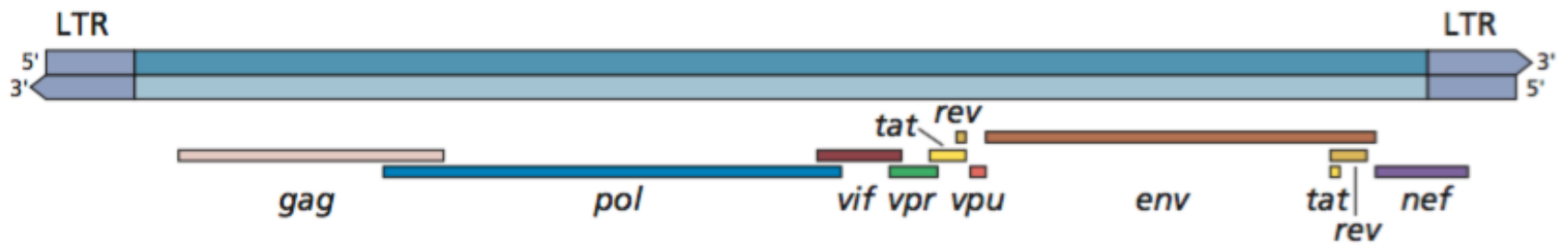
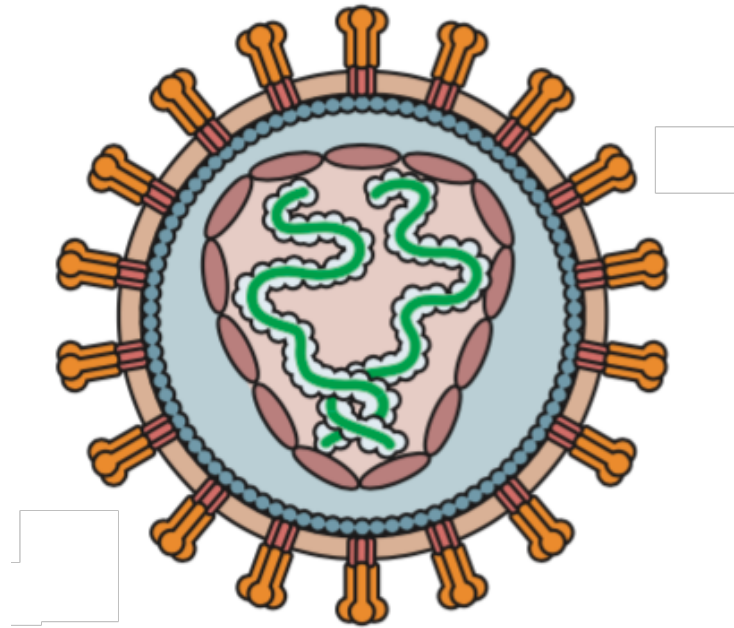
# ***Retroviridae***



- *Orthoretrovirinae* (subfamily)
  - Alpharetrovirus (Avian leukosis virus)
  - Betaretrovirus
  - Gammaretrovirus
  - Deltaretrovirus (Human T cell lymphotropic virus 1,2 ,3)
  - Epsilonretrovirus (Walleye dermal sarcoma virus)
  - Spumavirus
  - 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



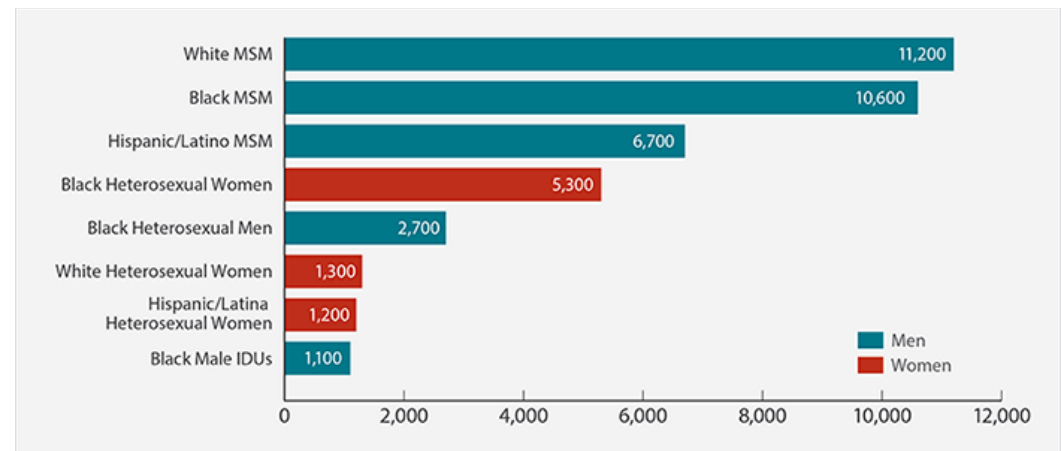
# **HIV and AIDS: Acquired ImmunoDeficiency Syndrome**

- 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 causes AIDS has been tested by inadvertent infection of people with HIV-contaminated blood



# HIV/AIDS pandemic

- In the US, HIV has killed over 600,000, exceeding all US combat-related deaths in all wars fought in the 20th century
- >1.2 million in the US are infected; 13% unaware
- 50,000 new infections/yr; 70% men, 30% women
- Half of all new infections in US occur in people 25 or younger



# Global summary of the AIDS epidemic | 2014

Number of people living  
with HIV in 2014

Total **36.9 million** [34.3 million – 41.4 million]  
Adults 34.3 million [31.8 million – 38.5 million]  
Women 17.4 million [16.1 million – 20.0 million]  
Children (<15 years) 2.6 million [2.4 million – 2.8 million]

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People newly infected  
with HIV in 2014

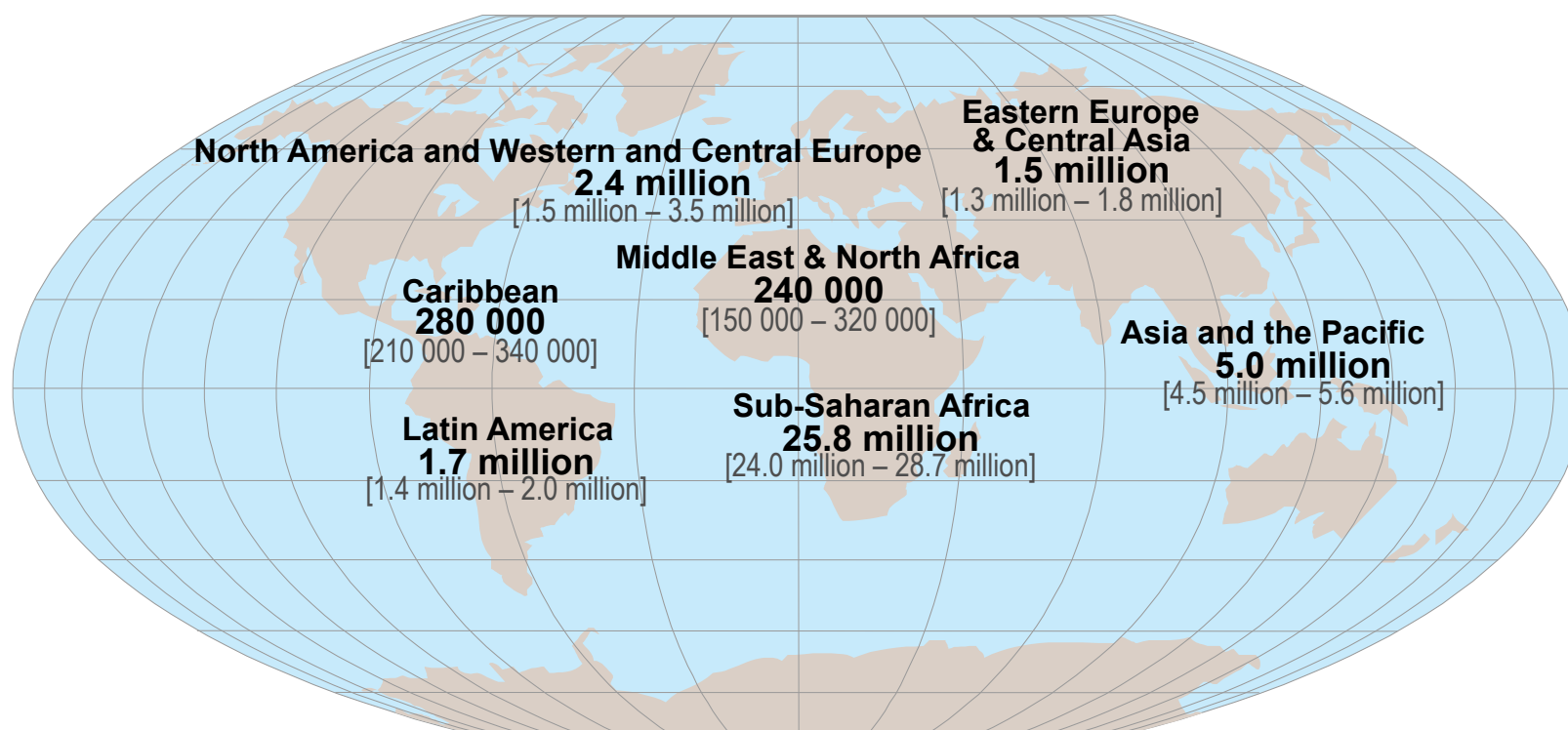
Total **2.0 million** [1.9 million – 2.2 million]  
Adults 1.8 million [1.7 million – 2.0 million]  
Children (<15 years) 220 000 [190 000 – 260 000]

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AIDS deaths in 2014

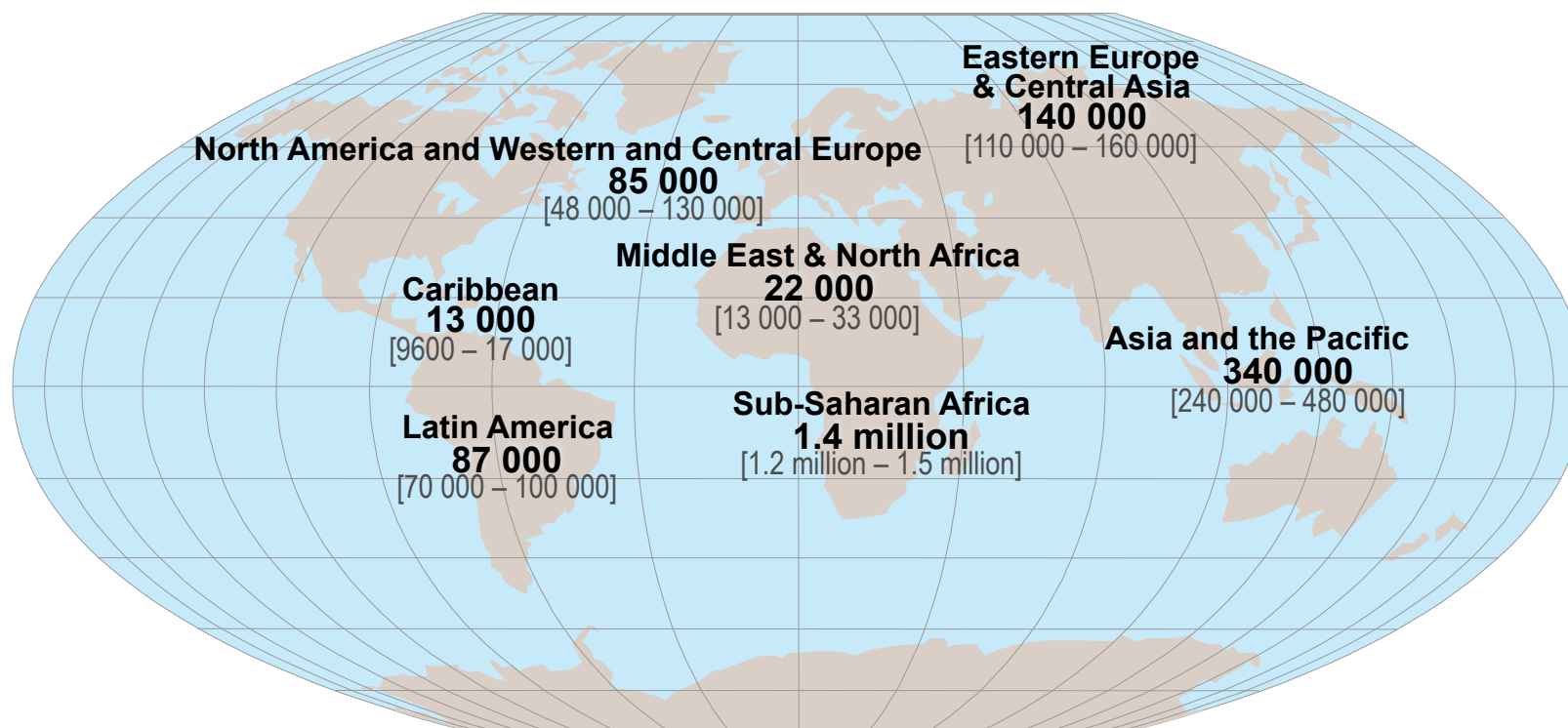
Total **1.2 million** [980 000 – 1.6 million]  
Adults 1.0 million [890 000 – 1.3 million]  
Children (<15 years) 150 000 [140 000 – 170 000]

# Adults and children estimated to be living with HIV | 2014



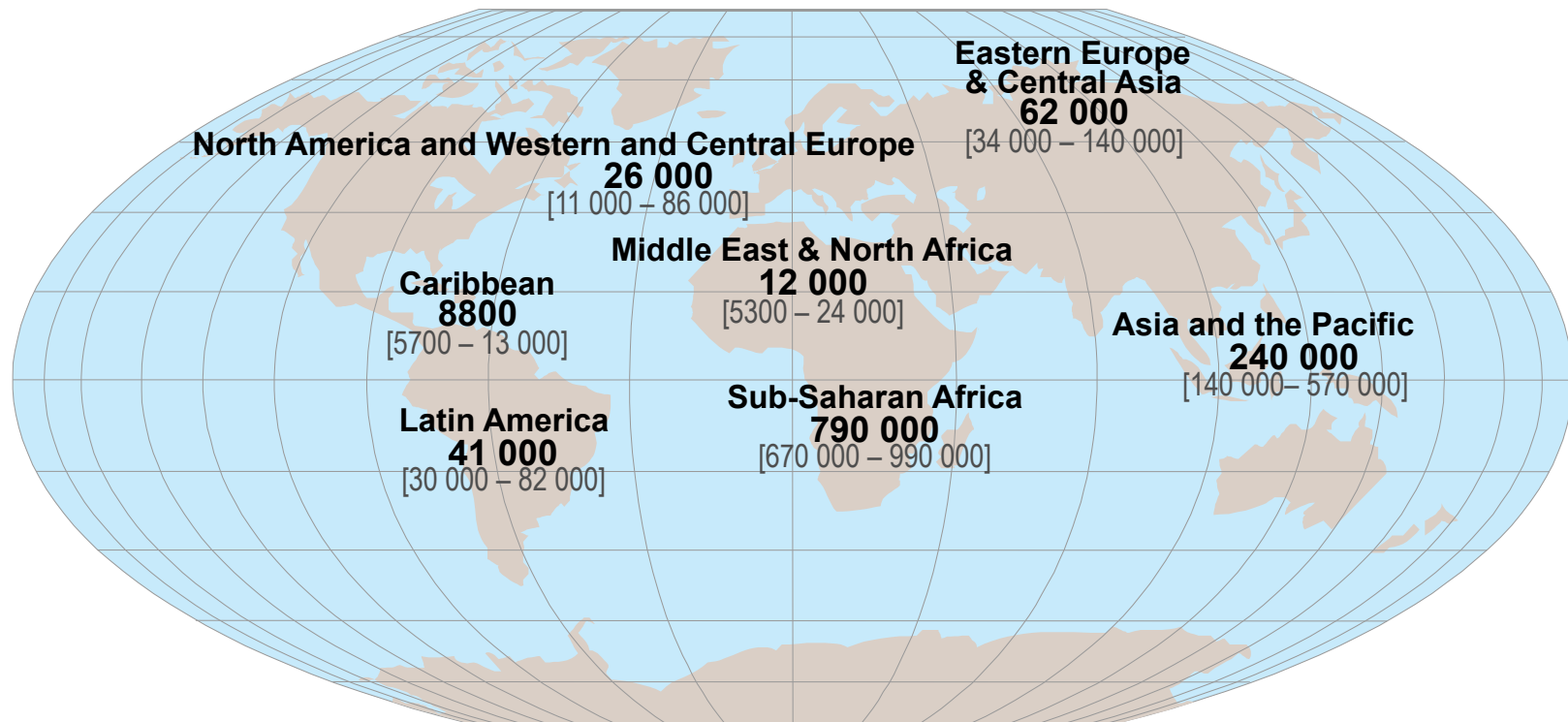
**Total: 36.9 million** [34.3 million – 41.4 million]

