HIV and AIDS

Lecture 23

Biology 3310/W4310

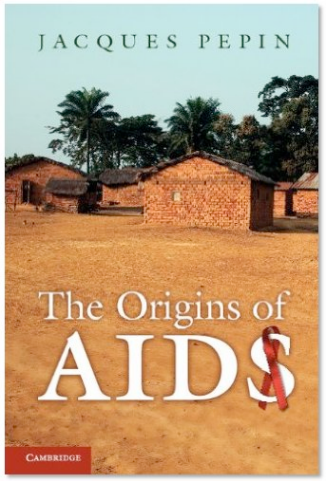
Virology

Spring 2017

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.



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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.

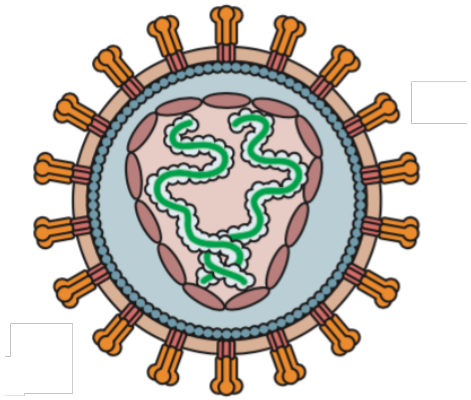
Patient 2: A previously healthy 30-year-old man developed *p. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement 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).

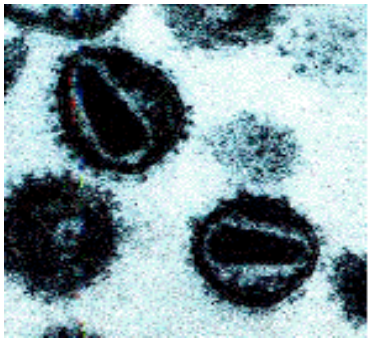
All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the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

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

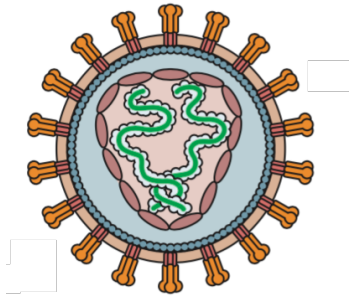


HIV is a lentivirus



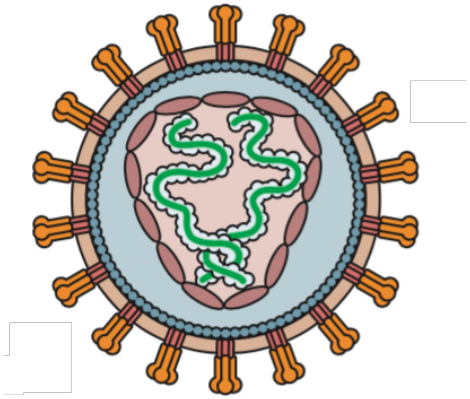
- First isolated in 1983 from the lymph node of a patient with lymphadenopathy in Paris
- 1984 blood test developed
- Electron microscopy and sequence analysis revealed HIV to be a lentivirus, known group of retroviruses

Retroviridae

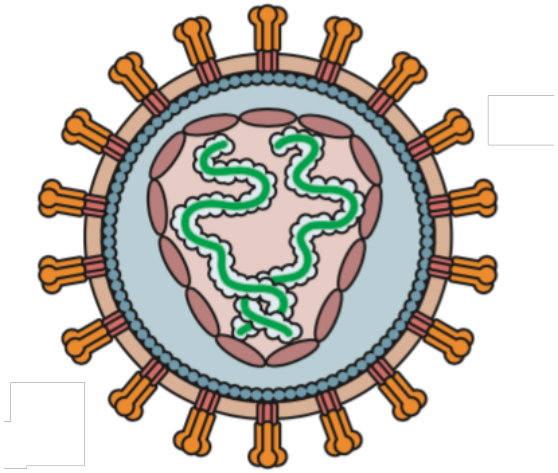


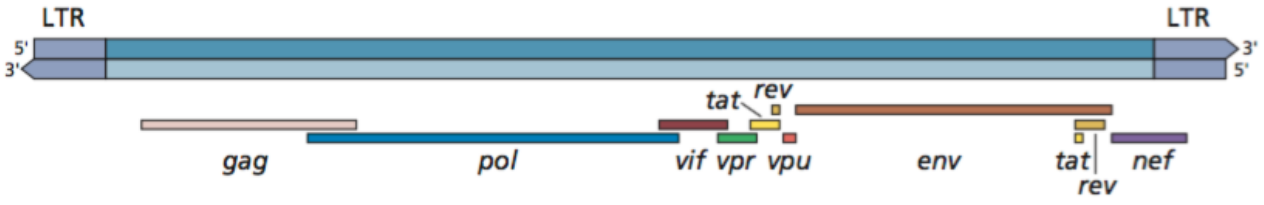
- *Orthoretrovirinae (subfamily)*
  - *Alpharetrovirus (Avian leukosis virus)*
  - *Betaretrovirus*
  - *Gammaretrovirus*
  - *Deltaretrovirus (Human T cell lymphotropic virus 1, 2 ,3)*
  - *Epsilonretrovirus (Walleye dermal sarcoma virus)*
  - *Spumavirus*
  - *Lentivirus (Human immunodeficiency virus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

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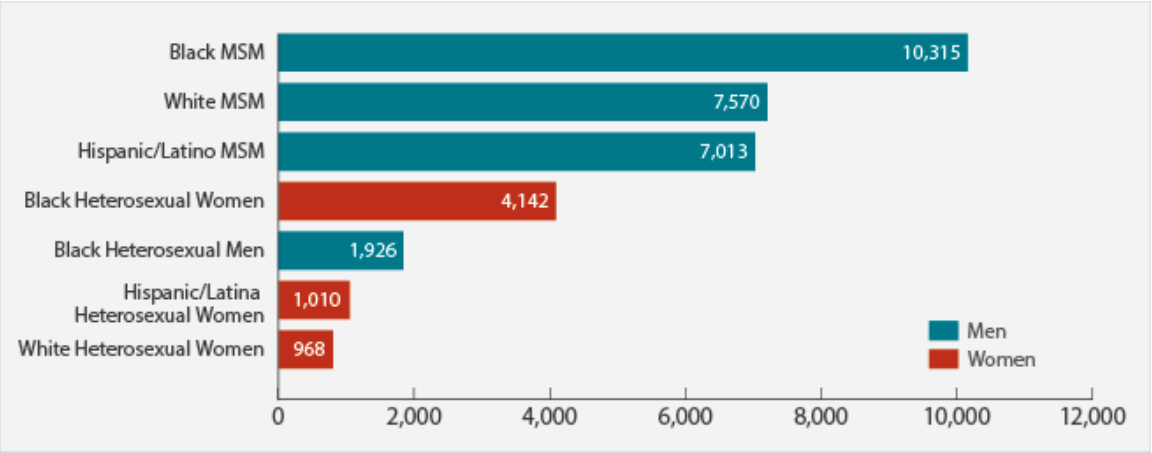
HIV and AIDS: Acquired ImmunoDeficiency Syndrome

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

HIV/AIDS pandemic in the US

- 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 living with HIV; 13% unaware
- 18,303 new infections in 2015; 70% men, 30% women
- Half of all new infections in US occur in people 25 or younger



2015

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

Global summary of the AIDS epidemic | 2015

Number of people living with HIV in 2015	Total	36.7 million
	Adults	34.9 million
	Women	17.8 million
	Children (<15 years)	1.8 million
People newly infected with HIV in 2015	Total	2.1 million
	Adults	1.9 million
	Children (<15 years)	150 000
AIDS deaths in 2015	Total	1.1 million
	Adults	1.0 million
	Children (<15 years)	110 000

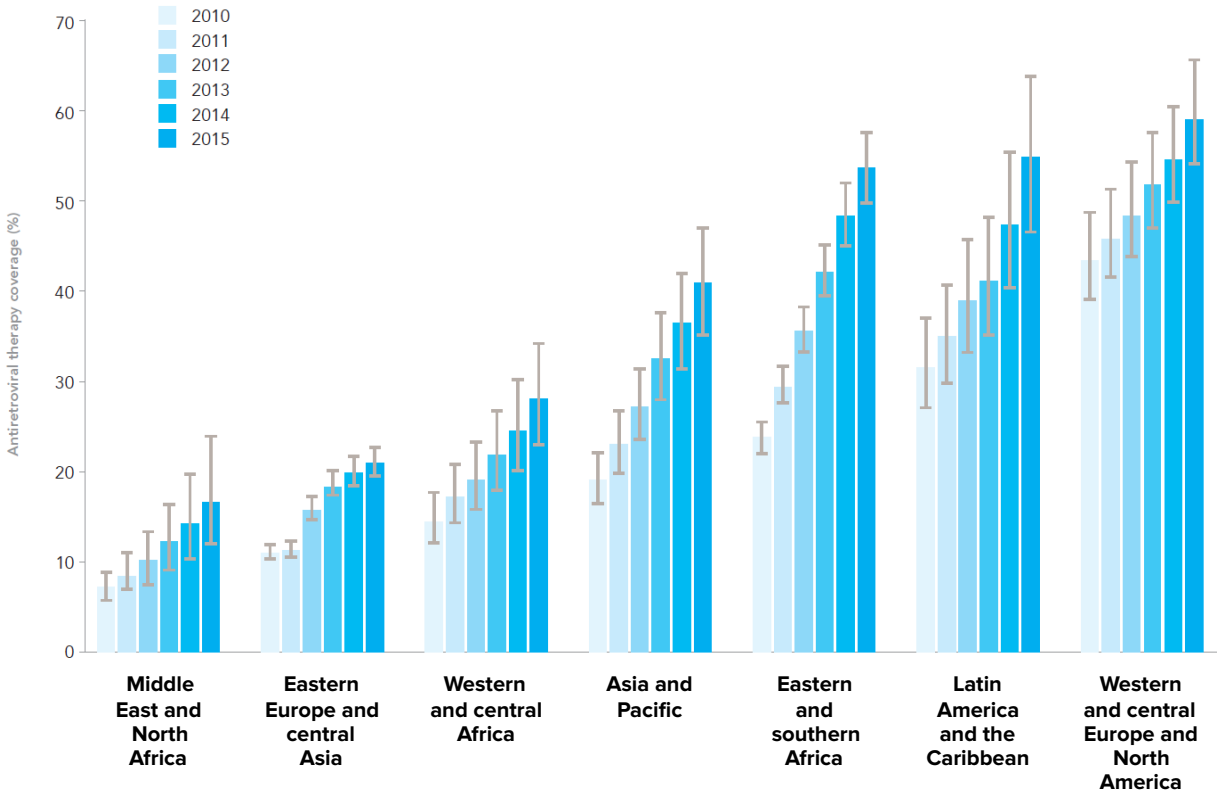
http://www.who.int/hiv/data/en/

HIV epidemic and response estimates, global and by region, 2010 and 2015

	People living with HIV (all ages)		New HIV infections (all ages)	
	2010	2015	2010	2015
Global	33.3 million [30.9 million–36.1 million]	36.7 million [34.0 million–39.8 million]	2.2 million [2.0 million–2.5 million]	2.1 million [1.8 million–2.4 million]
Asia and Pacific	4.7 million [4.1 million–5.5 million]	5.1 million [4.4 million–5.8 million]	310 000 [270 000–360 000]	290 000 [230 000–370 000]
Eastern and southern Africa	17.2 million [16.1 million–18.5 million]	19.1 million [17.7 million–20.5 million]	1.1 million [1.0 million–1.2 million]	960 000 [830 000–1.1 million]
Eastern Europe and Central Asia	1.0 million [950 000–1.1 million]	1.5 million [1.4 million–1.7 million]	120 000 [110 000–130 000]	190 000 [170 000–200 000]
Latin America and the Caribbean	1.8 million [1.5 million–2.1 million]	2.0 million [1.7 million–2.3 million]	100 000 86 000–120 000]	100 000 [86 000–120 000]
Middle East and North Africa	190 000 [150 000–240 000]	230 000 [160 000–330 000]	20 000 [15 000–29 000]	21 000 [12 000–37 000]
Western and central Africa	6.3 million [5.2 million–7.7 million]	6.5 million [5.3 million–7.8 million]	450 000 [350 000–560 000]	410 000 [310 000–530 000]
Western and central Europe and North America	2.1 million [1.9 million–2.3 million]	2.4 million [2.2 million–2.7 million]	92 000 [89 000–97 000]	91 000 [89 000–97 000]