# Estimated number of adults and children newly infected with HIV | 2014



**Total: 2.0 million** [1.9 million – 2.2 million]

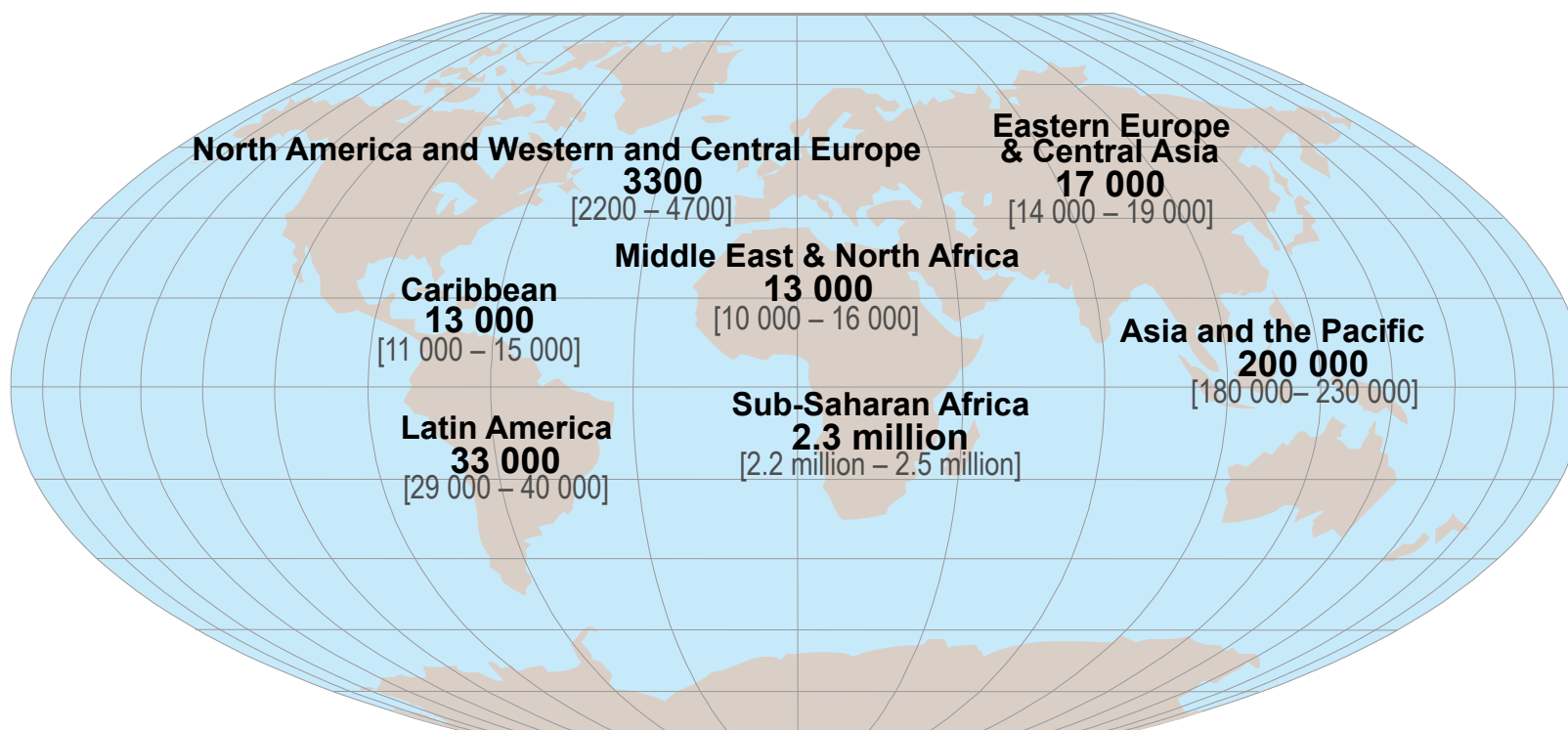
# Estimated adult and child deaths from AIDS | 2014



**Total: 1.2 million** [980 000 – 1.6 million]

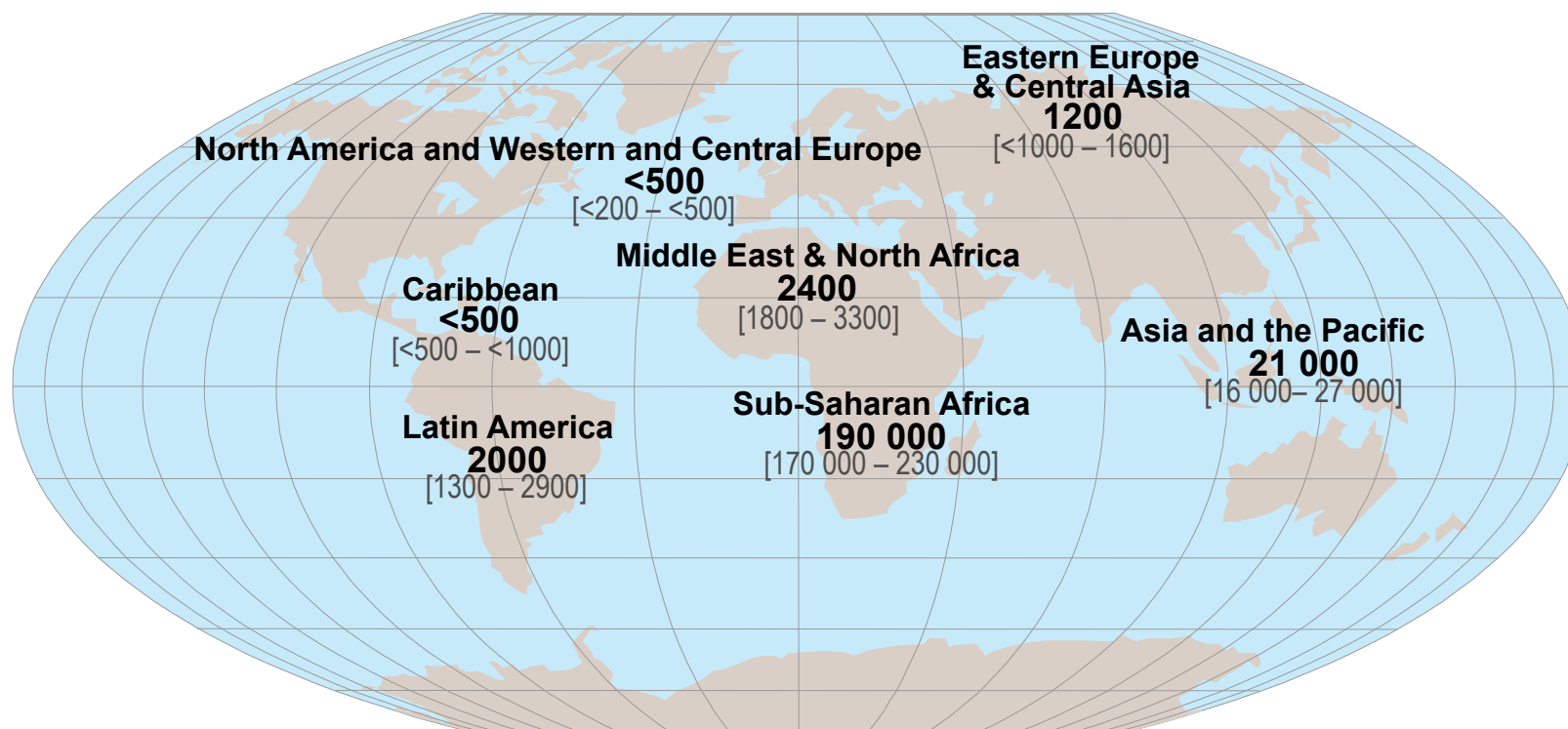


# Children (<15 years) estimated to be living with HIV | 2014



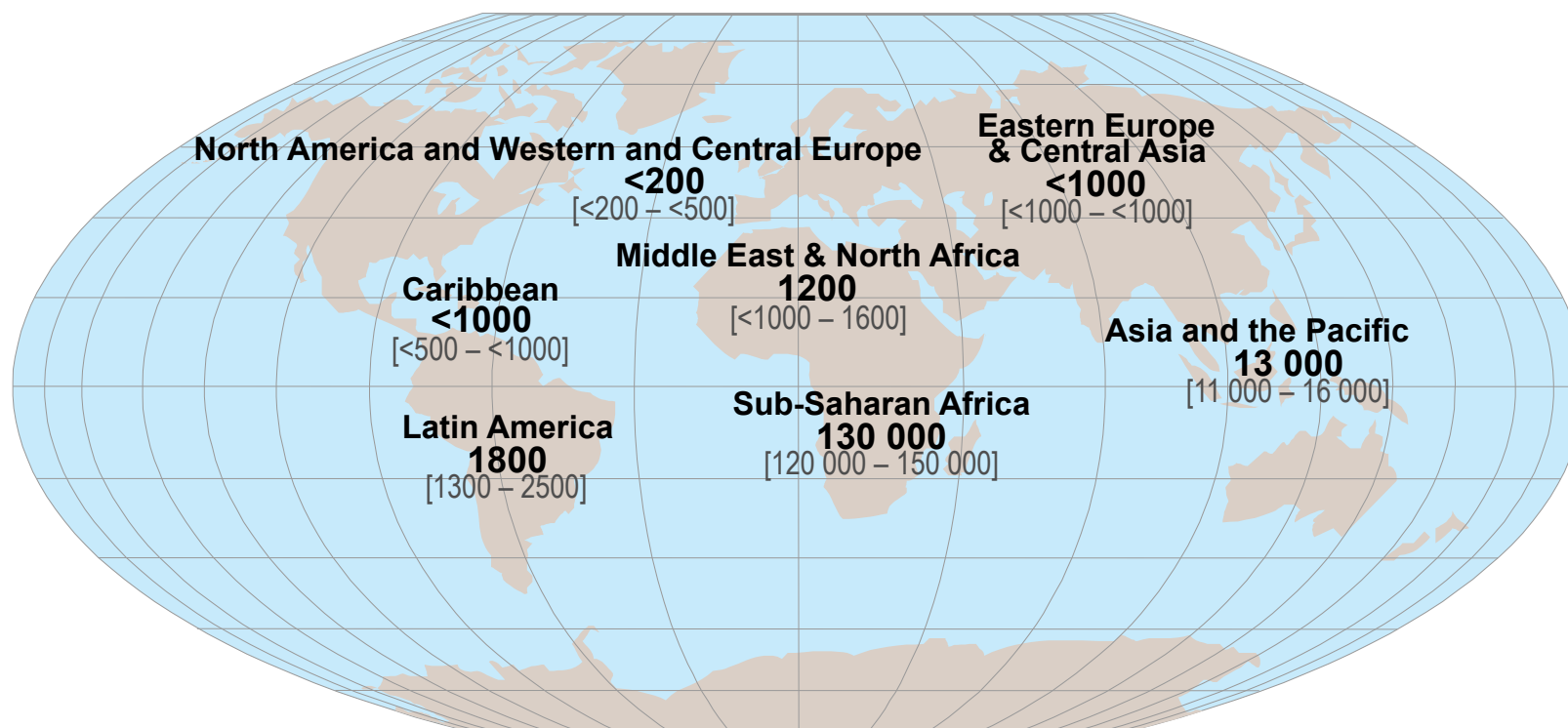
**Total: 2.6 million** [2.4 million – 2.8 million]

# Estimated number of children (<15 years) newly infected with HIV | 2014



**Total: 220 000** [190 000 – 260 000]

# Estimated deaths in children (<15 years) from AIDS | 2014



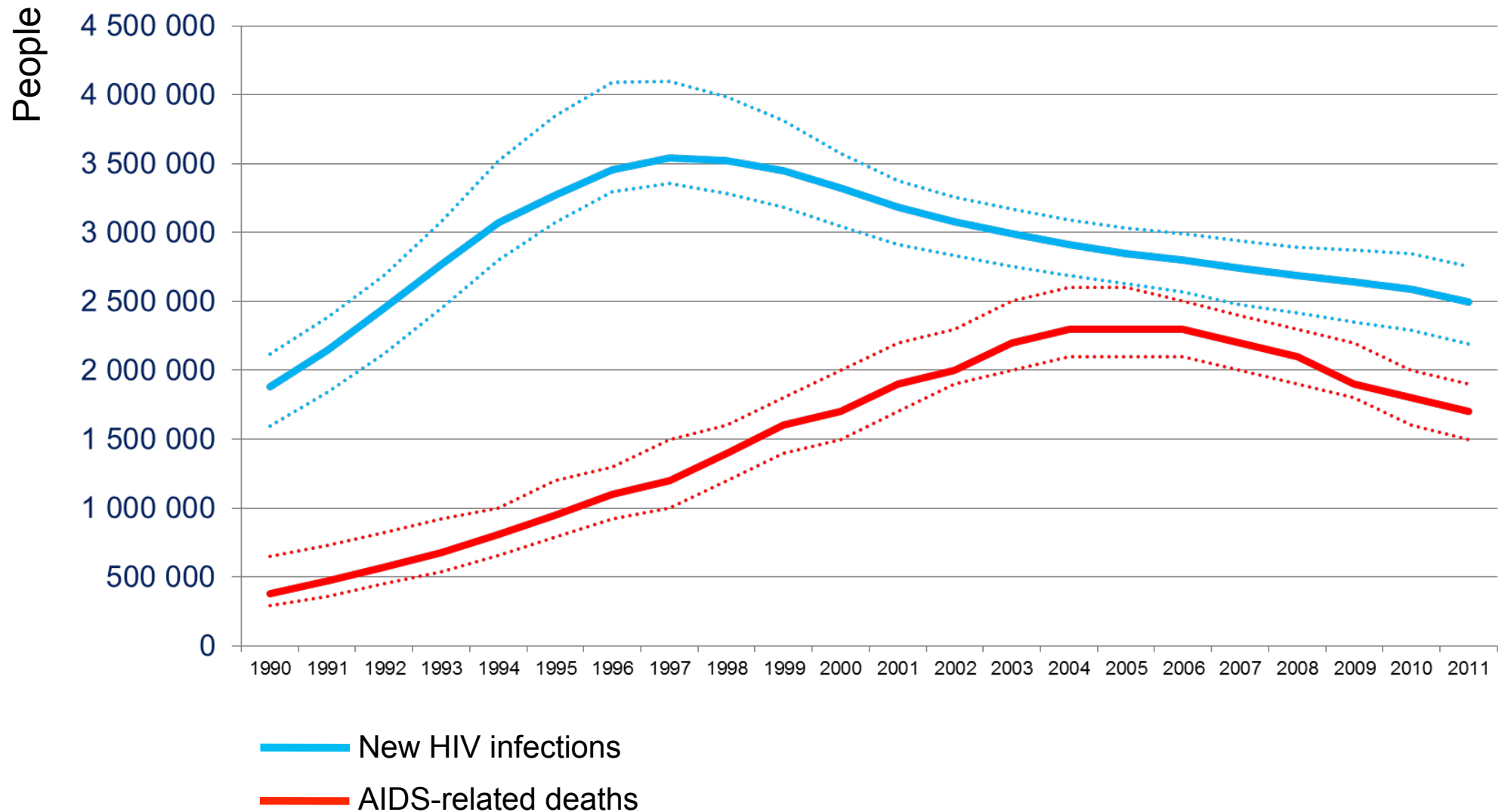
**Total: 150 000** [140 000 – 170 000]