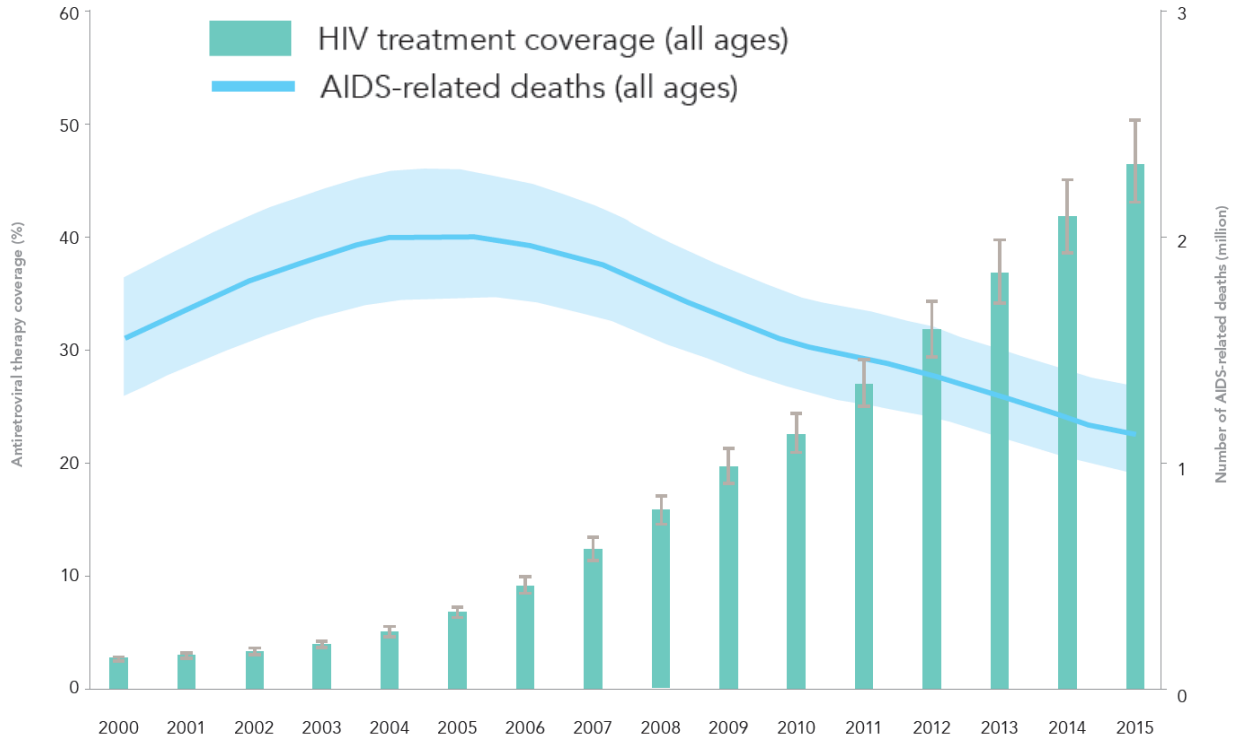
Sources: GARPR 2016; UNAIDS 2016 estimates.

Antiretroviral therapy coverage among people living with HIV, by region, 2010–2015



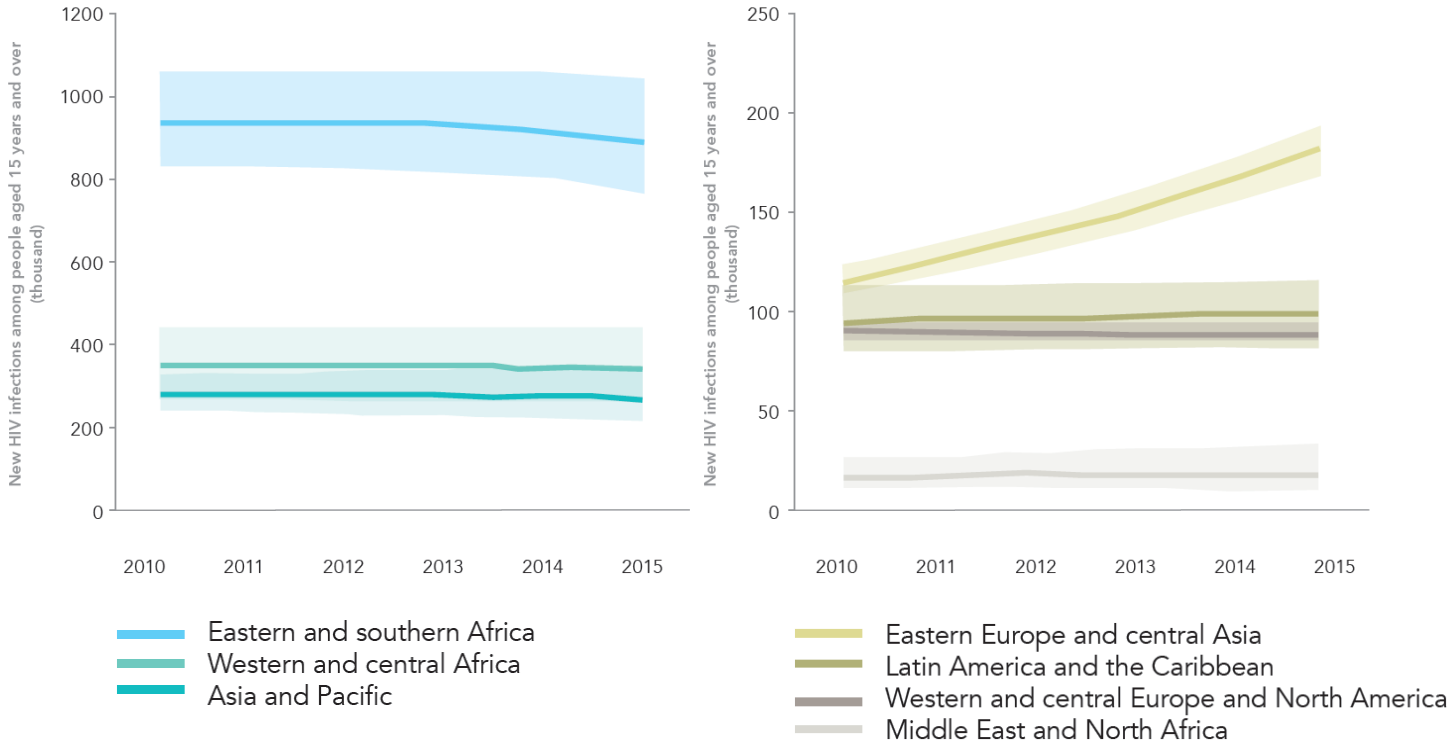
Sources: GARPR 2016; UNAIDS 2016 estimates.

Antiretroviral therapy coverage and number of AIDS-related deaths, global, 2000–2015



Sources: GARPR 2016; UNAIDS 2016 estimates.

New HIV infections among people aged 15 years and over, by region, 2010–2015



Source: UNAIDS 2016 estimates.

About 5,700 new HIV infections a day, 240 per hour

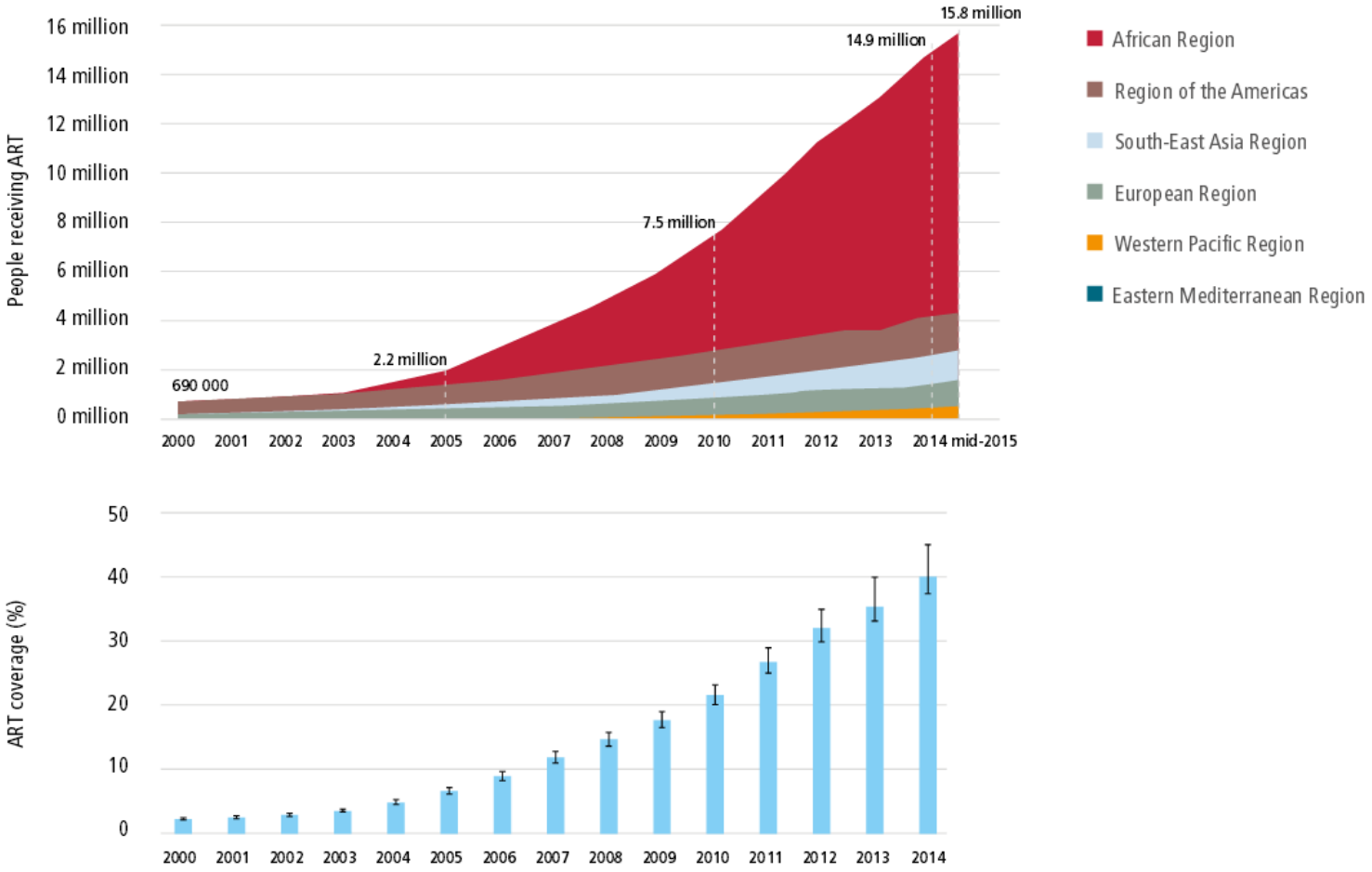
- About 665 in Sub Saharan Africa
- About 600 in children <15 yo
- About 5,000 in adults >15 yo
  - 48% among women
  - 30% among young people (15-24 yo)

http://www.who.int/hiv/data/en/

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

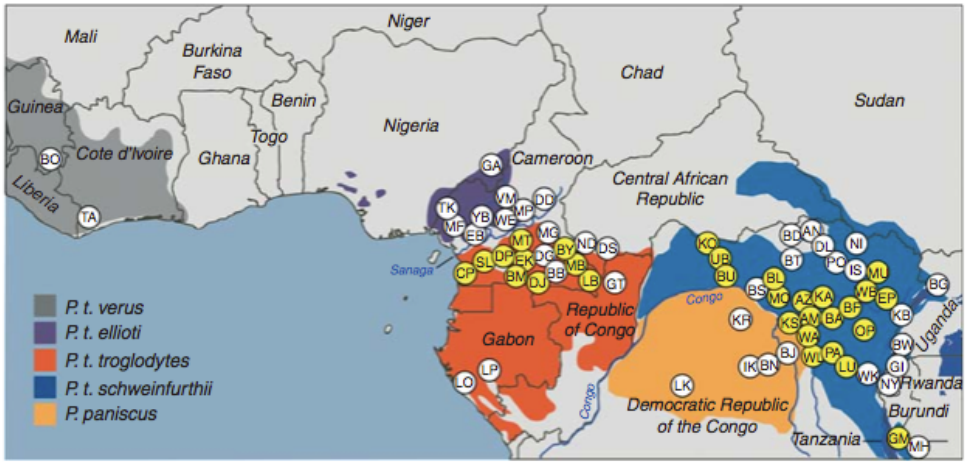
- Testing of archival samples suggested that HIV-1 was present in the 1960s and 1970s in several locations in central Africa but not in West or East Africa
- Serum sample ZR59 from a DRC adult male (1959) found positive for HIV-1 in 1998
- Lymph node sample from DRC adult female (1960)