# About 5,600 new HIV infections a day in 2014

- About 665 in Sub Saharan Africa
- About 600 in children <15 yo
- About 5,000 n adults >15 yo
  - 48% among women
  - 30% among young people (15-24 yo)

# New HIV infections and AIDS-related deaths

Globally new HIV infections peaked in 1997



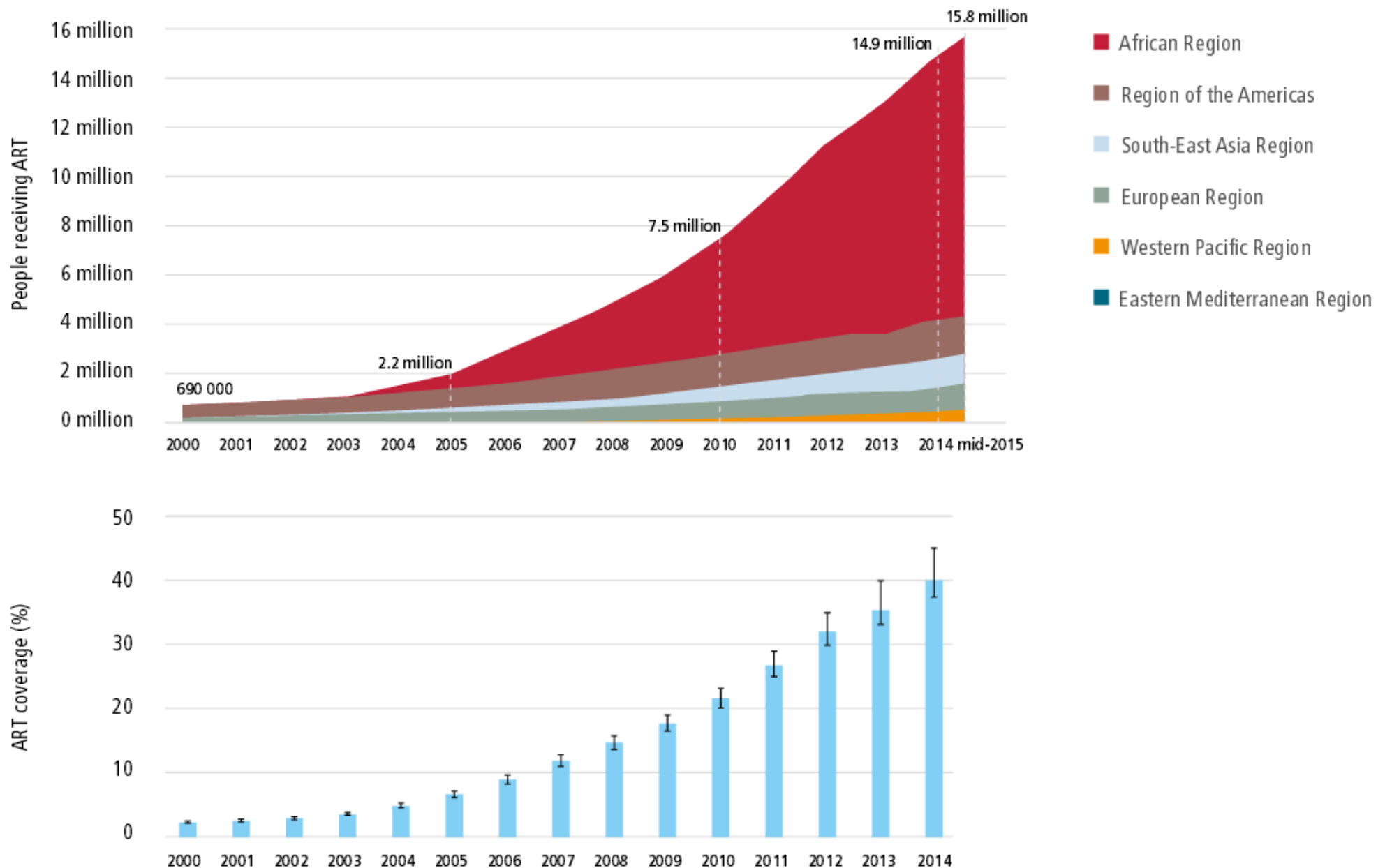


# Control of AIDS



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

## Estimated numbers of people receiving antiretroviral therapy globally and by WHO Region and percentage coverage globally, 2000–2015



Source: Global AIDS Response Progress Reporting (UNAIDS/UNICEF/WHO) and UNAIDS/WHO estimates.

# 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
- AIDS is becoming a Third World disease
  - Spreading unabated in sub-Saharan Africa

# 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)

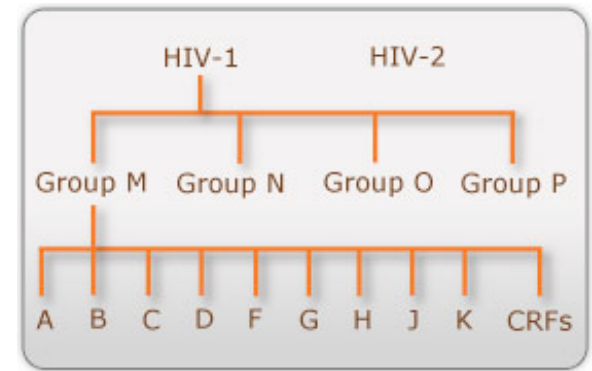


# Out of Africa



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

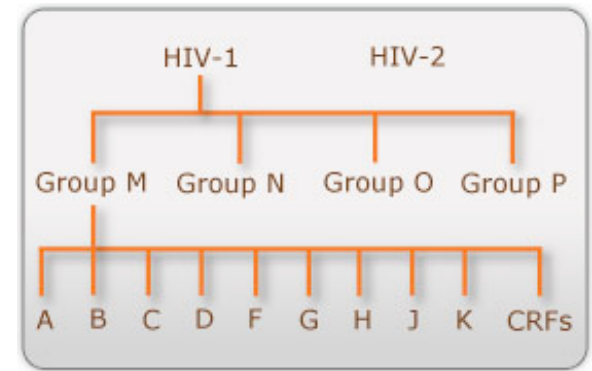
# HIV-1 diversity



- 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

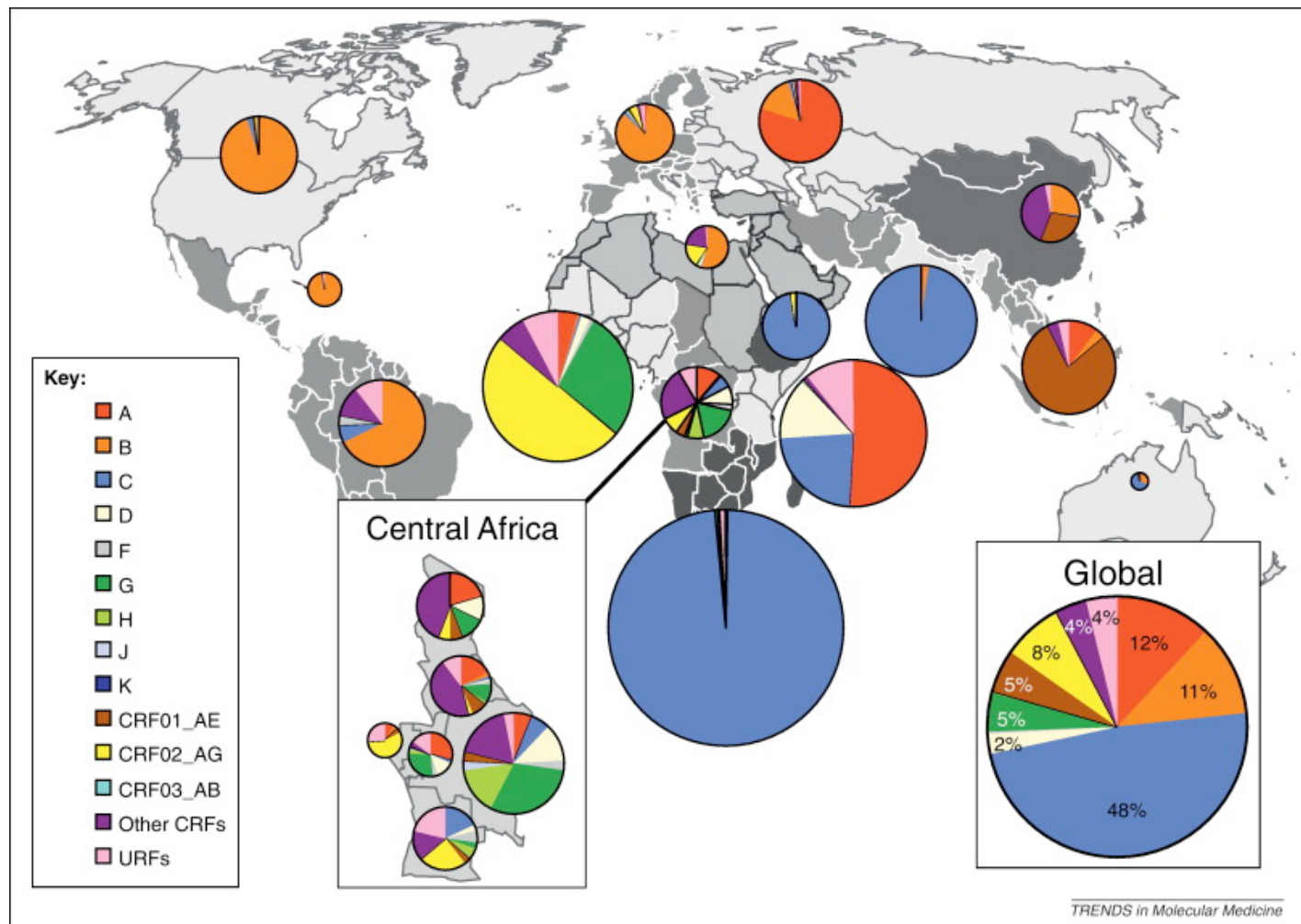
# HIV-1 subtypes

- 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

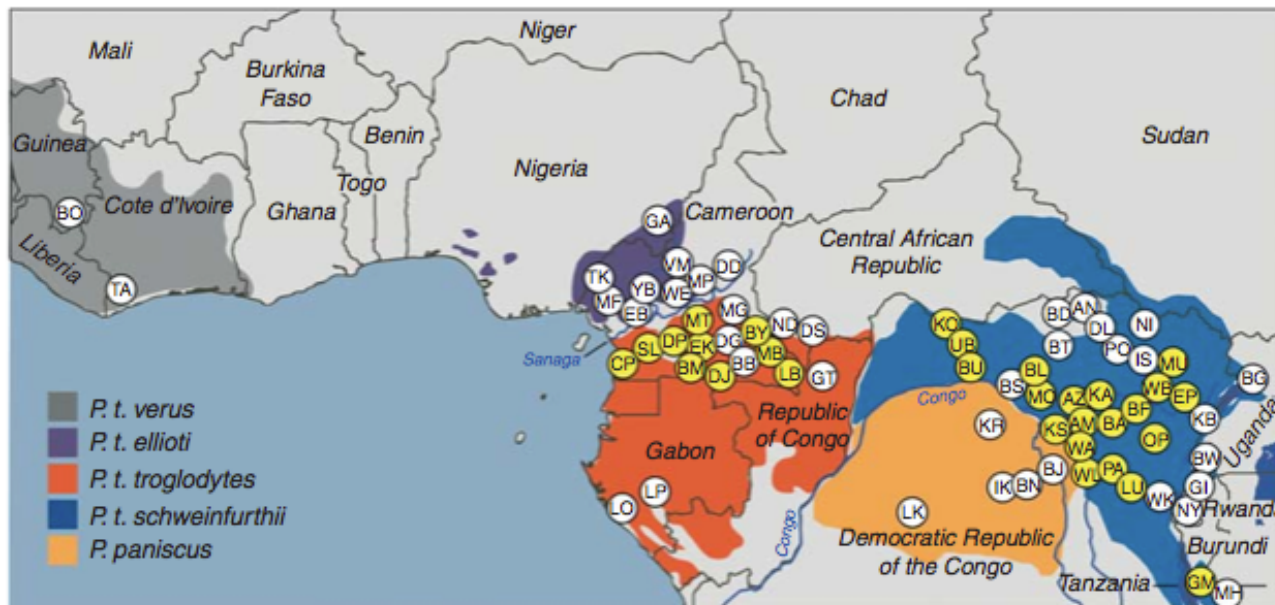
- Subtype C (50%), B and A (10-12%), G (6%), CRF02\_AG (5%), CRF01\_AE (5%), D (2.5%) of all HIV-1 infections
- Subtypes F, H, J, K limited transmission (<1%)





# 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



# 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, similar to AIDS

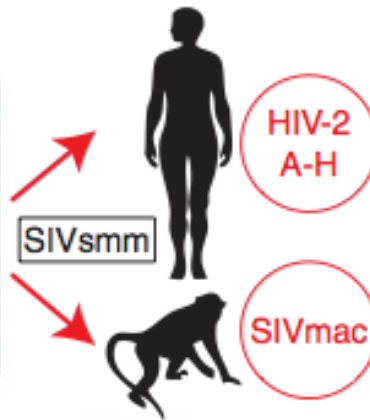




Sykes's monkey



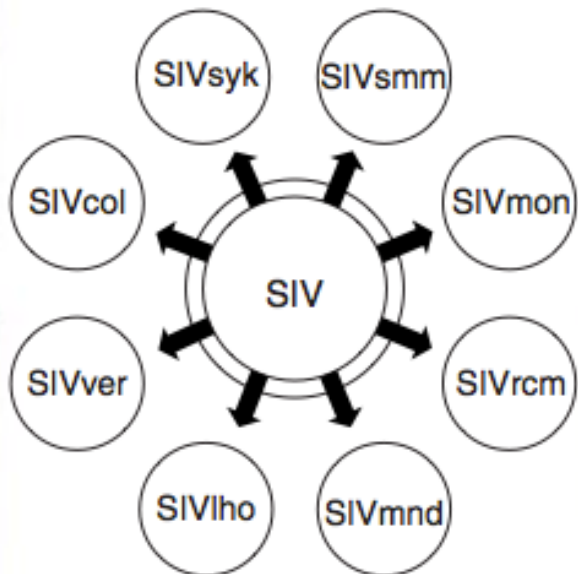
Sooty mangabey



Mantled guereza



Vervet monkey



Mona monkey



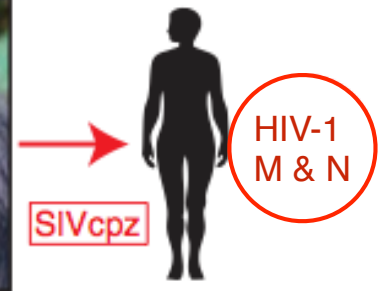
Red-capped mangabey

SIVgsn/SIVmus/SIVmon

*P.t.t.* of central Africa



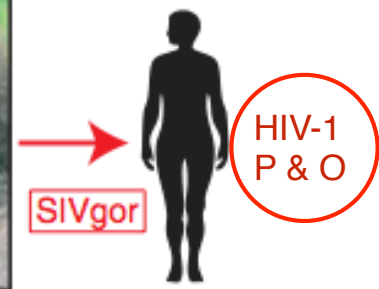
Chimpanzee



SIVrcm



Western gorilla



L'Hoest's monkey

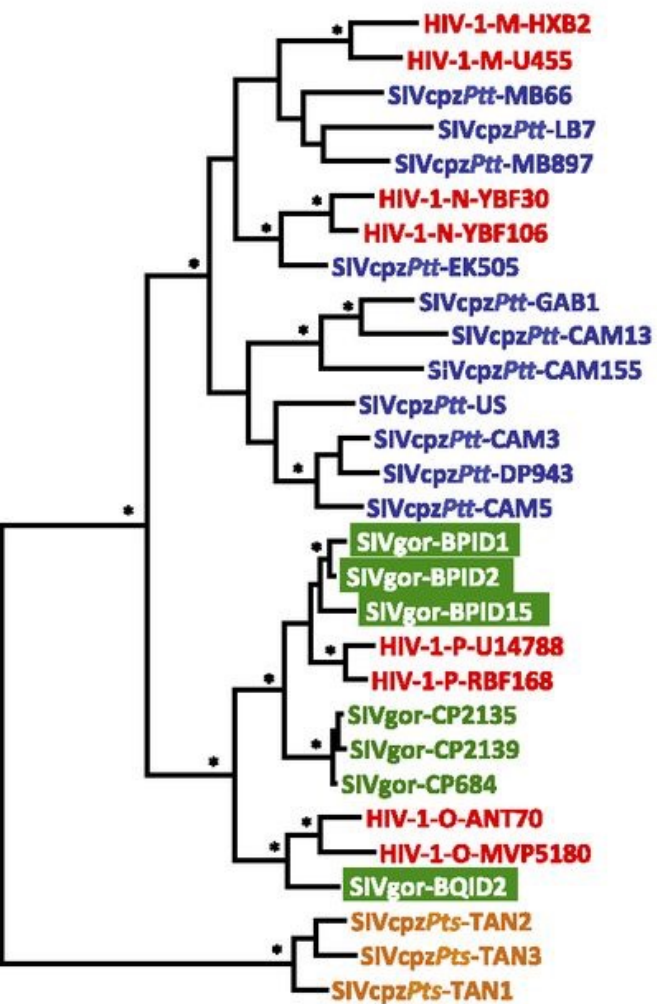


Mandrill

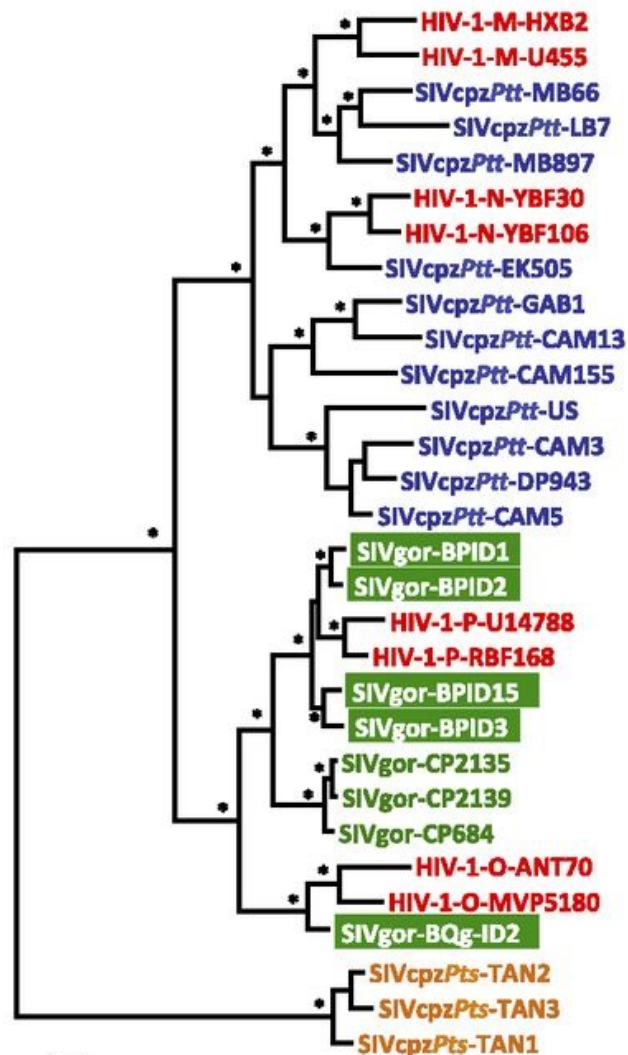
# Phylogenetics

- Phylogenetic trees measure the genetic distance between organisms, and identify the nearest relatives
- Each division in the tree is a 'node', the common ancestor of the organisms or the isolates identified to its right
- After such branching, the organisms and their sequences evolve independently. The 'root' (at the extreme left) is the assumed common ancestor of all organisms in the tree
- To construct a phylogenetic tree, compare differences in nucleotide sequences of many isolates of putatively related organisms
- Confidence increases if same findings obtained for multiple genes

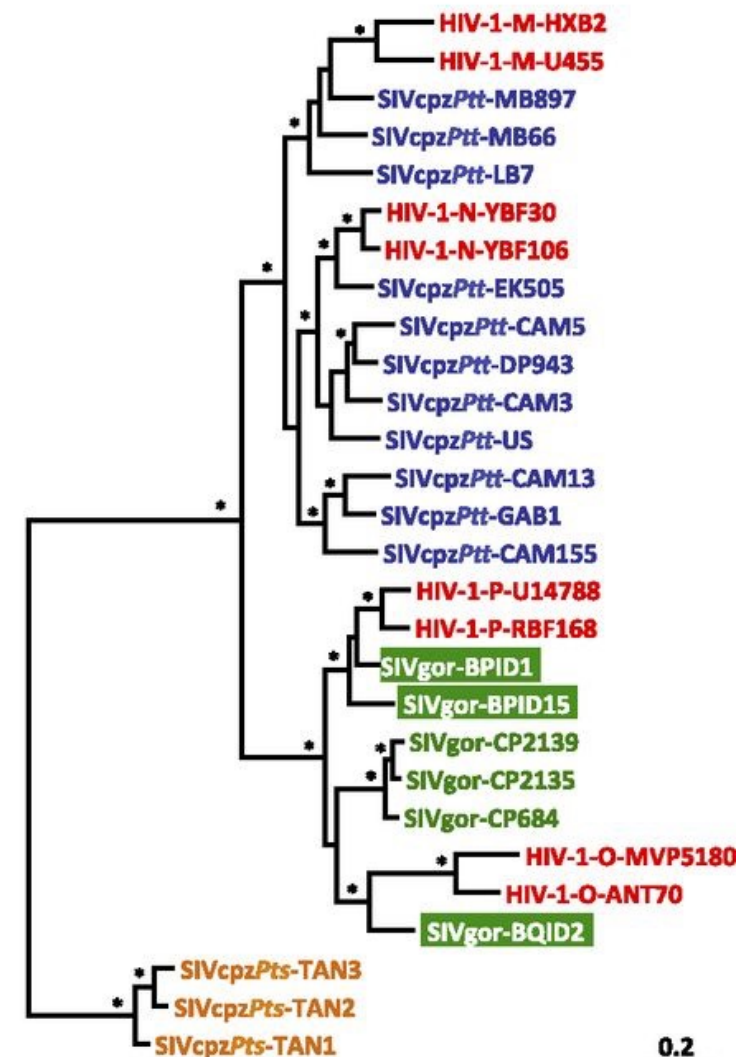
A Gag (488aa)



B Pol (927aa)



C Env/Nef (854aa)



# How did SIVcpz infect humans?

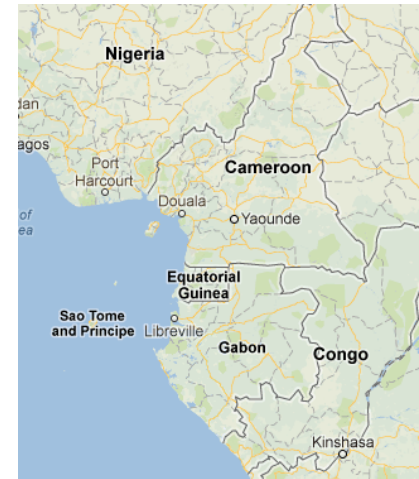
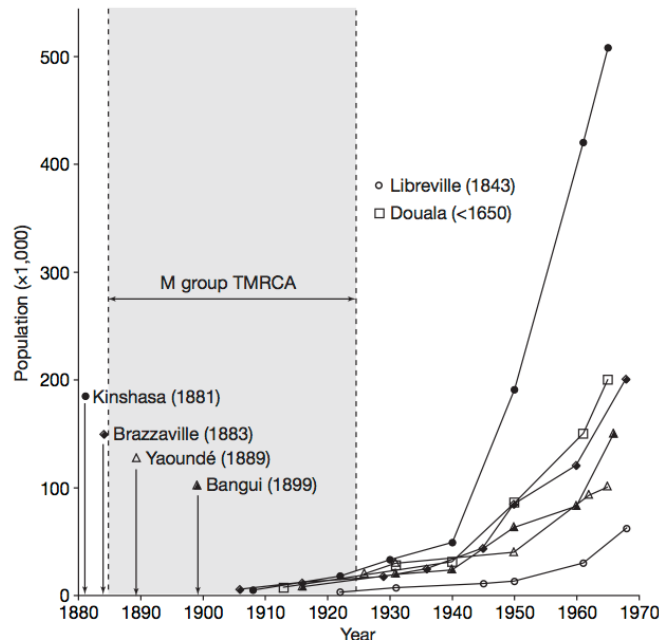
- The cut hunter: bushmeat hunting
- Cutaneous or mucous membrane exposure to infected chimpanzee blood, body fluids
- Calculations suggest that in 1921 number of people infected with SIVcpz was  $<10$ , but probably only one spread and multiplied
- Such cross-species infections probably have occurred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

# 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
- Kinshasa was epicenter, early spread concurrent with development of colonial cities



# Spread of HIV-1



- Leopoldville 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

# HIV-2

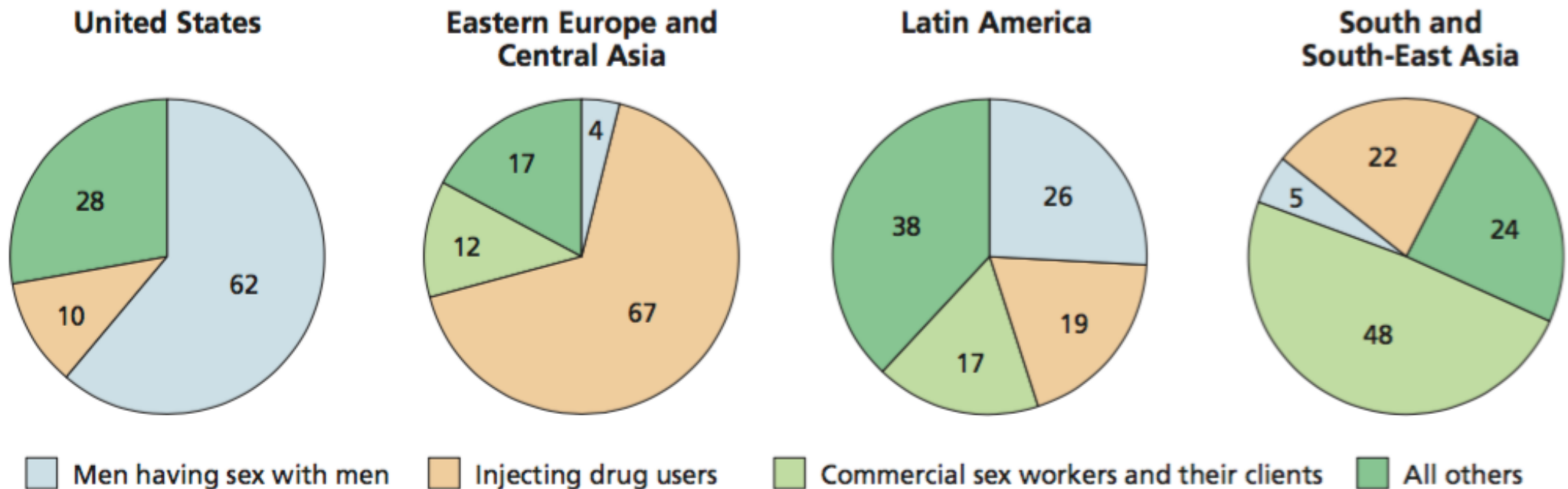
- First isolated Guinea-Bissau, 30-40% identity HIV-1
- Restricted primarily to populations in West Africa
- Less virulent (most infections do not progress to AIDS), transmissible than HIV-1, no mother-infant spread
- Crossover from sooty mangabey
- 8 distinct lineages, each arose from separate infection





# Transmission

- HIV is not a particularly infectious virus, not contagious like measles virus ( $R_0$  2-5)
- Not spread by respiratory, alimentary, or vector routes