Out of Africa

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

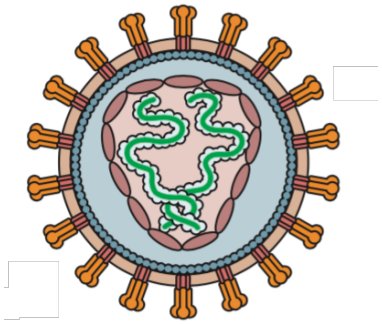
What was the source of HIV-1?

- 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

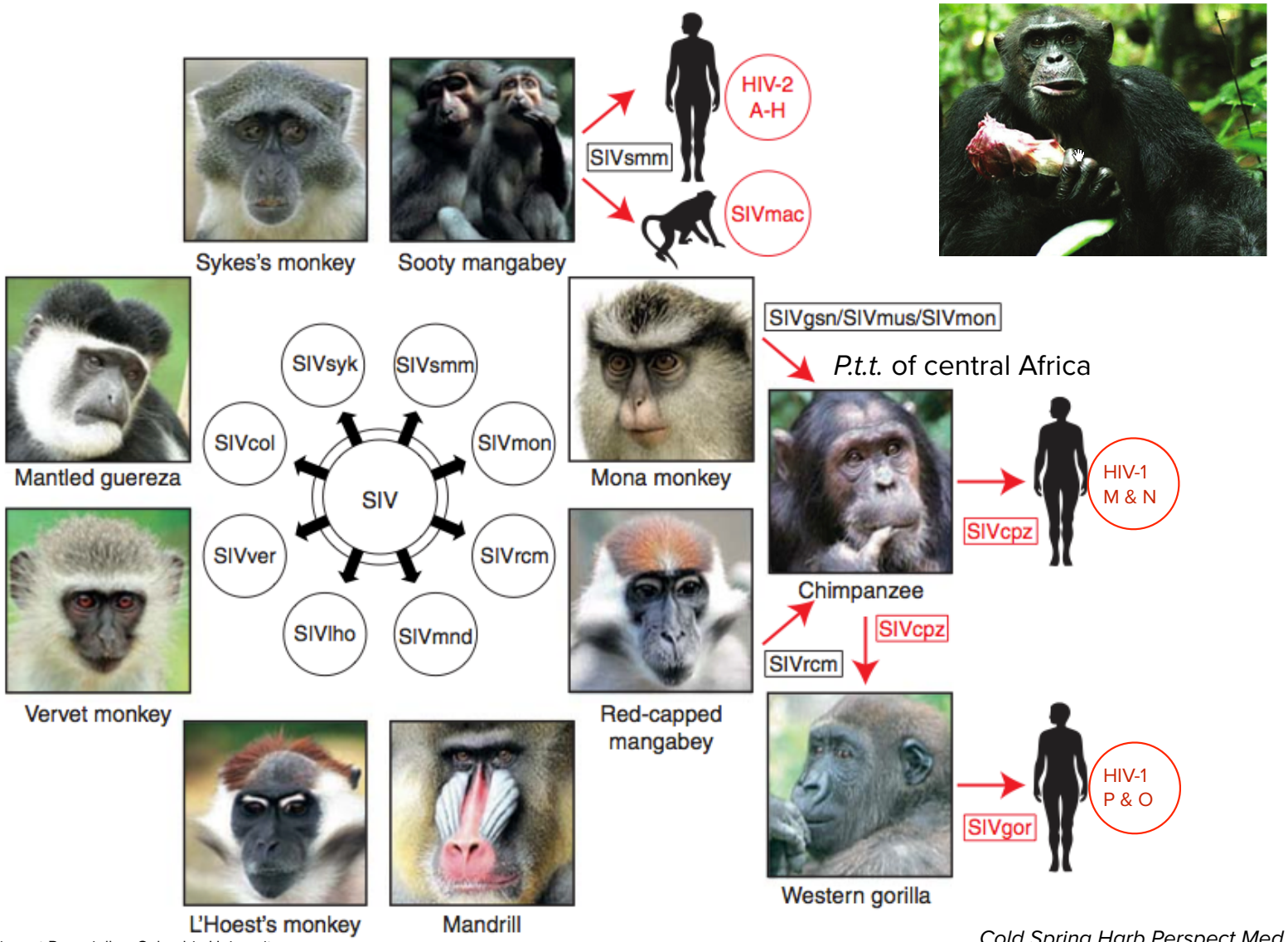


Cold Spring Harb Perspect Med 2011;1:a006841

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



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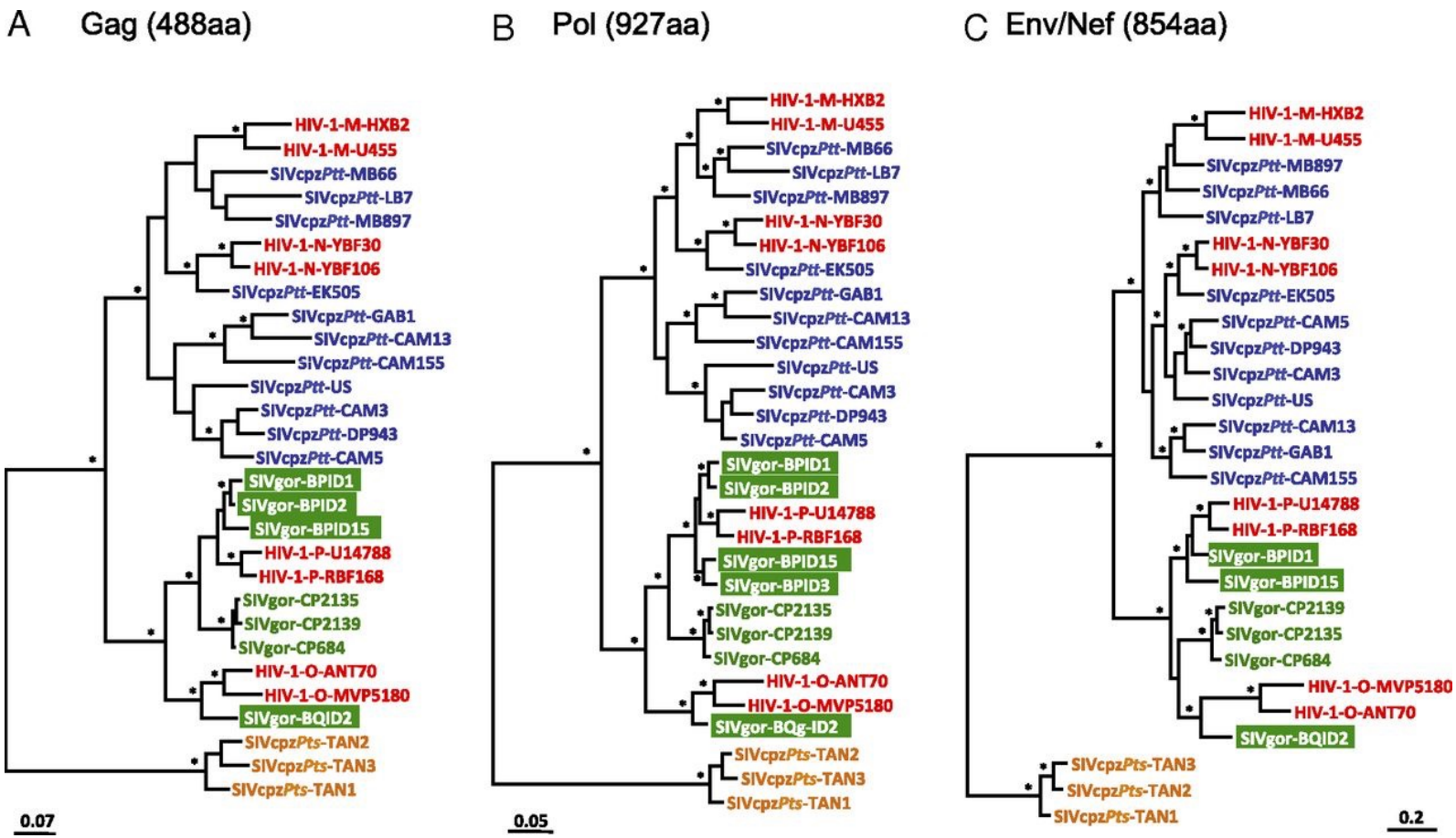


PNAS 112(2015) doi: 10.1073/pnas.1502022112

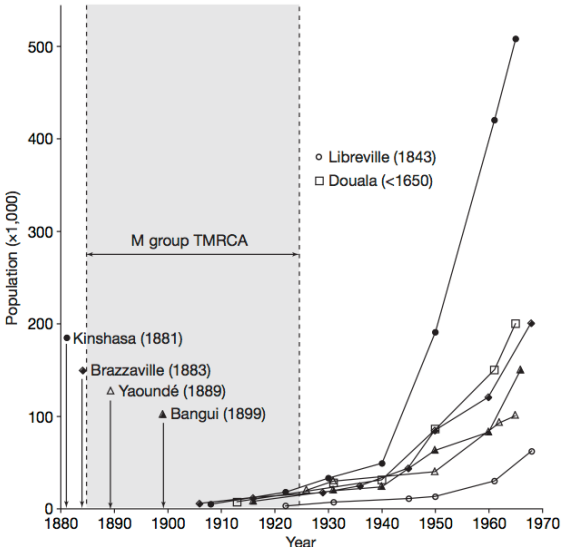
How did SIVcpz infect humans?

- 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

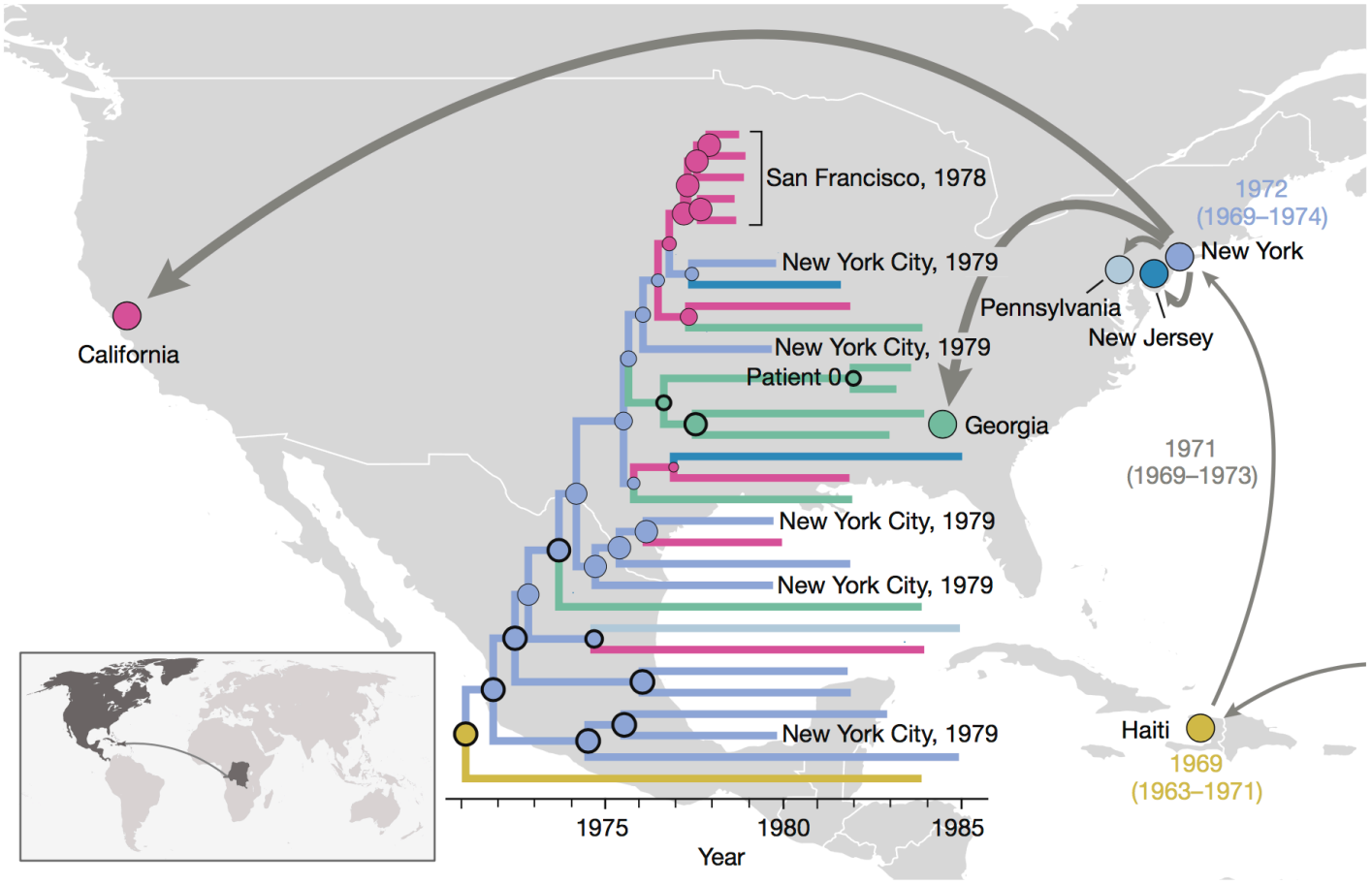


- Leopoldville was the most dynamic city in the region, attracted large numbers of migrants and traders
- The cut hunter might have traveled there, visited a brothel, then a STD clinic
- Then amplification by non-sterile syringes, sex (some women had 1,000 clients/yr)
- Haiti and the Belgian Congo

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

Early HIV/AIDS in North America

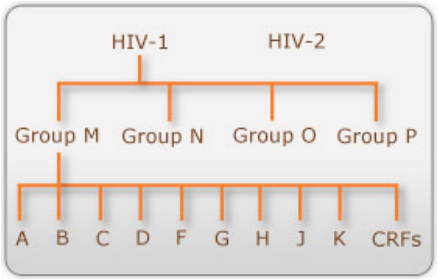


doi:10.1038/nature19827

HIV-2

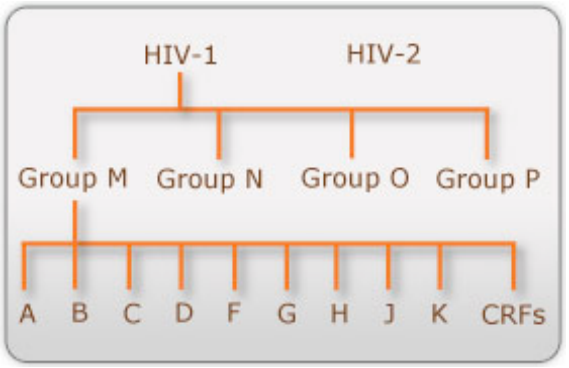
- First isolated Guinea-Bissau, 30-40% identity HIV-1
- Restricted primarily to populations in West Africa
- Less virulent (most infections do not progress to AIDS), transmissible than HIV-1, no mother-infant spread
- Crossover from sooty mangabey
- 8 distinct lineages, each arose from separate infection

HIV-1 diversity



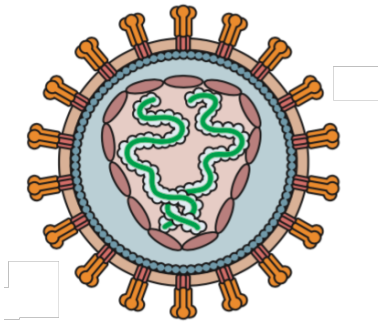
- Four groups based on sequence alignment
- Group M (main): 99% of all HIV-1 infections
- Group O (outlier): <1% of infections, limited to Cameroon, Gabon, neighboring countries
- Group N: Only 13 cases, Cameroon
- Group P: Only 2 cases, Cameroon
- *Each from an independent transmission event of SIV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

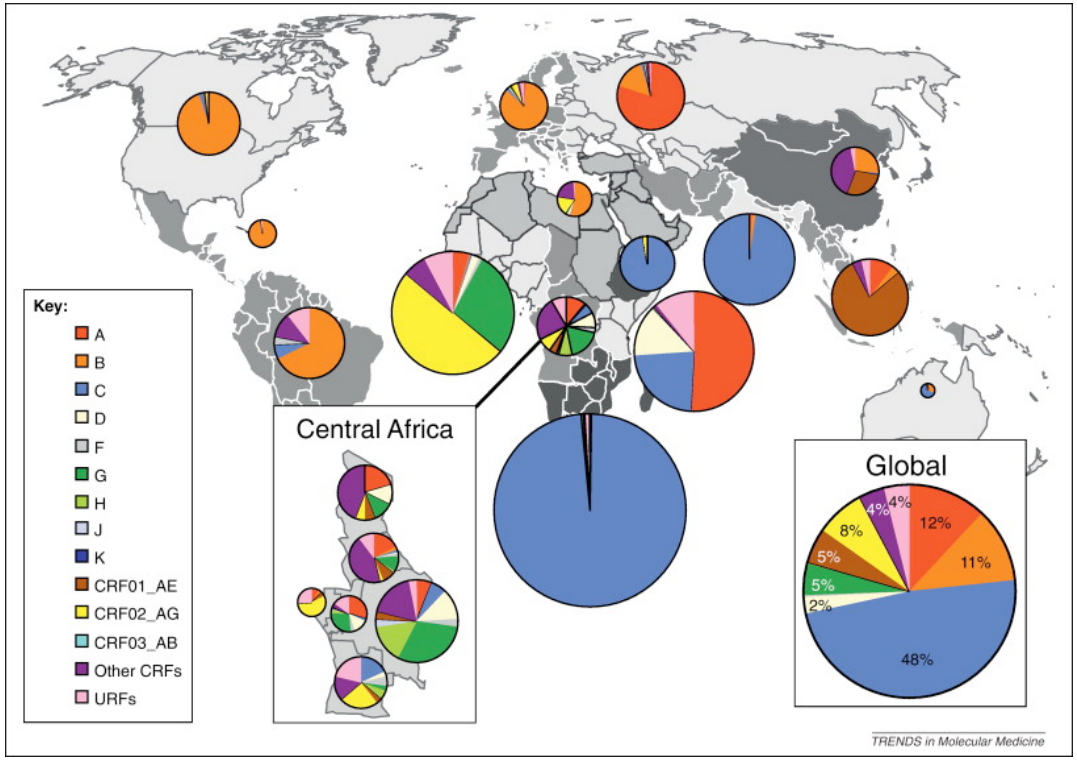


- HIV-1 evolves in one direction to numerous subtypes and recombinants
- Therefore can reconstruct sequence of progress in region or country by examining local distribution of subtypes
- Facilitated in 1990s by new tools enabling examination of nucleotide sequences from large number of isolates
- Extreme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

HIV-1 subtypes

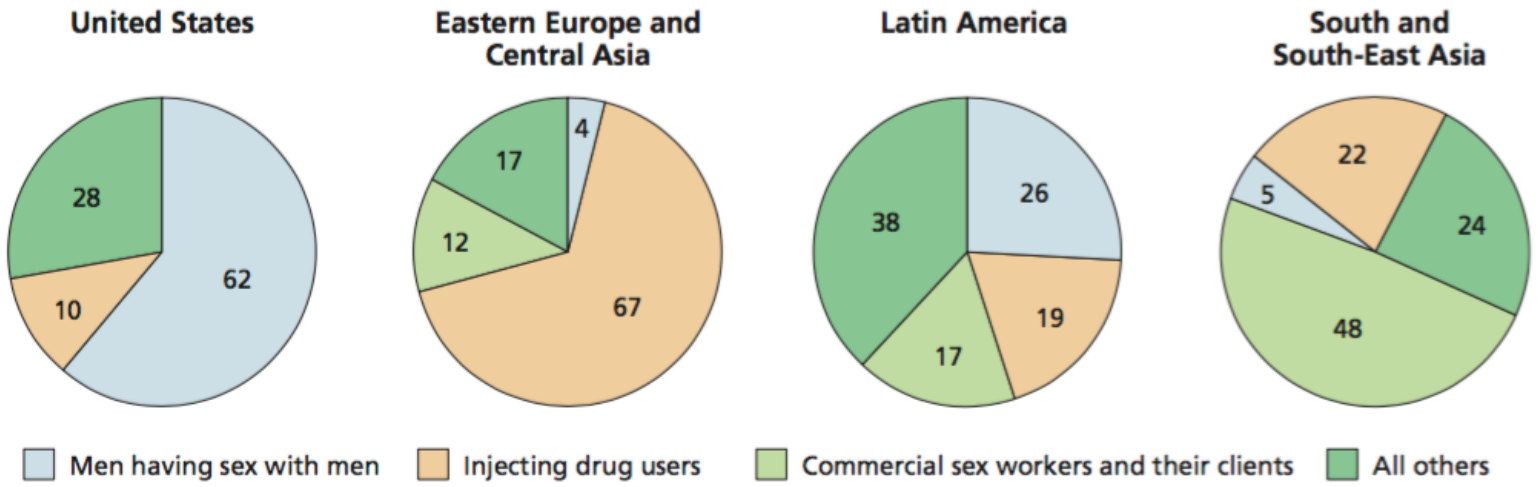
- Some subtypes associated in specific locations with modes of transmission
- Founder effect: subtype will *predominate* in at-risk group
- Example: subtype B found in 96% of white homosexuals in South Africa (imported from US); subtype C accounts for 81% of infections of black heterosexuals

- 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%)