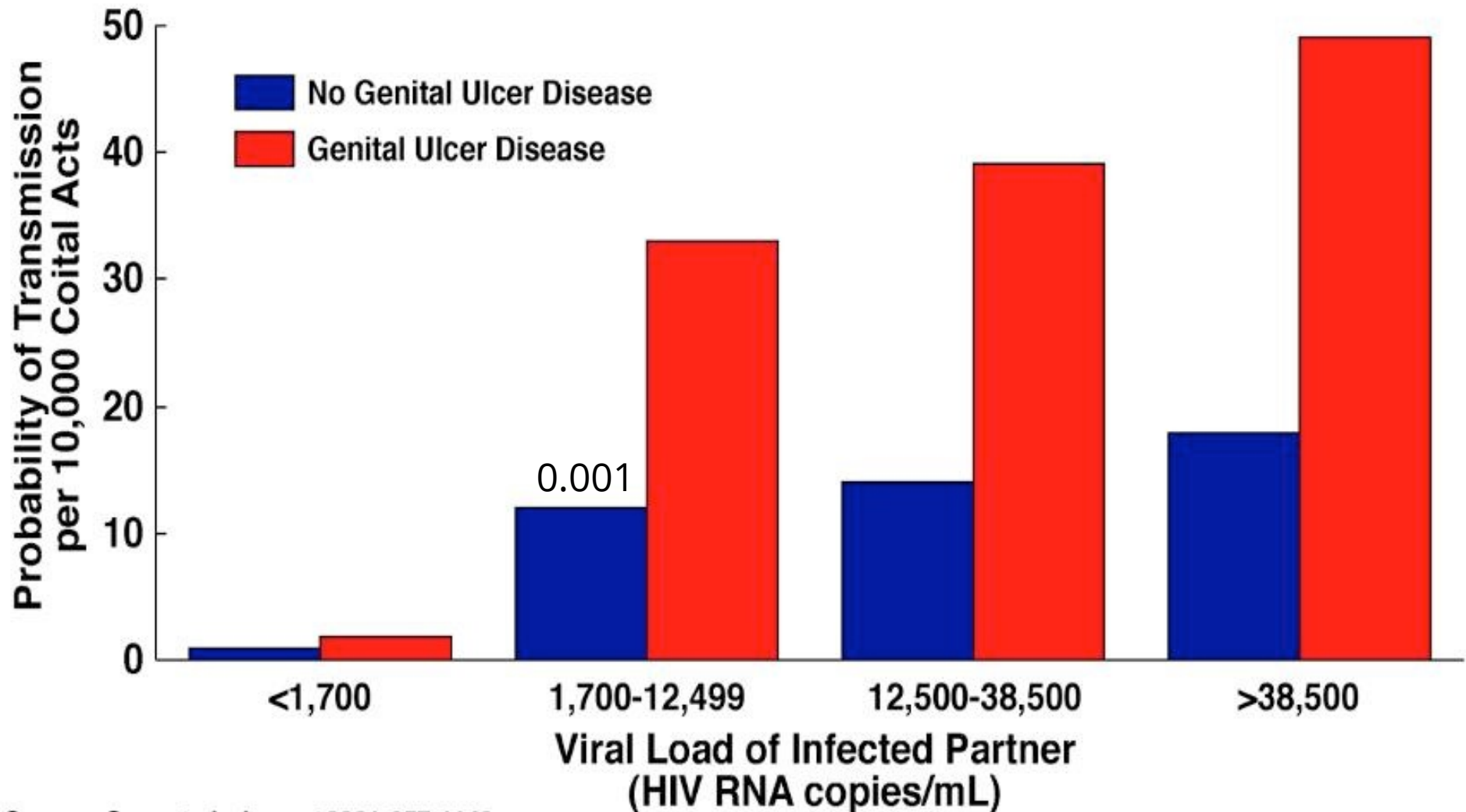


Mother to child at birth, ~5%

# Isolation of infectious HIV-1 from body fluids

	Fluid	Virus isolation <sup>b</sup>	Estimated quantity of virus <sup>c</sup>
	<b>Cell-free fluid</b>		
→	Cerebrospinal fluid	21/40	10–10,000
	Ear secretions	1/8	5–10
	Feces	0/2	None detected
	Milk	1/5	<1
→	Plasma	33/33	1–5,000 <sup>d</sup>
	Saliva	3/55	<1
→	Semen	5/15	10–50
	Sweat	0/2	None detected
	Tears	2/5	<1
	Urine	1/5	<1
	Vaginal-cervical	5/16	<1
	<b>Infected cells</b>		
	Bronchial fluid	3/24	Not determined
→	PBMC	89/92	0.001–1% <sup>d</sup>
	Saliva	4/11	<0.01%
→	Semen	11/28	0.01–5%
	Vaginal-cervical fluid	7/16	Not determined

# Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda



Source: Gray et al., *Lancet* 2001;257:1149

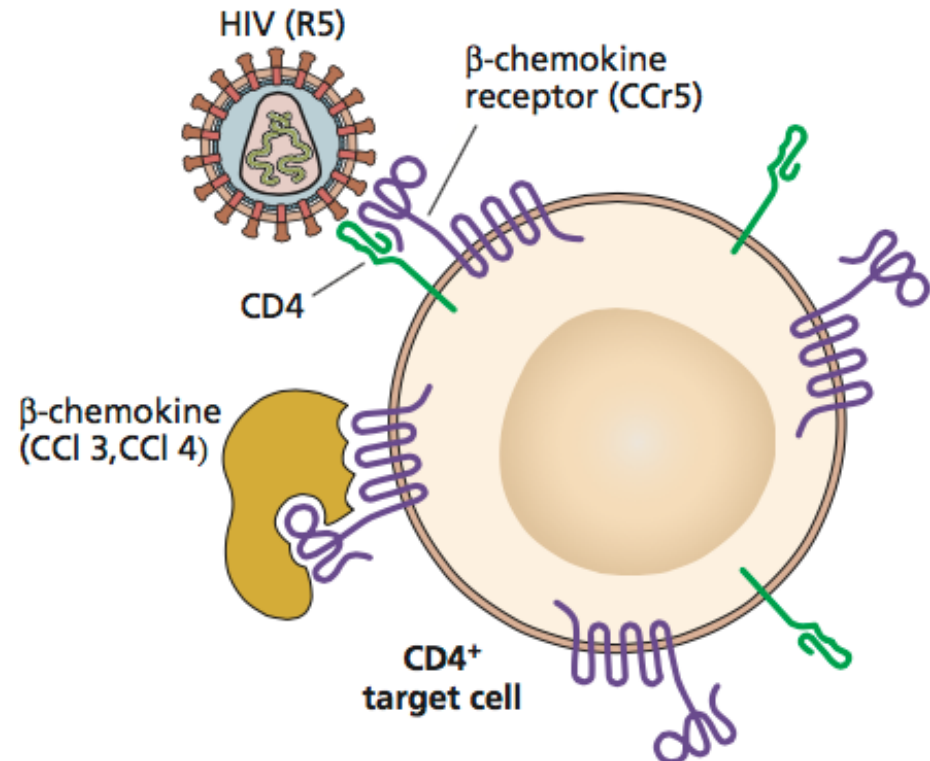
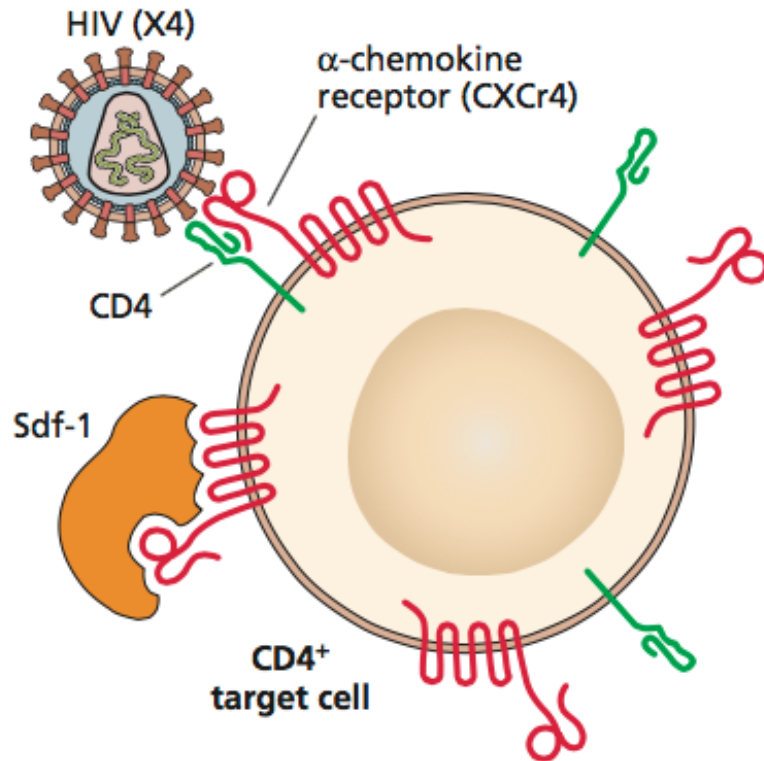
# Risk of transmission of HIV-1

Mode	Risk
<b>Sexual transmission</b>	
Female-to-male	1 in 700 to 1 in 3,000
Male-to-female	1 in 200 to 1 in 2,000
Male-to-male	1 in 10 to 1 in 1,600
<b>Parenteral</b>	
Transfusion of infected blood	95 in 100
Needle sharing	1 in 150
Needle stick	1 in 200
Needle stick /AZT PEP	1 in 10,000
<b>Mother to infant</b>	
Without AZT	1 in 4
With AZT	<1 in 10

# Transmission

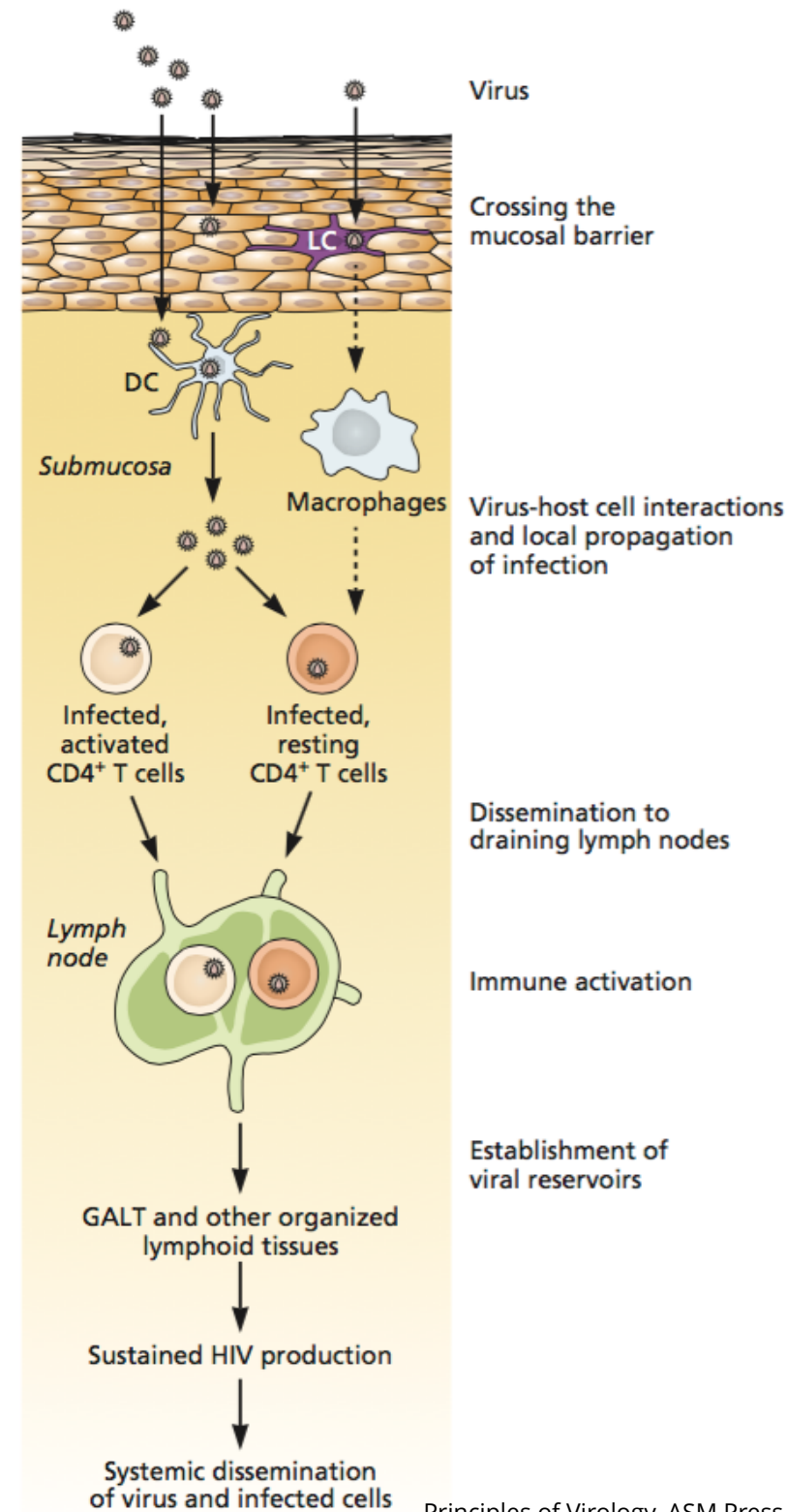
- HIV-1 infectivity reduced by air drying (99%/24 hr)
- By heating (56°C/30 min)
- By 10% bleach or 70% alcohol
- By pH extremes (<6 or >10)
- STD/IVDU bypass these!