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



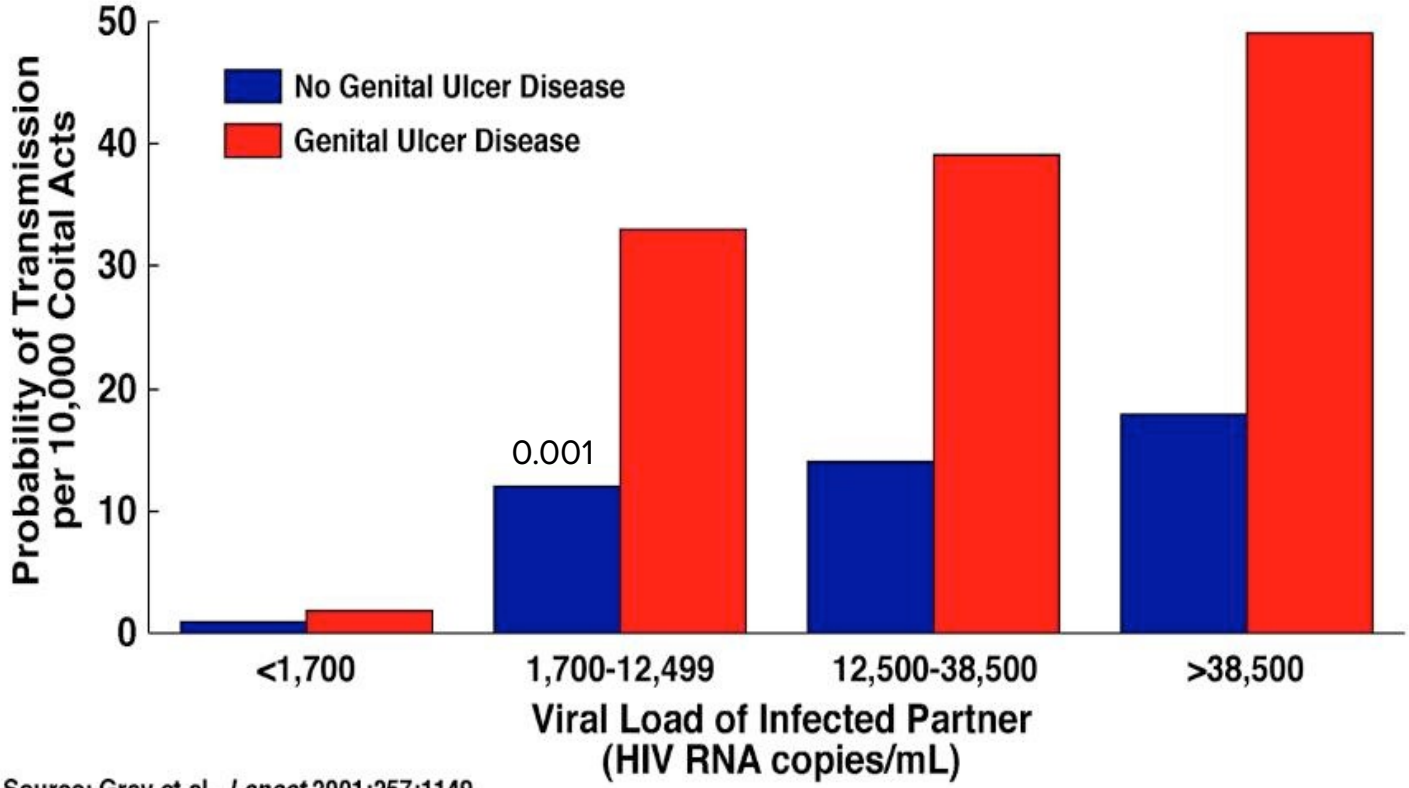
Mother to child at birth, ~5%

Isolation of infectious HIV-1 from body fluids

Fluid	Virus isolation[b]	Estimated quantity of virus[c]
Cell-free fluid		
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[d]
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
Infected cells		
Bronchial fluid	3/24	Not determined
PBMC	89/92	0.001–1%[d]
Saliva	4/11	<0.01%
Semen	11/28	0.01–5%
Vaginal-cervical fluid	7/16	Not determined

Principles of Virology, ASM Press

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



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

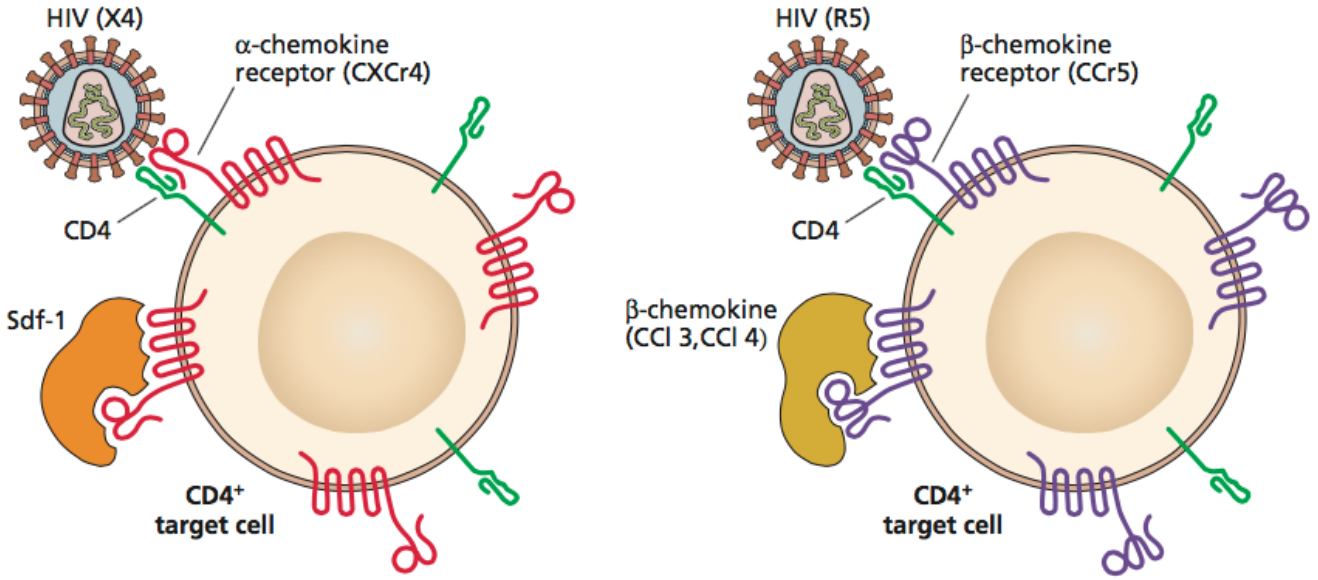
Risk of transmission of HIV-1

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

Transmission

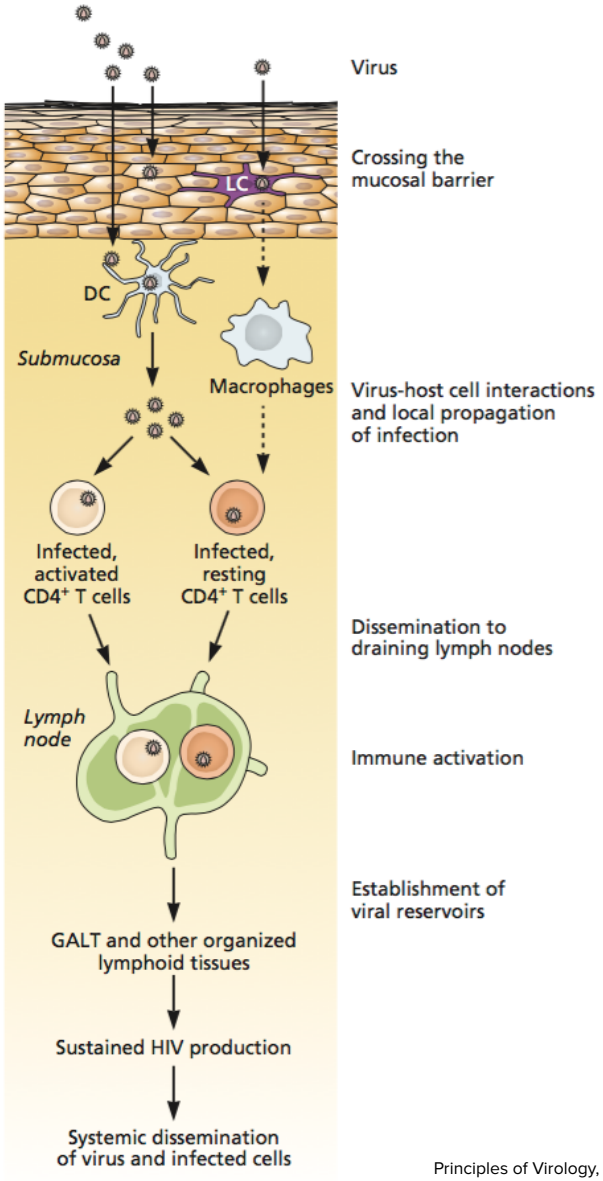
- HIV-1 infectivity reduced by air drying (99%/24 hr)
- By heating (56°C/30 min)
- By 10% bleach or 70% alcohol
- By pH extremes (<6 or >10)
- STD/IVDU bypass these!