# Co-receptors



# 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

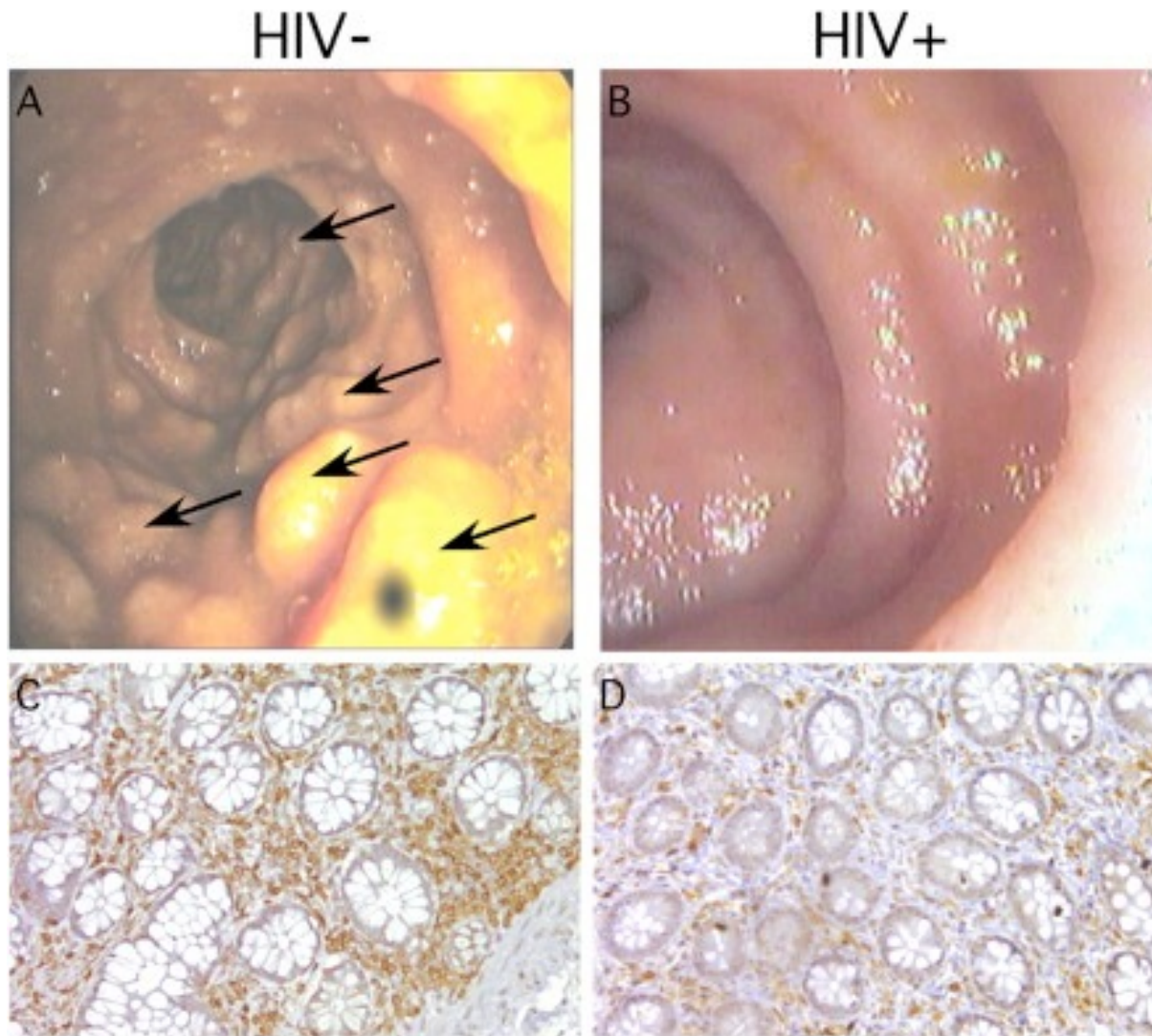


# Primary HIV Infection: Clinical characteristics

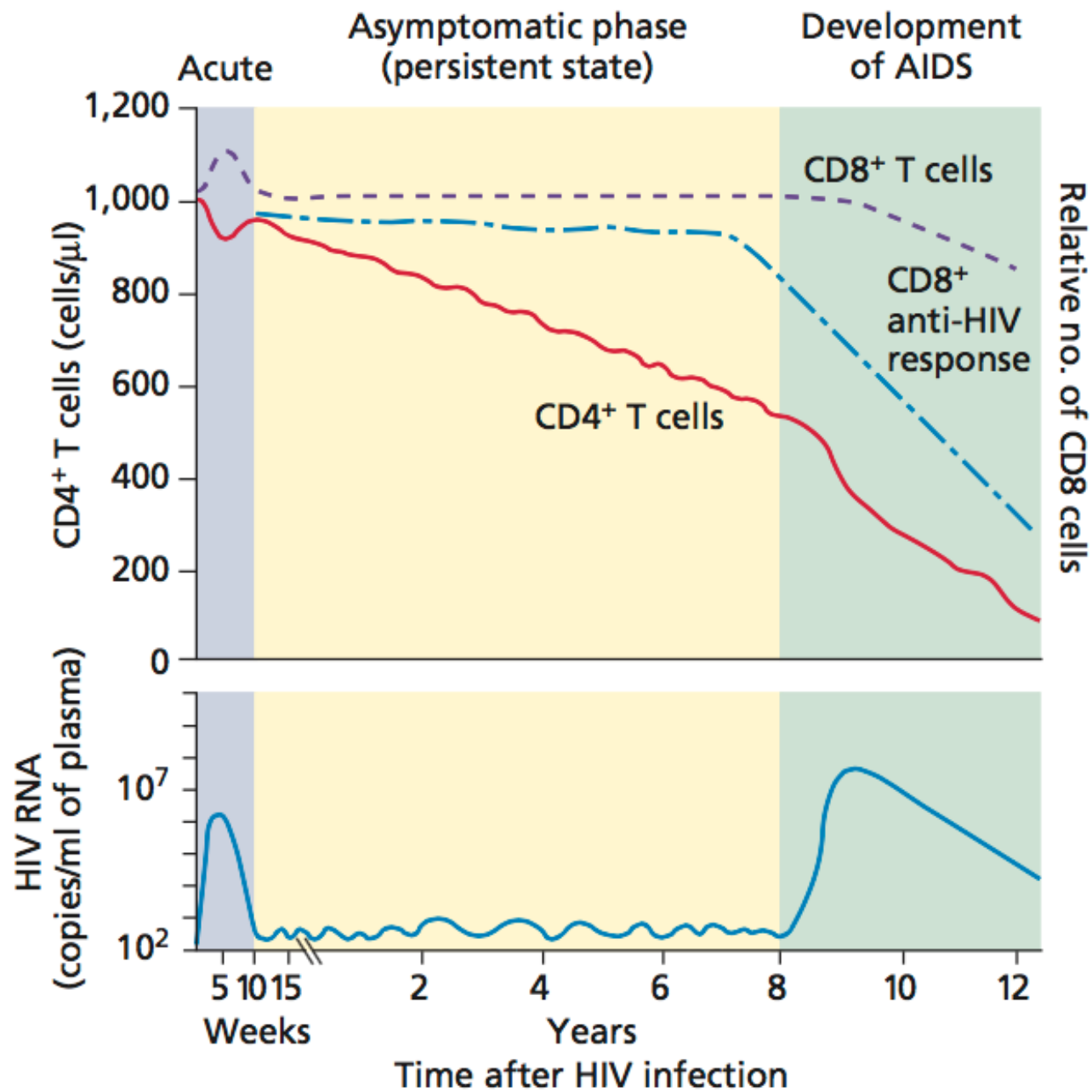
- 50-90% of infections are symptomatic
- Symptoms generally occur 5-30 days after exposure
- Symptoms and signs
  - Fever, fatigue, malaise, arthralgias, headache, nausea, vomiting, diarrhea
  - Lymphadenopathy, pharyngitis, rash, weight loss, mucocutaneous ulcerations, aseptic meningitis
  - Leukopenia, thrombocytopenia, elevated liver enzymes
- Median duration of symptoms: 14 days



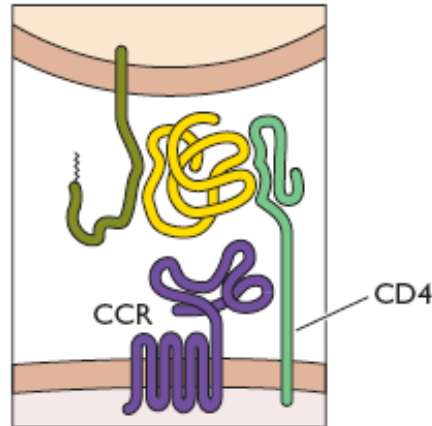
# GI associated lymphoid tissue following acute infection



Absence of lymphoid cell aggregates in terminal Ileum



# Host genes that determine susceptibility



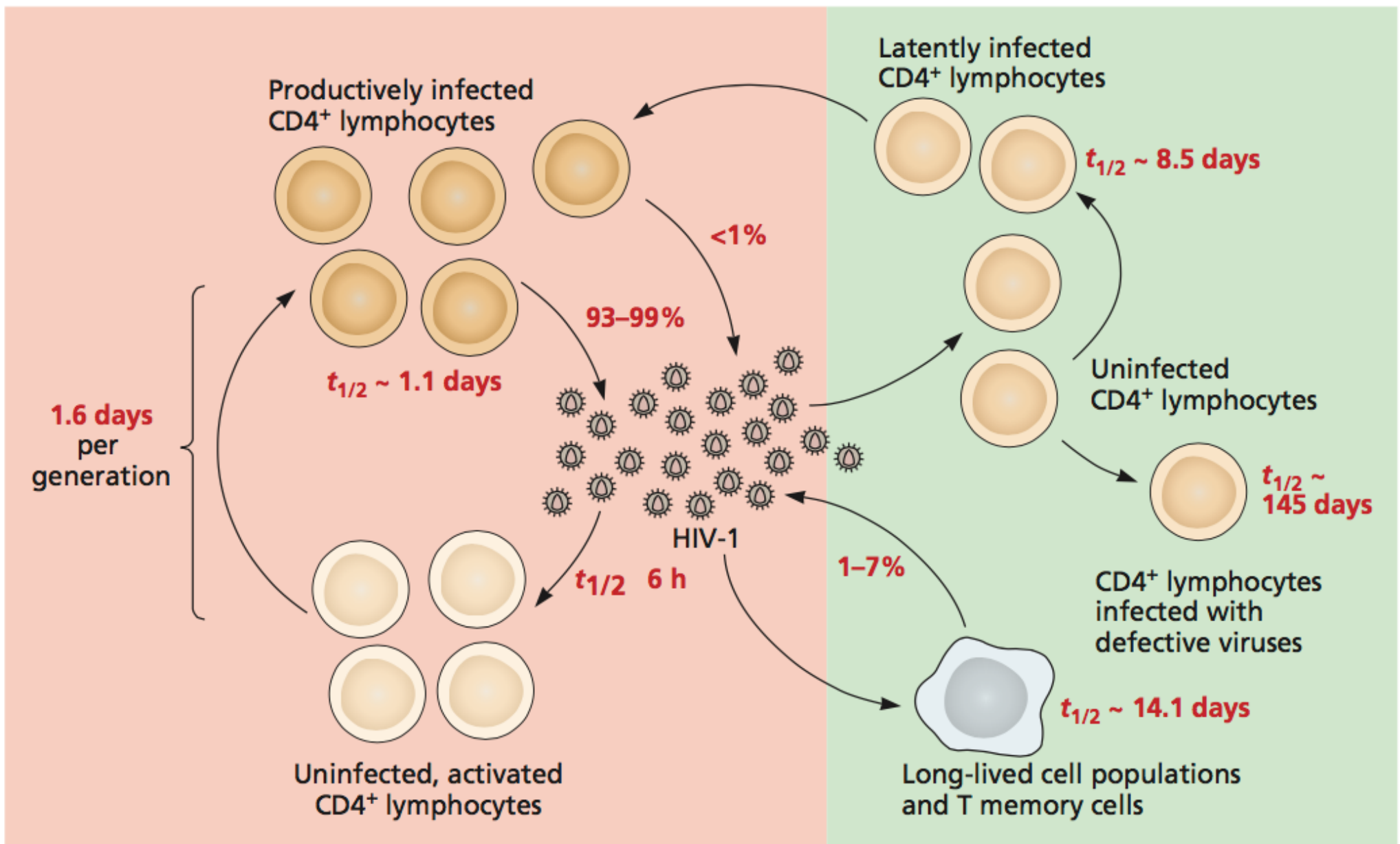
- Ccr5-delta32 mutation protects vs HIV-1 infection
- Present in 4-16% of European descent
- Stem cell therapy cured German AIDS patient (<http://www.virology.ws/2014/09/06/the-berlin-patient/>)
- Disrupting *ccr5* with nucleases, crispr/cas

# Established HIV Infection

- Active viral replication throughout course of disease
- Major reservoirs of infection exist outside of blood
  - Lymphoreticular tissues (Gastrointestinal tract - GALT)
  - Central nervous system
  - Genital tract
- At least  $10 \times 10^9$  virions produced and destroyed each day
- $T_{1/2}$  of HIV in plasma is  $<6$  h and may be as short as 30 min

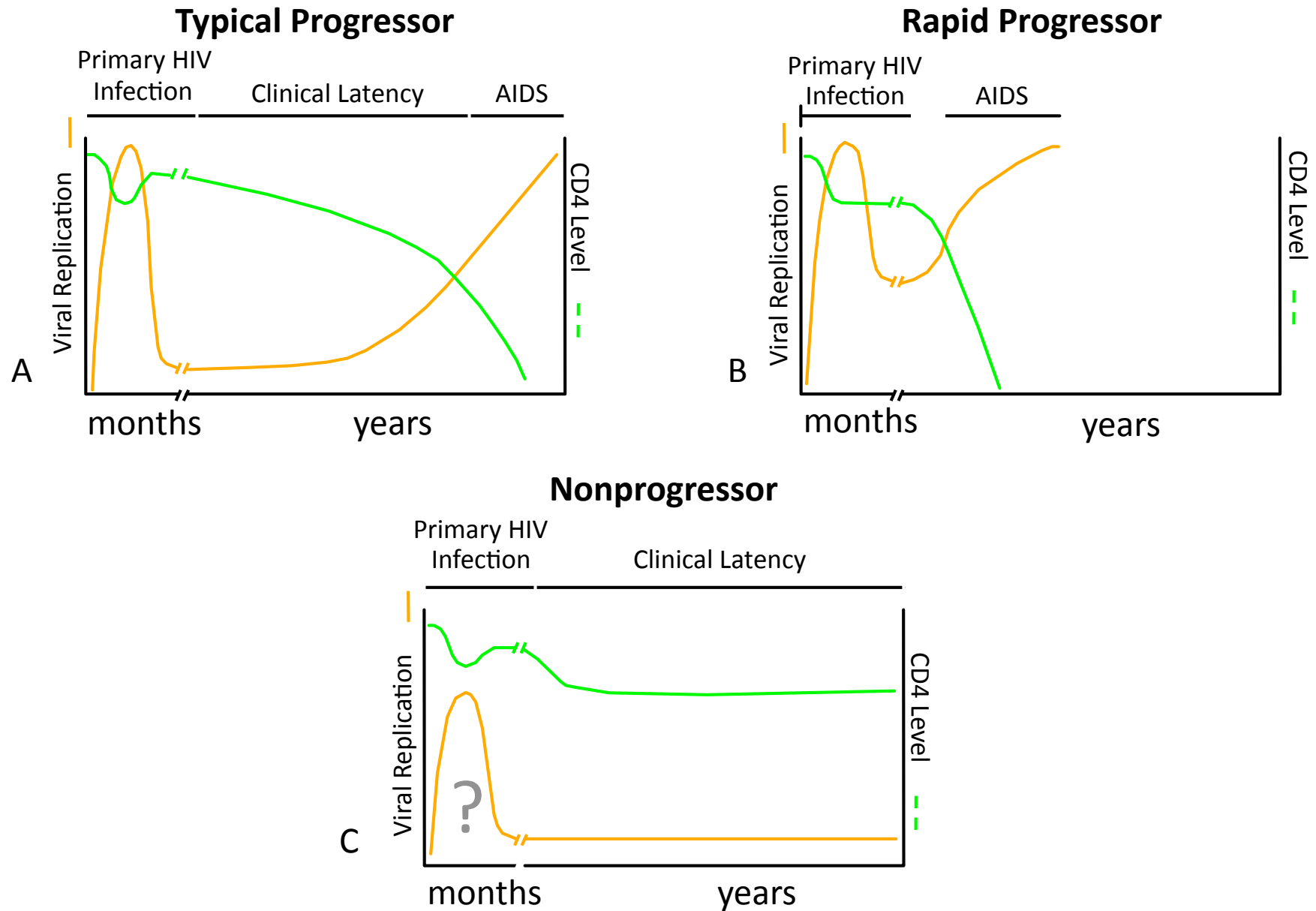
## Blood compartment

## Other compartments



Multipotent hematopoietic progenitor cells - latent reservoir

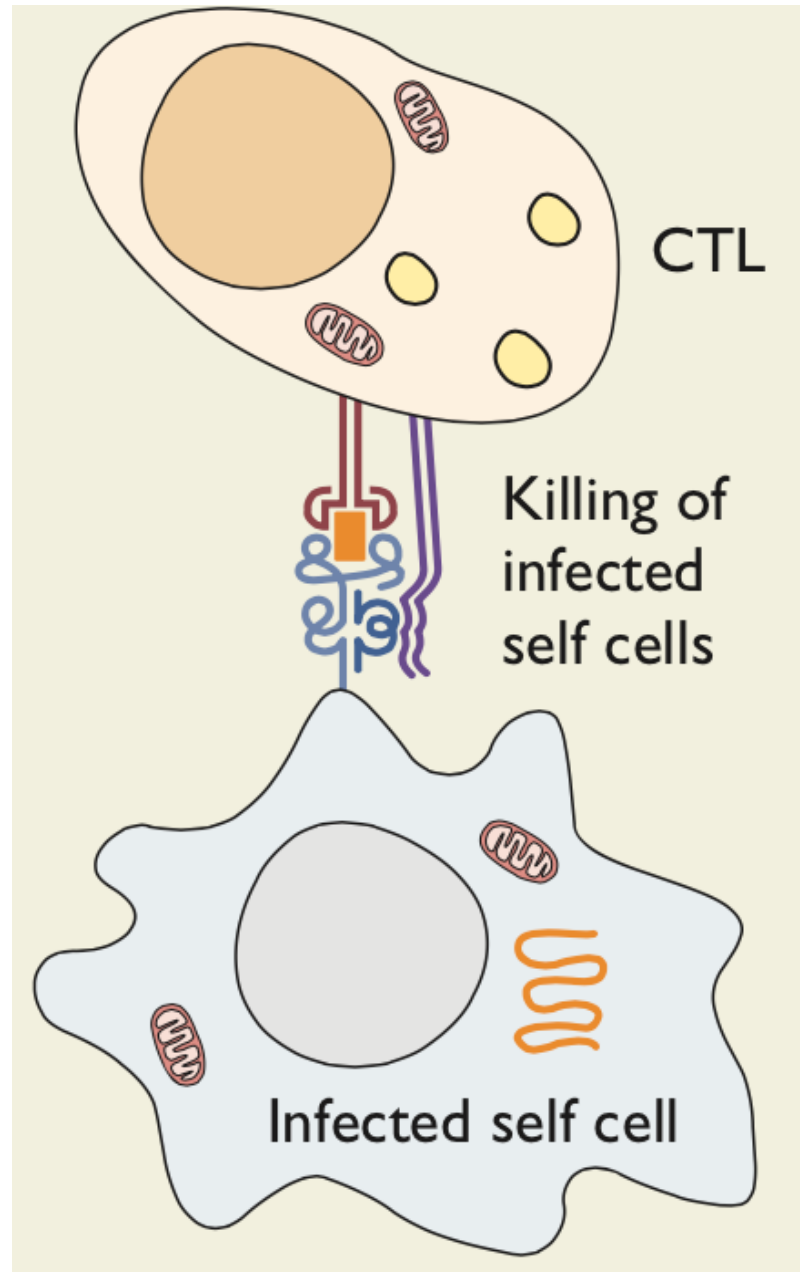
# The variable course of HIV-1 infection



# Elite HIV Controllers





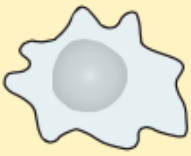
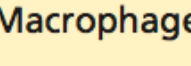
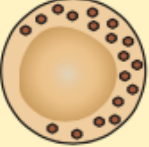
- Individuals who maintain normal CD4 counts and undetectable viral loads (<50 copies HIV RNA/ml of plasma) for >10 years in the absence of antiretroviral therapy
  - Estimated at 1/300 infected persons
- Associated with favorable HLA types (esp HLA B57 and B27) and T-cell responses (CD4 and CD8) to Gag
- Persistent viremia (1-30 copies of RNA/ml) demonstrable
- Not associated with attenuated viruses

# Virus susceptibility mapping to MHC



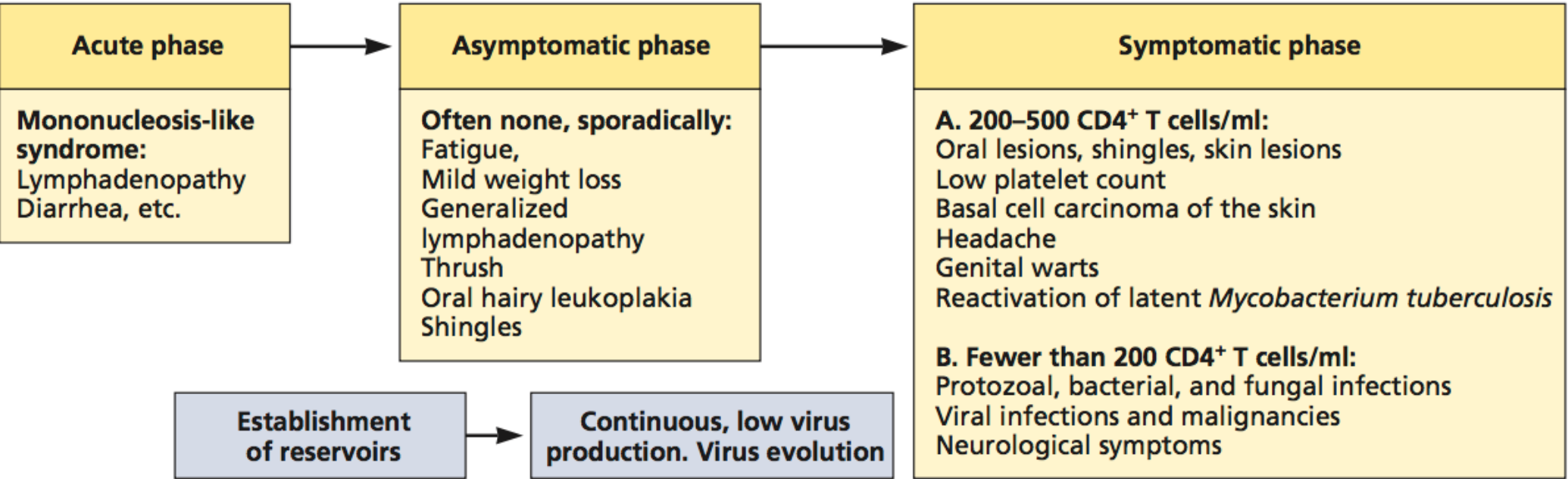


# Immune cell dysfunction in AIDS

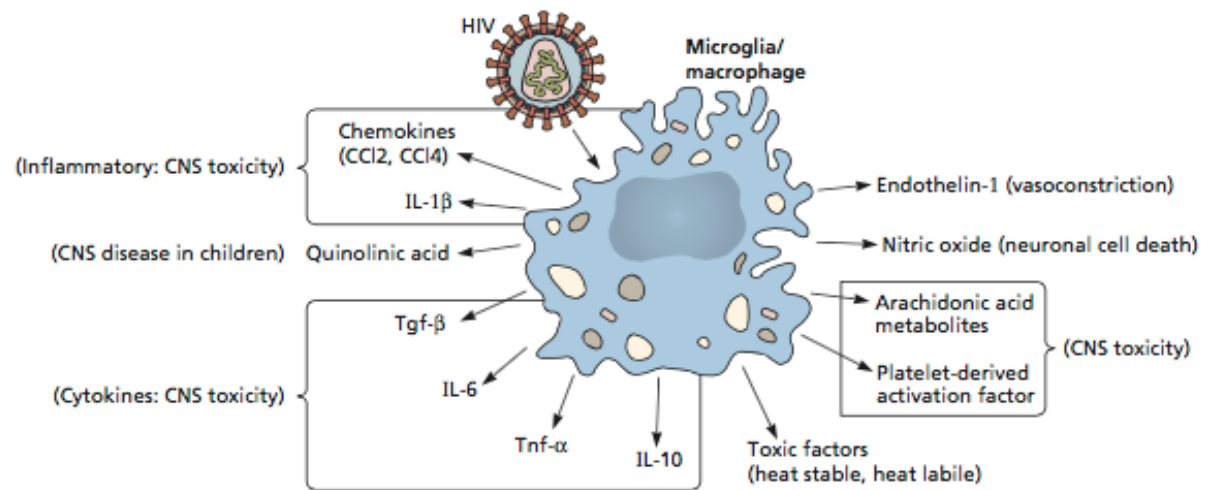
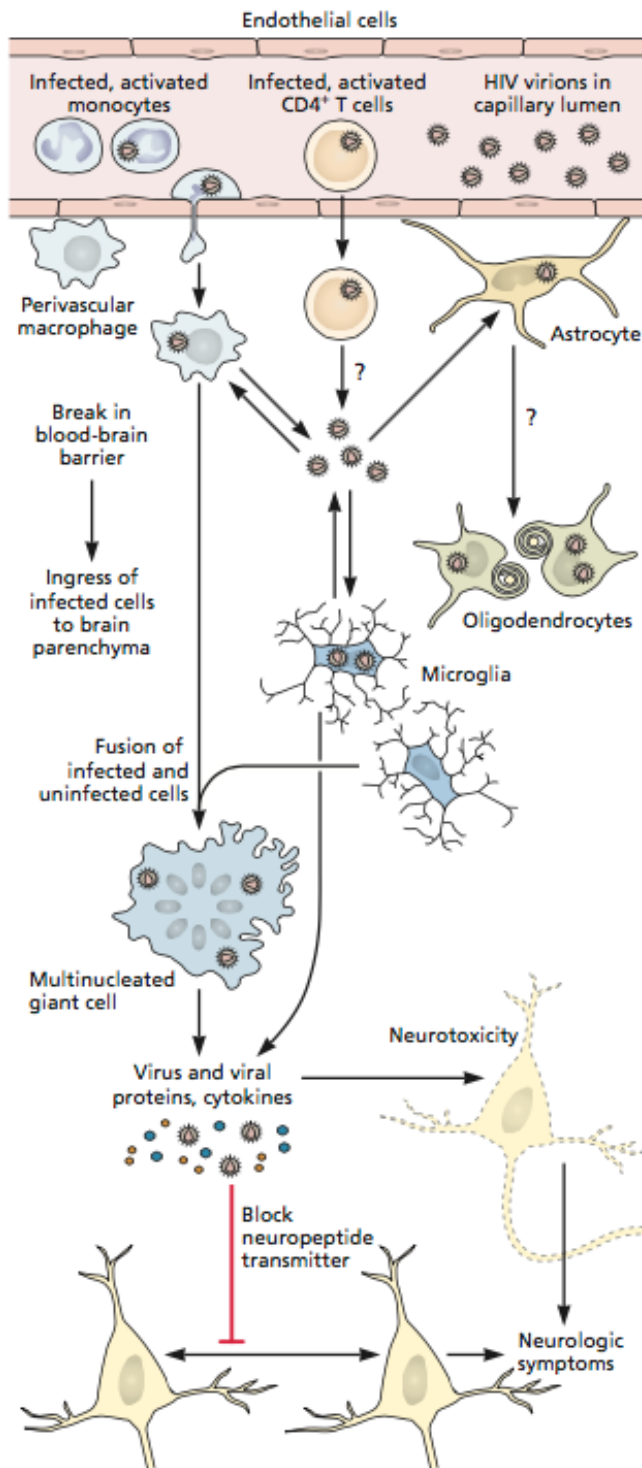
	Cell-type affected	Major dysfunction
Adaptive immunity	<b>CD4<sup>+</sup> T cells</b> 	Total number decreases Expression of IL-2 decreases Expression of IFN $\gamma$ decreases
	<b>CD8<sup>+</sup> T cells</b> 	Total number increases and then decreases Loss of anti-HIV activity
	<b>B cells</b> 	Abnormal proliferation Poor antigen response Production of autoantibodies
Innate immunity	<b>Monocytes</b> 	Total number decreases Antigen-presentation decreases Fc receptor function decreases  Bystander killing by increased cytokine production
	<b>Dendritic cells</b> 	
	<b>Macrophages</b> 	
	<b>NK cells</b> 	Cytotoxicity function decreases

# AIDS

- <200 CD4+ T cells/ml
- Protozoal: *Pneumocystis*, *Toxoplasma*, *Isospora*, *Cryptosporidium*, microsporidia
- Bacterial: *Mycobacterium*, *Treponema*
- Fungal: *Candida*, *Cryptococcus*, *Histoplasma*
- Viral: CMV, HSV
- Immune activation: HIV replicates better in activated T cells
- Malignancies: EBV lymphoma, Kaposi's sarcoma, anogenital carcinoma
- Neurological symptoms: aseptic meningitis, myelopathies, neuropathies, AIDS dementia complex



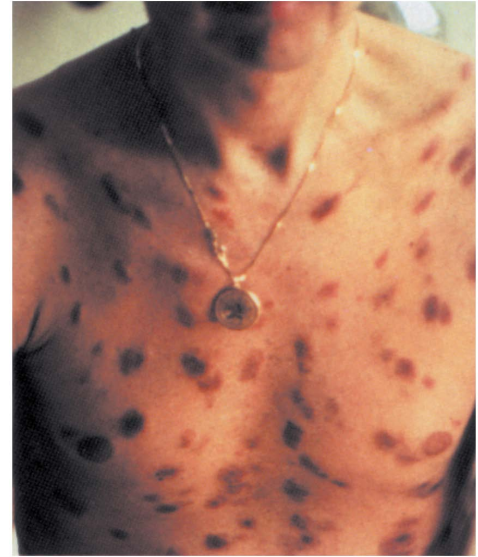
# Neurological symptoms



# HIV and cancer

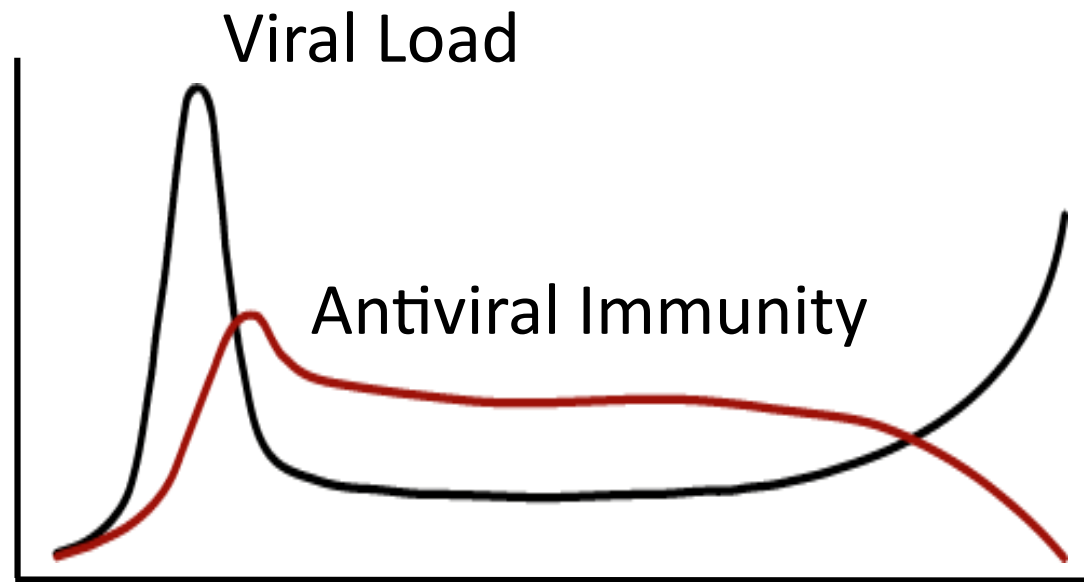
- HIV-1 infection leads to increase incidence of malignancy: 40% of infected individuals
- An indirect effect of dysregulation of the immune system
  - Absence of proper immune surveillance
  - High levels of cytokines leads to inappropriate cell proliferation, replication of oncogenic viruses (EBV,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

# Is an HIV-1 vaccine possible?

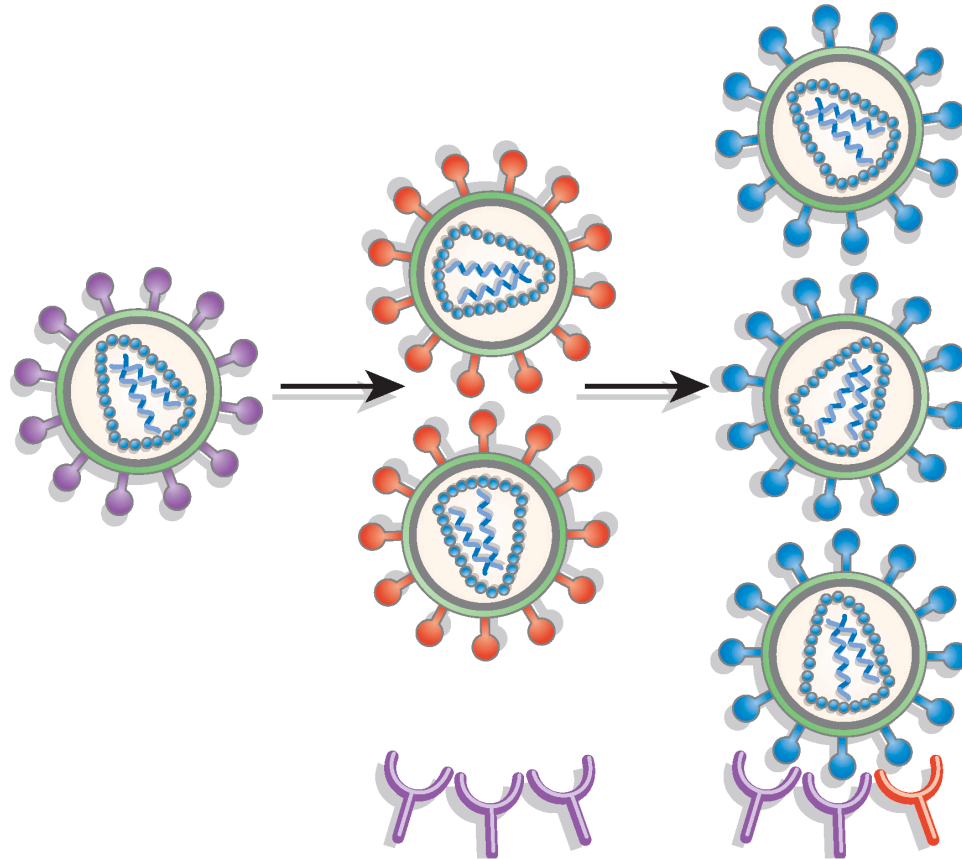


How does HIV-1 persist despite effective anti-viral immunity?