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

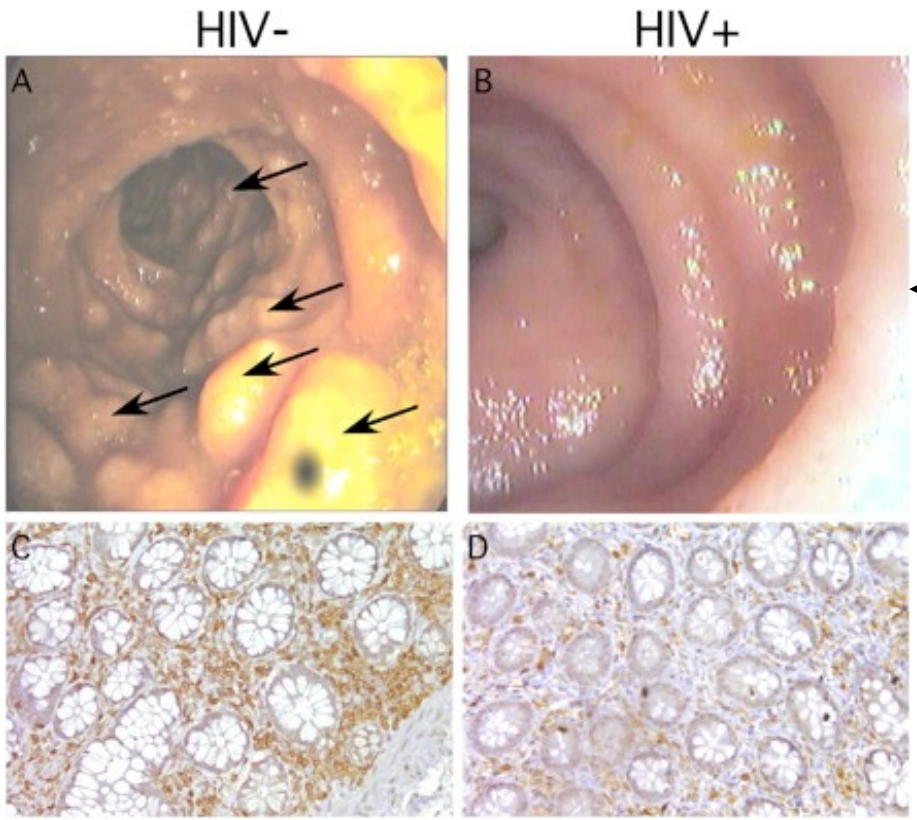


Principles of Virology, ASM Press

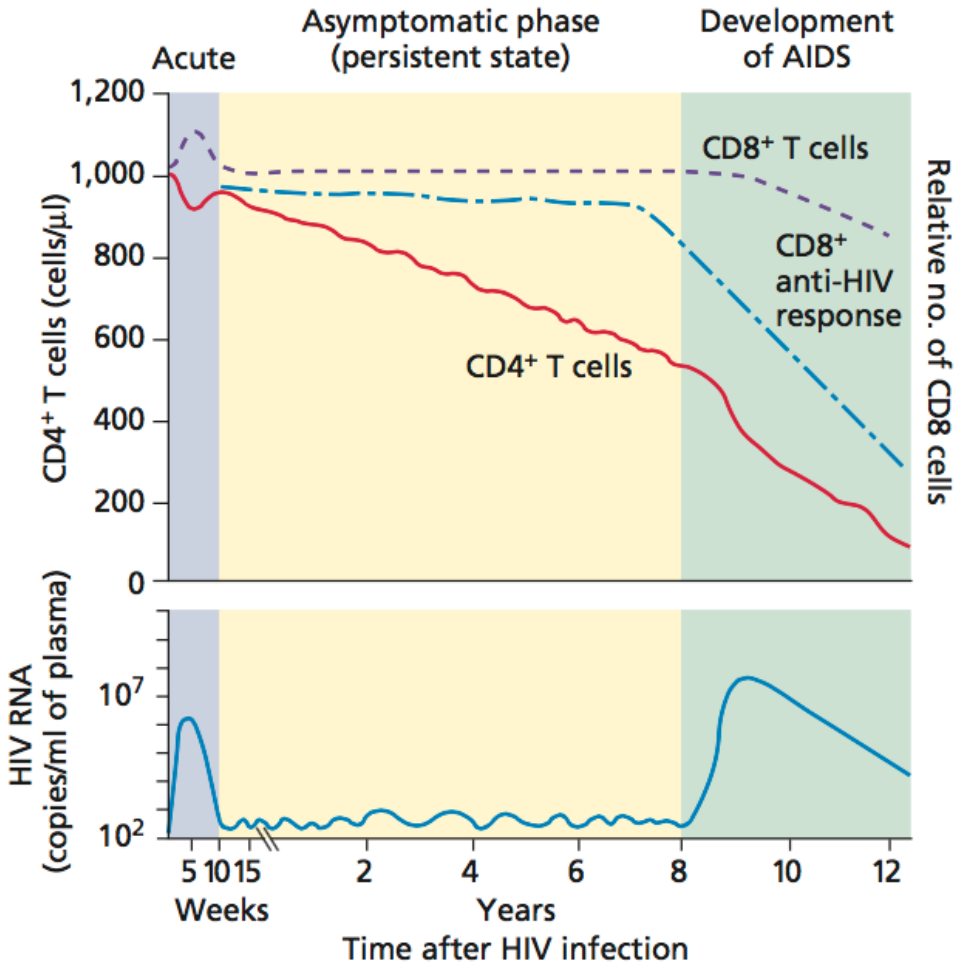
Primary HIV Infection: Clinical characteristics

- 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



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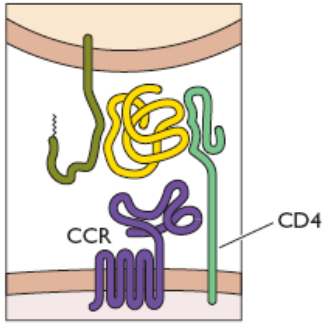
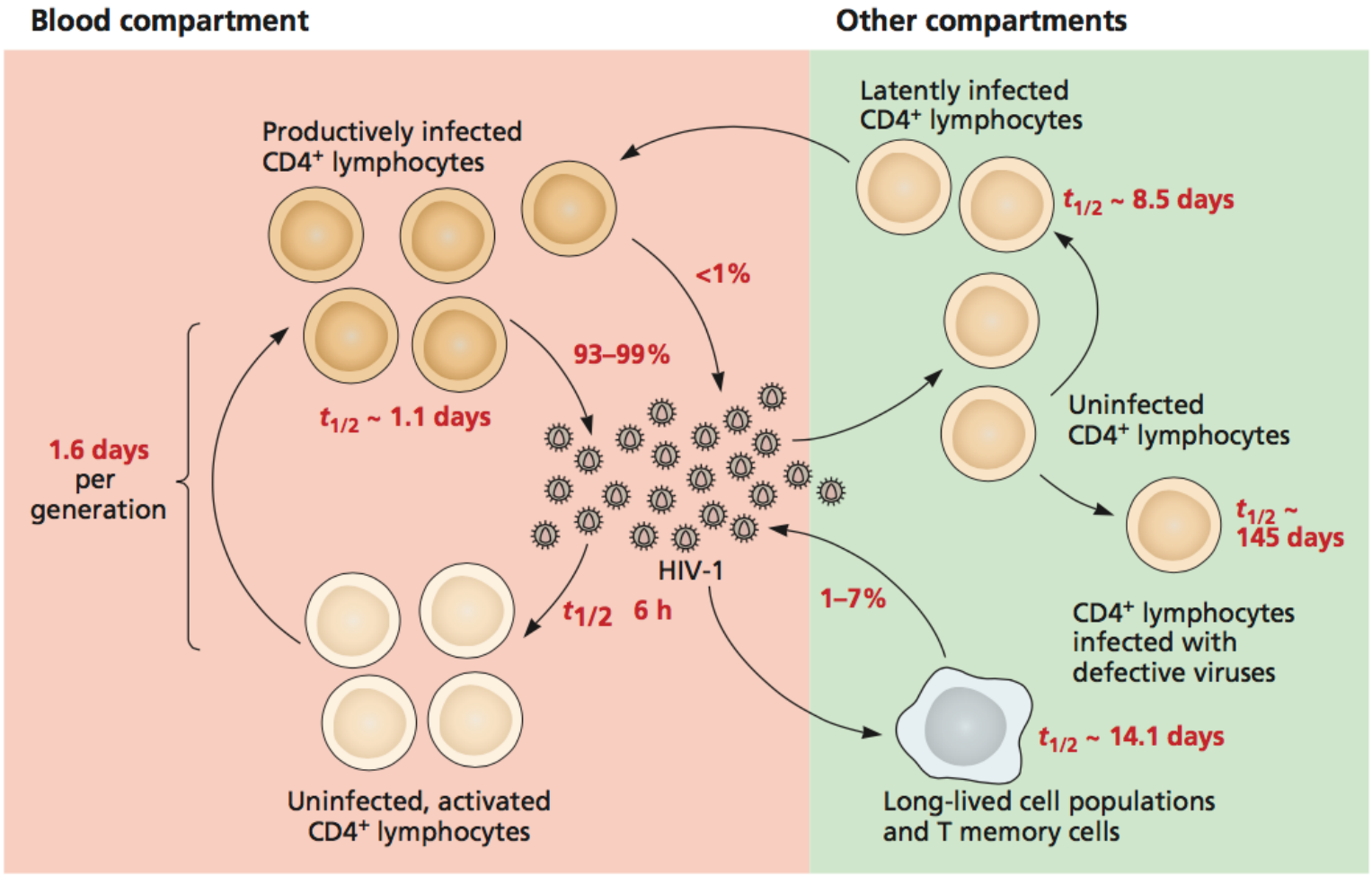
Host genes that determine susceptibility



- 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 10×10^9 virions produced and destroyed each day
- $T_{1/2}$ of HIV in plasma is <6 h and may be as short as 30 min



Multipotent hematopoietic progenitor cells - latent reservoir

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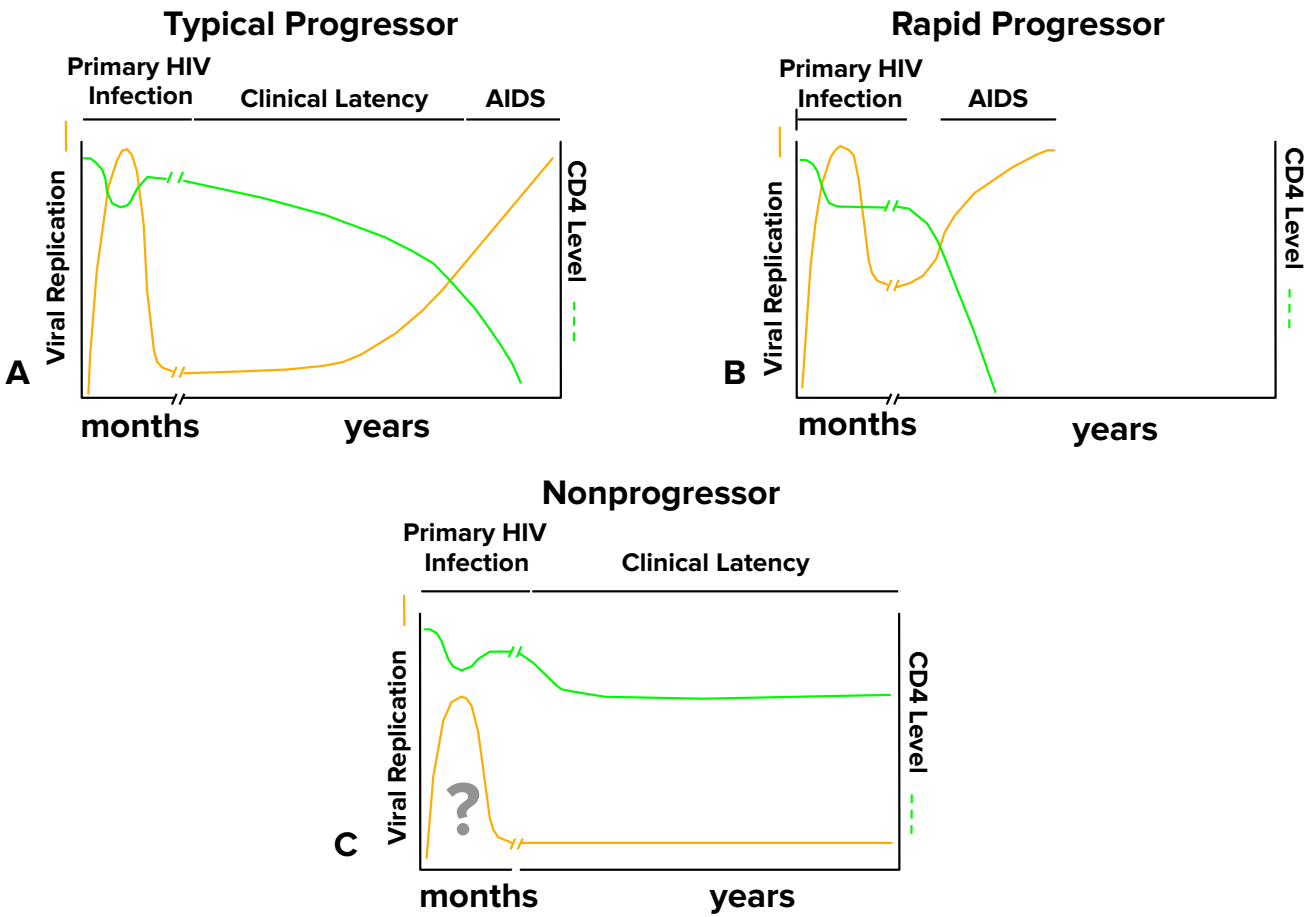
The variable course of HIV-1 infection



Elite HIV Controllers

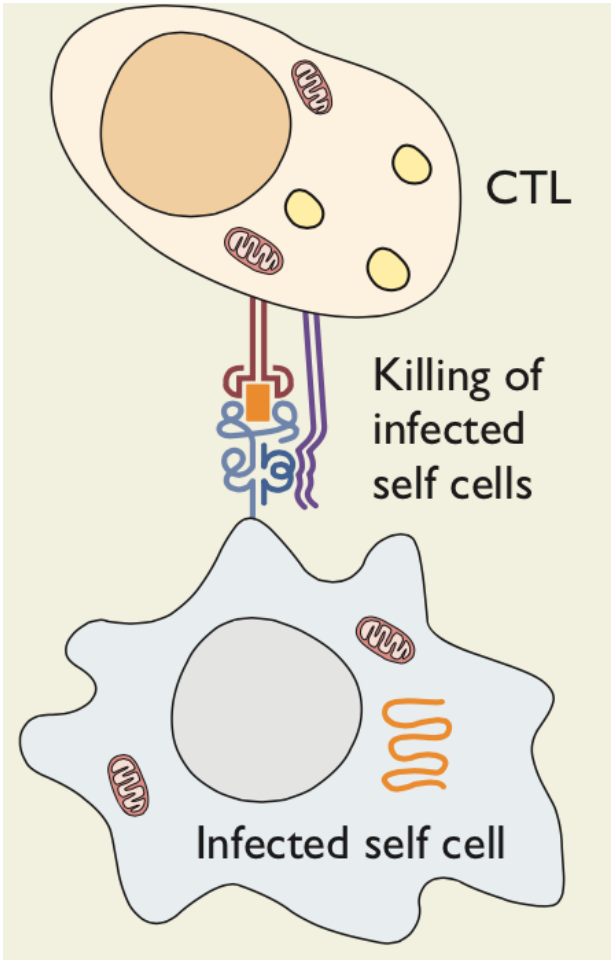
- Individuals who maintain normal CD4 counts and undetectable viral loads (1-30 copies HIV RNA/ml of plasma) for >10 years in the absence of antiretroviral therapy

  - Estimated at 1/300 infected persons

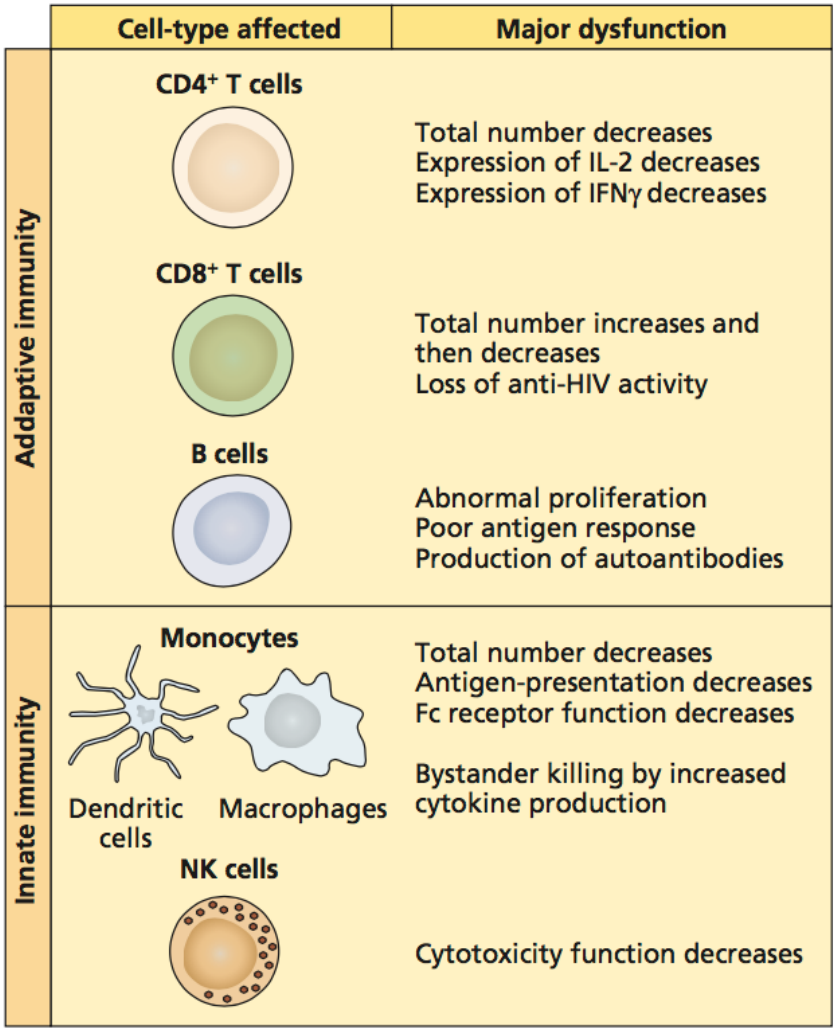
- Associated with favorable HLA (MHC) types (esp HLA B57 and B27) and T-cell responses (CD4 and CD8) to Gag

- Not associated with attenuated viruses

Virus susceptibility mapping to MHC



Immune cell dysfunction in AIDS



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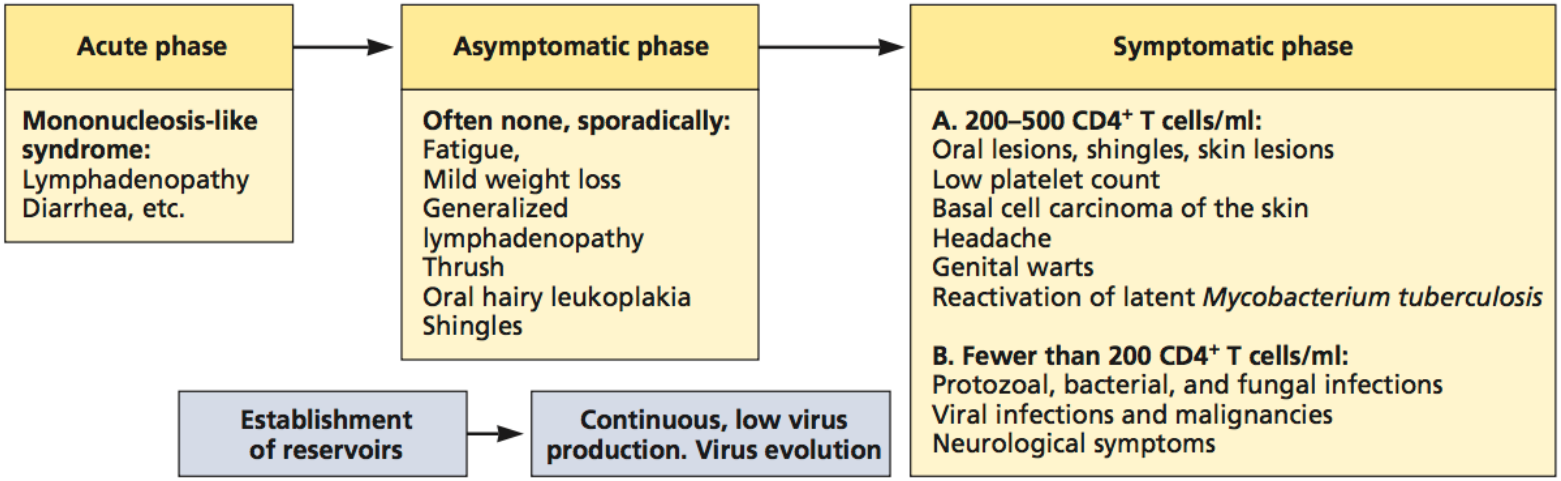
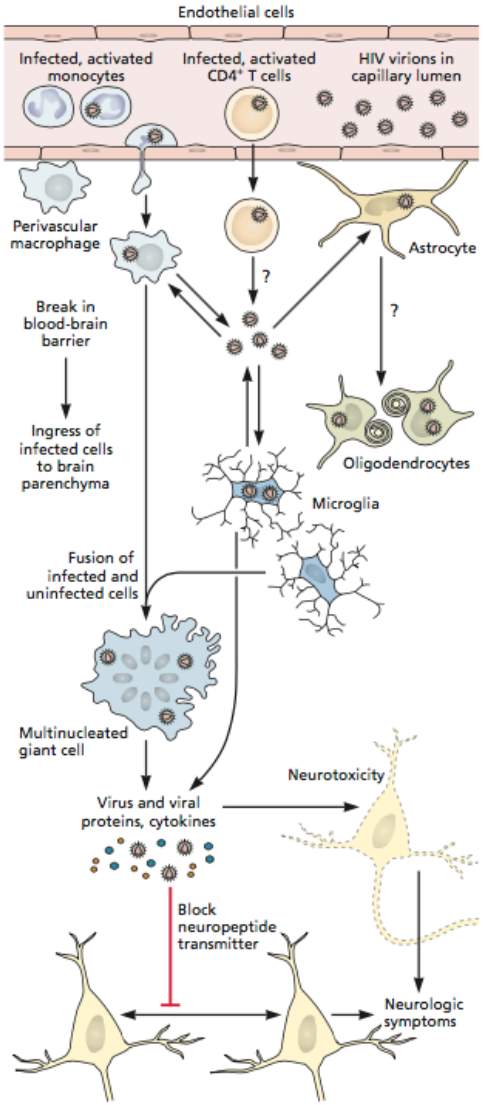
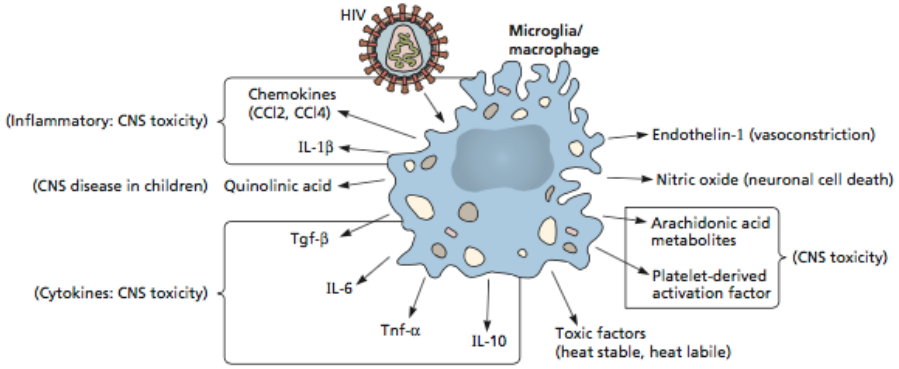
AIDS

- <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


Acute phase
Mononucleosis-like syndrome:
Lymphadenopathy
Diarrhea, etc.
Asymptomatic phase
Often none, sporadically:
Fatigue,
Mild weight loss
Generalized lymphadenopathy
Thrush
Oral hairy leukoplakia
Shingles
Symptomatic phase
A. 200–500 CD4+ T cells/ml:
Oral lesions, shingles, skin lesions
Low platelet count
Basal cell carcinoma of the skin
Headache
Genital warts
Reactivation of latent Mycobacterium tuberculosis
B. Fewer than 200 CD4+ T cells/ml:
Protozoal, bacterial, and fungal infections
Viral infections and malignancies
Neurological symptoms
Establishment of reservoirs
Continuous, low virus production. Virus evolution

Neurological symptoms





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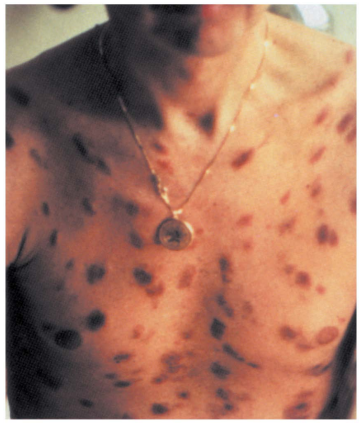
HIV and cancer

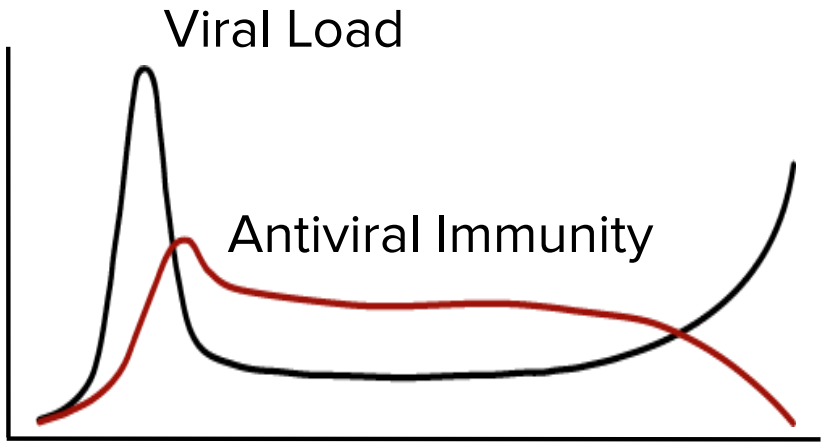
- HIV-1 infection leads to increase incidence of malignancy: 40% of infected individuals
- An indirect effect of dysregulation of the immune system
  - Absence of proper immune surveillance
  - High levels of cytokines leads to inappropriate cell proliferation, replication of oncogenic viruses (EBV,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