How does it eventually outstrip immune control?

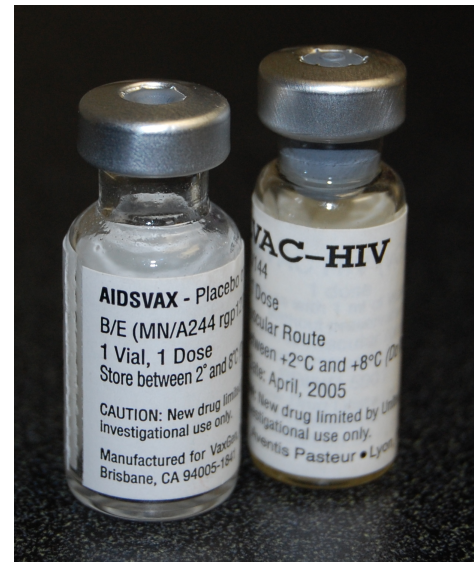
HIV-1 superinfection occurs less frequently than initial infection

# HIV-1 escape from neutralizing antibody



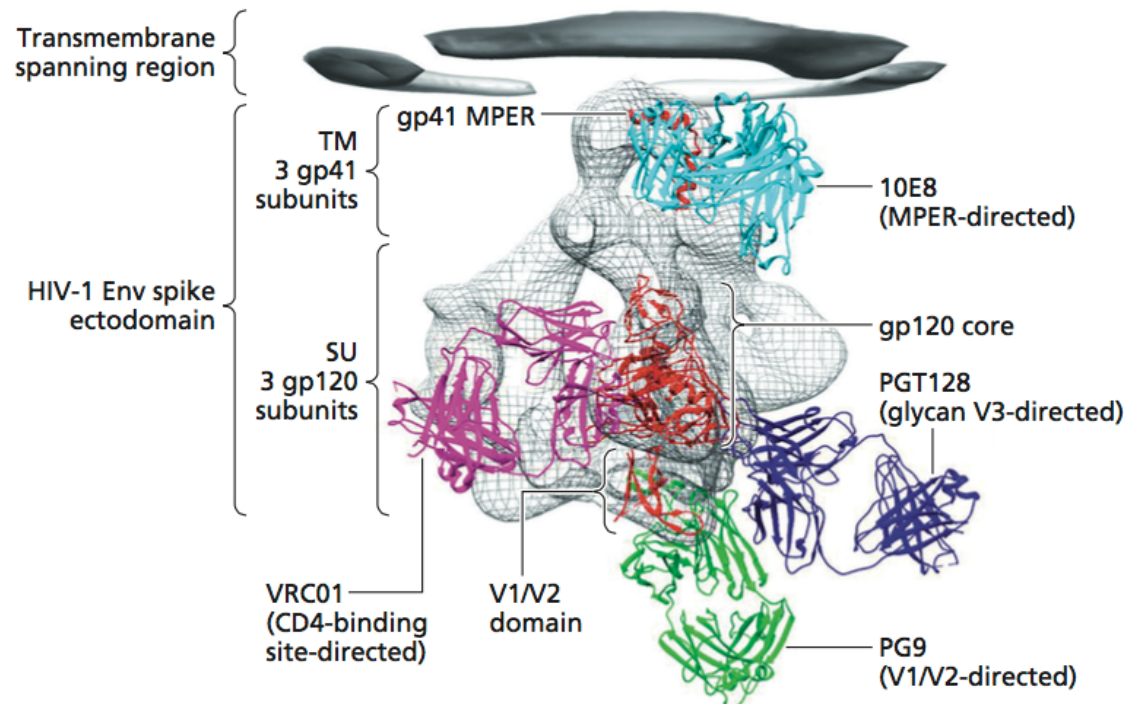


# RV144



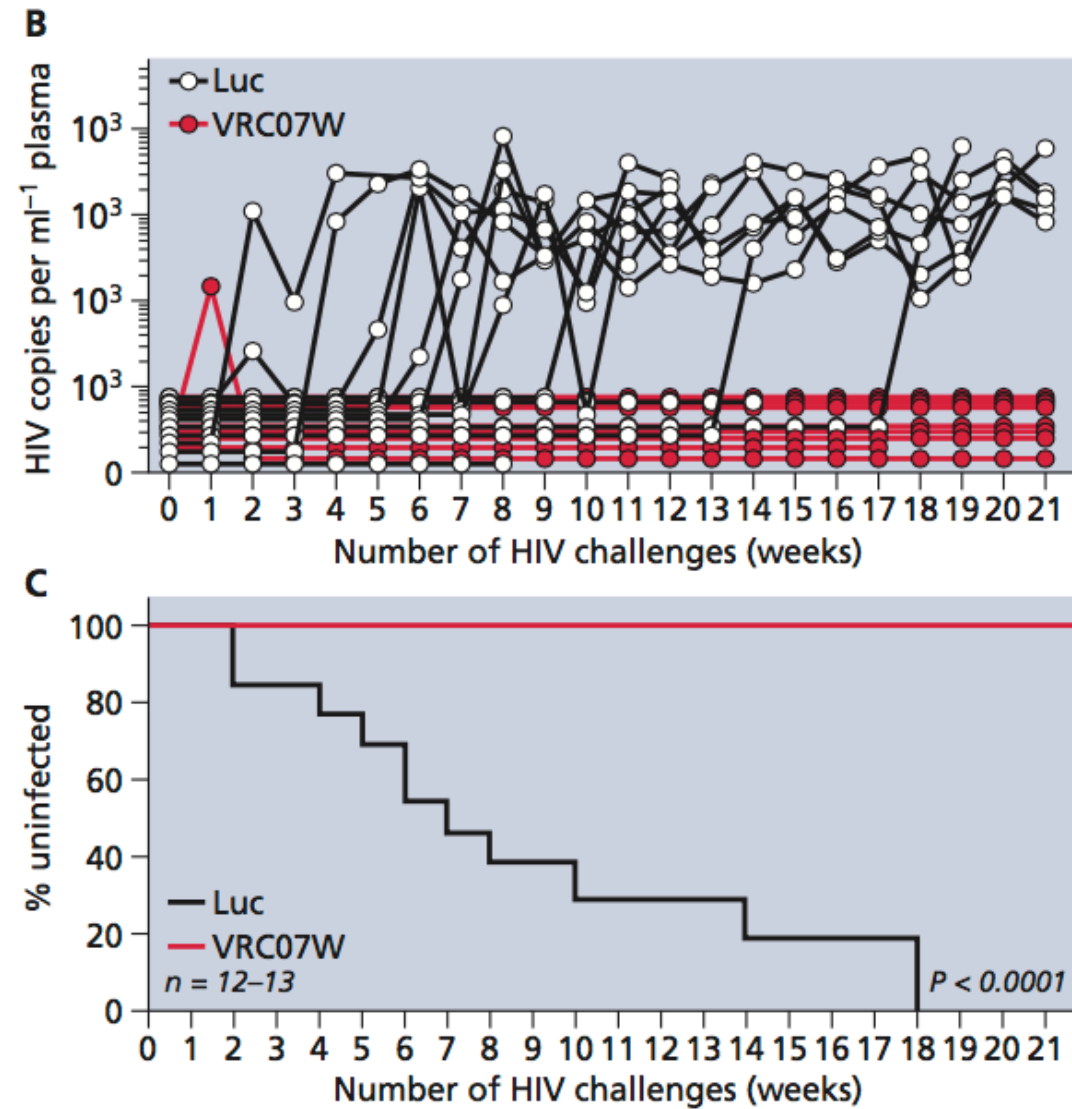
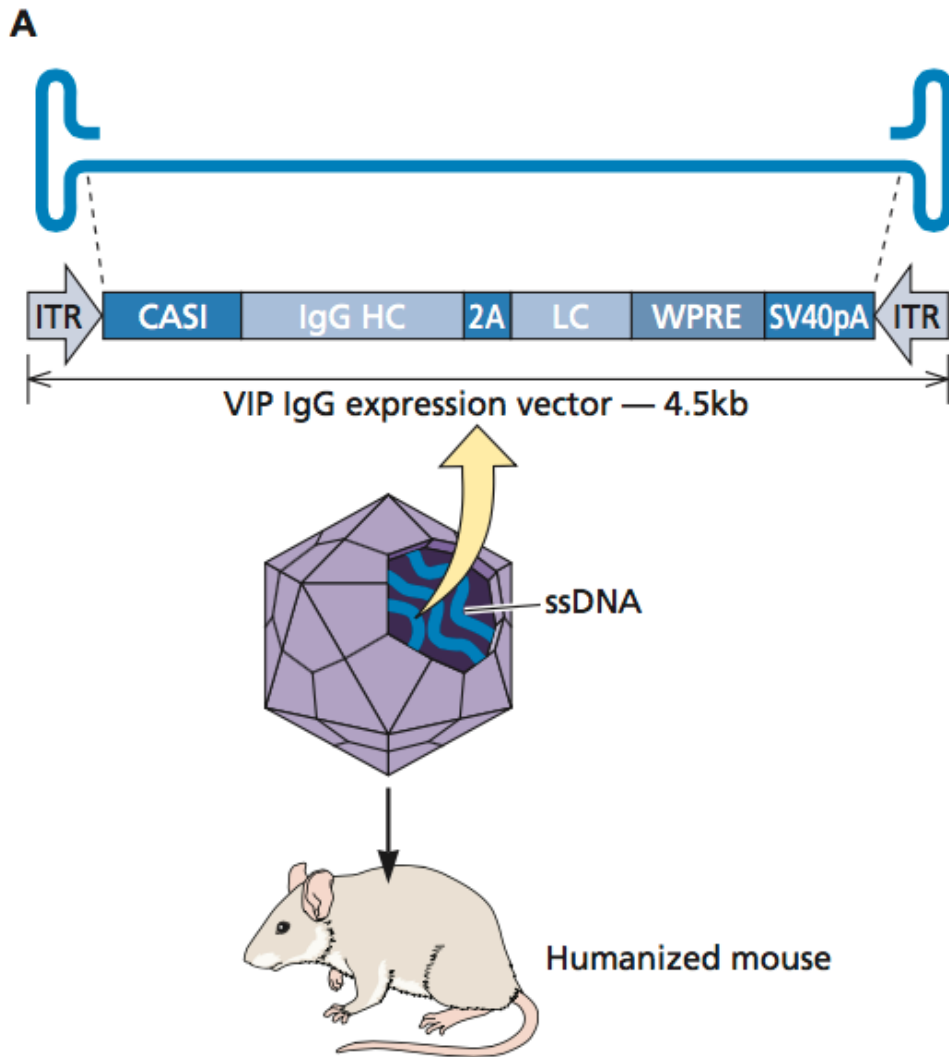
- Prime-boost: ALVAC-HIV (env, gag, pol in canarypox vector) and AIDSVAX B/E (recombinant gp120 protein)
- 16,000 adult volunteers in Thailand
- 6 prime, 6 boost injections
- Lowered rate of HIV-1 infection by 31.2% compared with placebo
- n=51 vs n=74

# Broadly neutralizing antibodies

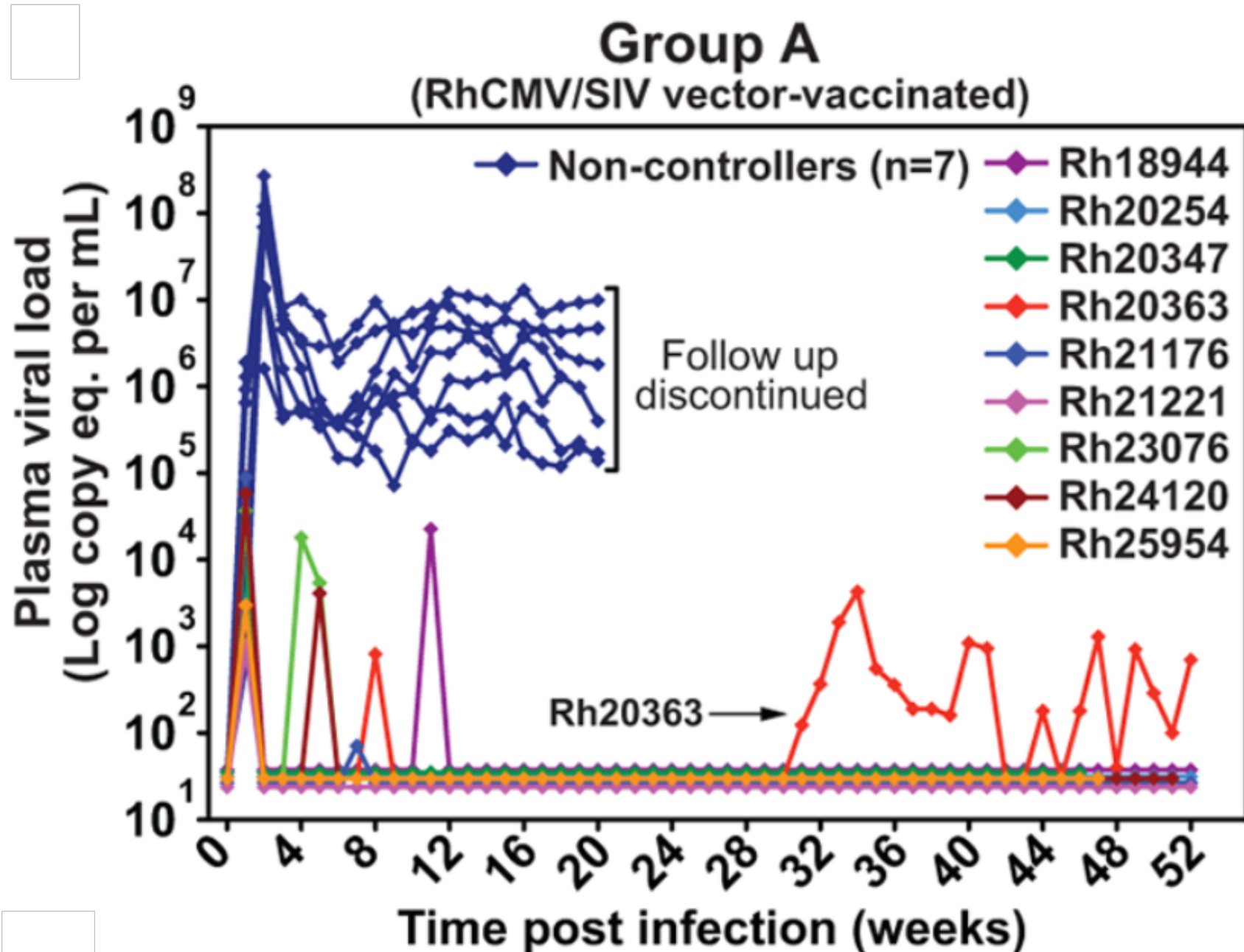


- Have been identified in 20% of HIV-1 infected individuals
- Neutralize broadly across subtypes
- Recognize conserved epitopes on Env glycoprotein

# Immunoprophylaxis vs AIDS



# Immune clearance of SIV in macaques





~1921: Patient zero



78,000,000 infections  
39,000,000 deaths