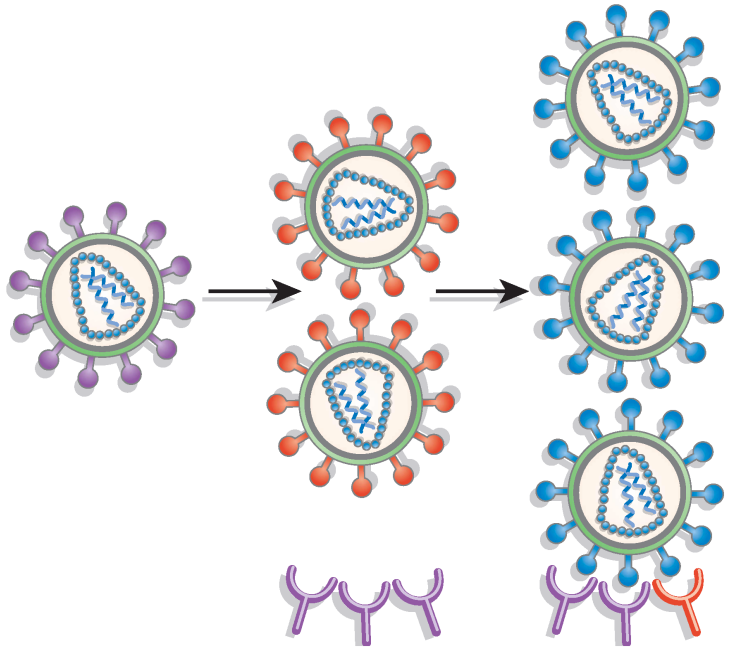


How does HIV-1 persist despite effective anti-viral immunity?

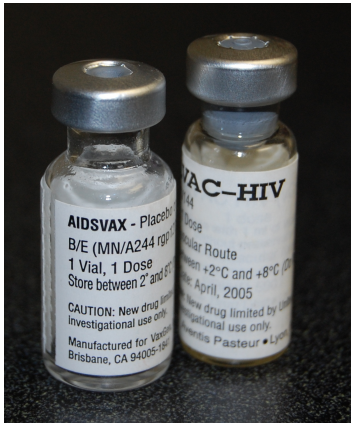
How does it eventually outstrip immune control?

HIV-1 superinfection occurs less frequently than initial infection

HIV-1 escape from neutralizing antibody



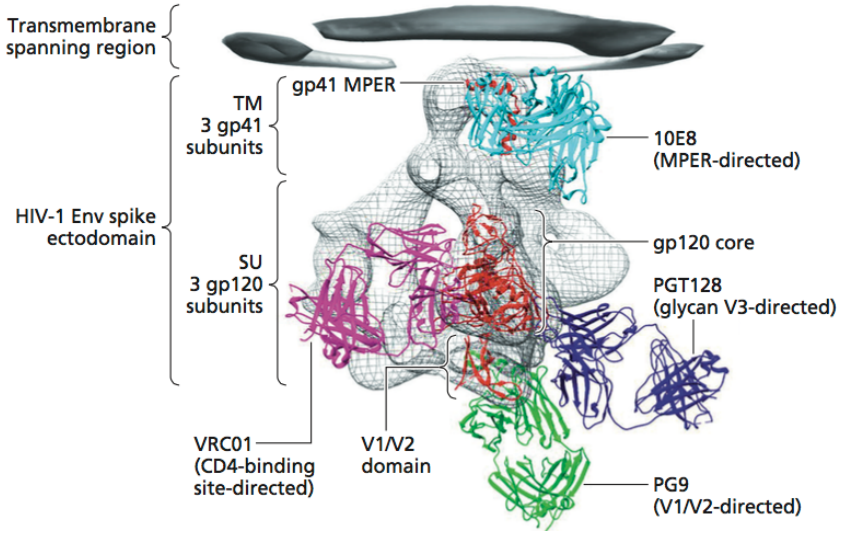
RV144



- 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

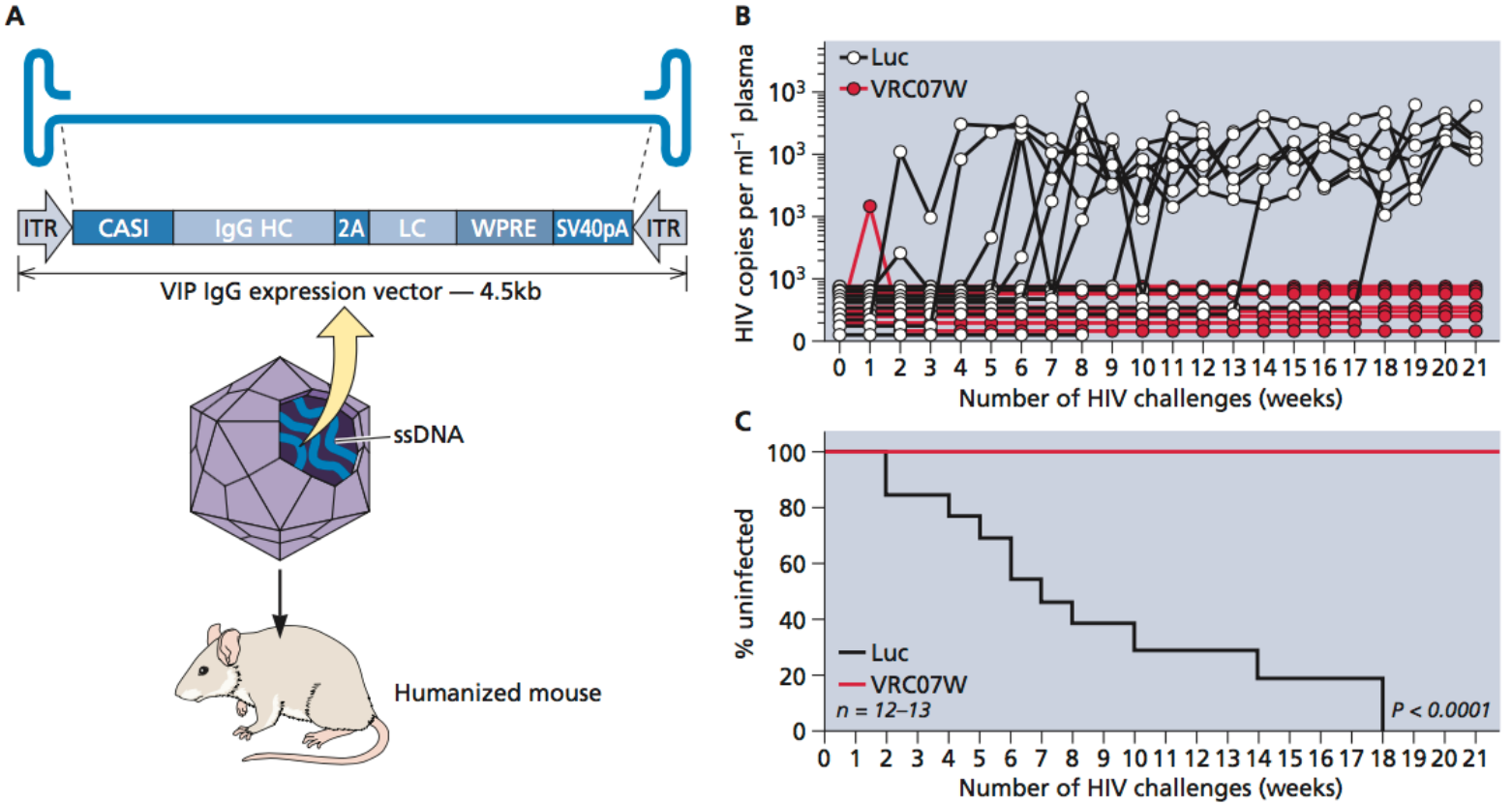
http://www.nejm.org/doi/full/10.1056/NEJMoa0908492

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



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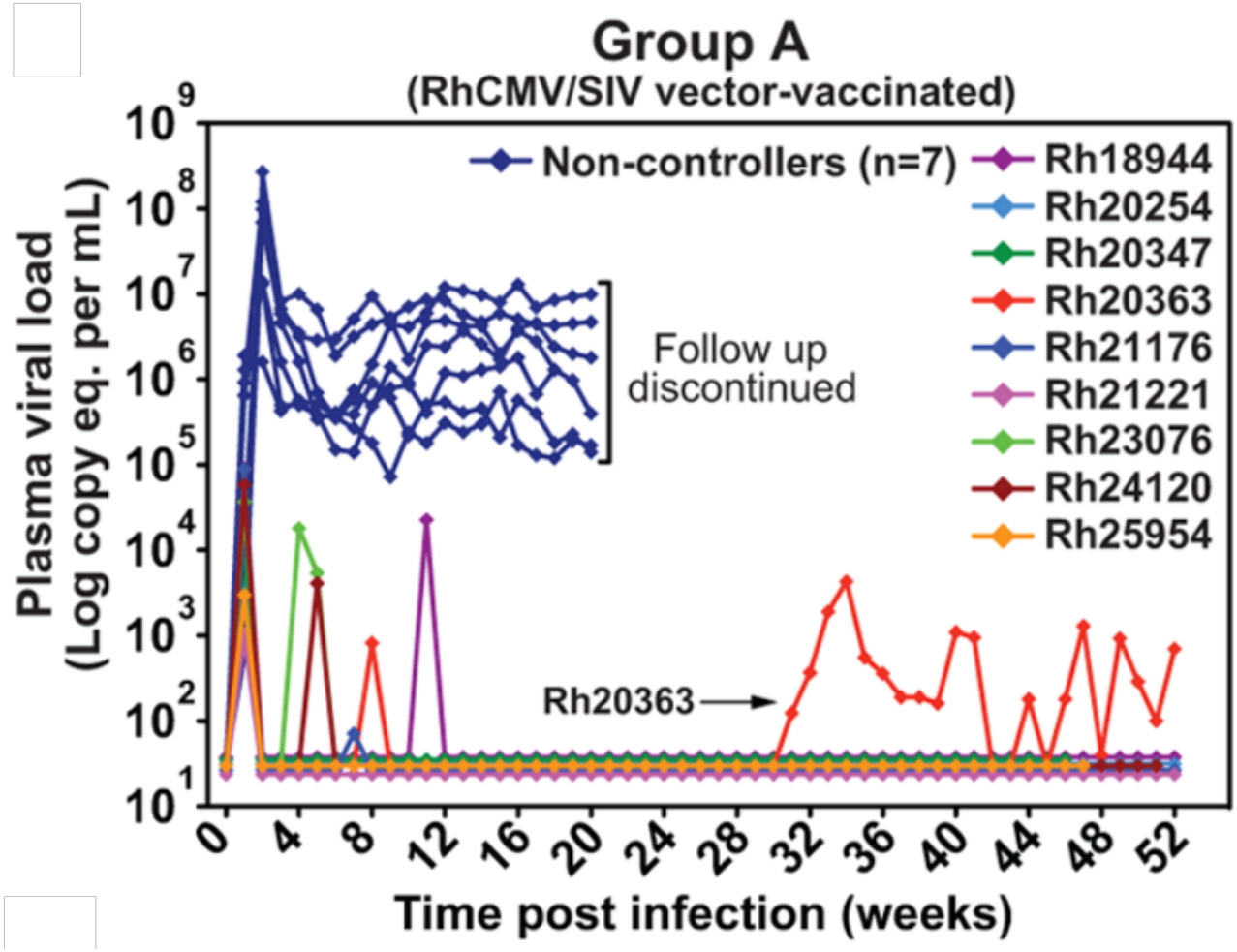
Immune clearance of SIV in macaques



Nature. 2013 October 3; 502(7469)

SIV

~1921: Patient zero

HIV

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