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Human immunodeficiency virus (HIV)

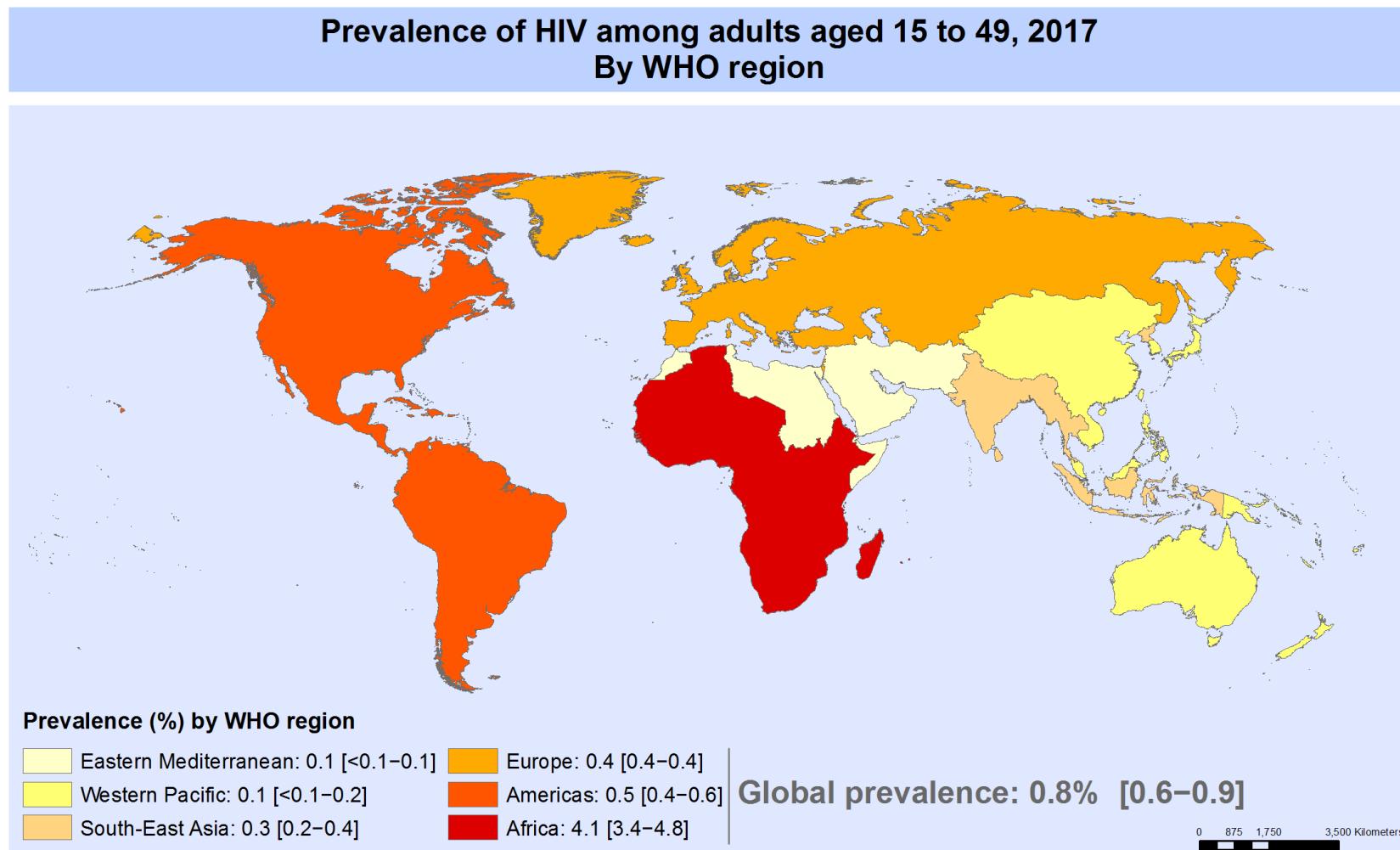
BIOL345 2021

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36.9 million people living with HIV worldwide



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Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization



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AIDS

Acquired immunodeficiency syndrome

- Non-functioning immune system (low CD4-T)
- Increase number of opportunistic infections (Candida, TB, Pneumonia)
- If untreated will eventually lead to death
- ~ 1 Million people die of AIDS each year

Transmission routes

- Sexual contact
- Contaminated blood (needle sharing, blood transfusions)
- Mother to child (pregnancy, birth or breast feeding)

HIV IS NOT TRANSMITTED BY



Air or Water



Saliva, Sweat, Tears, or
Closed-Mouth Kissing

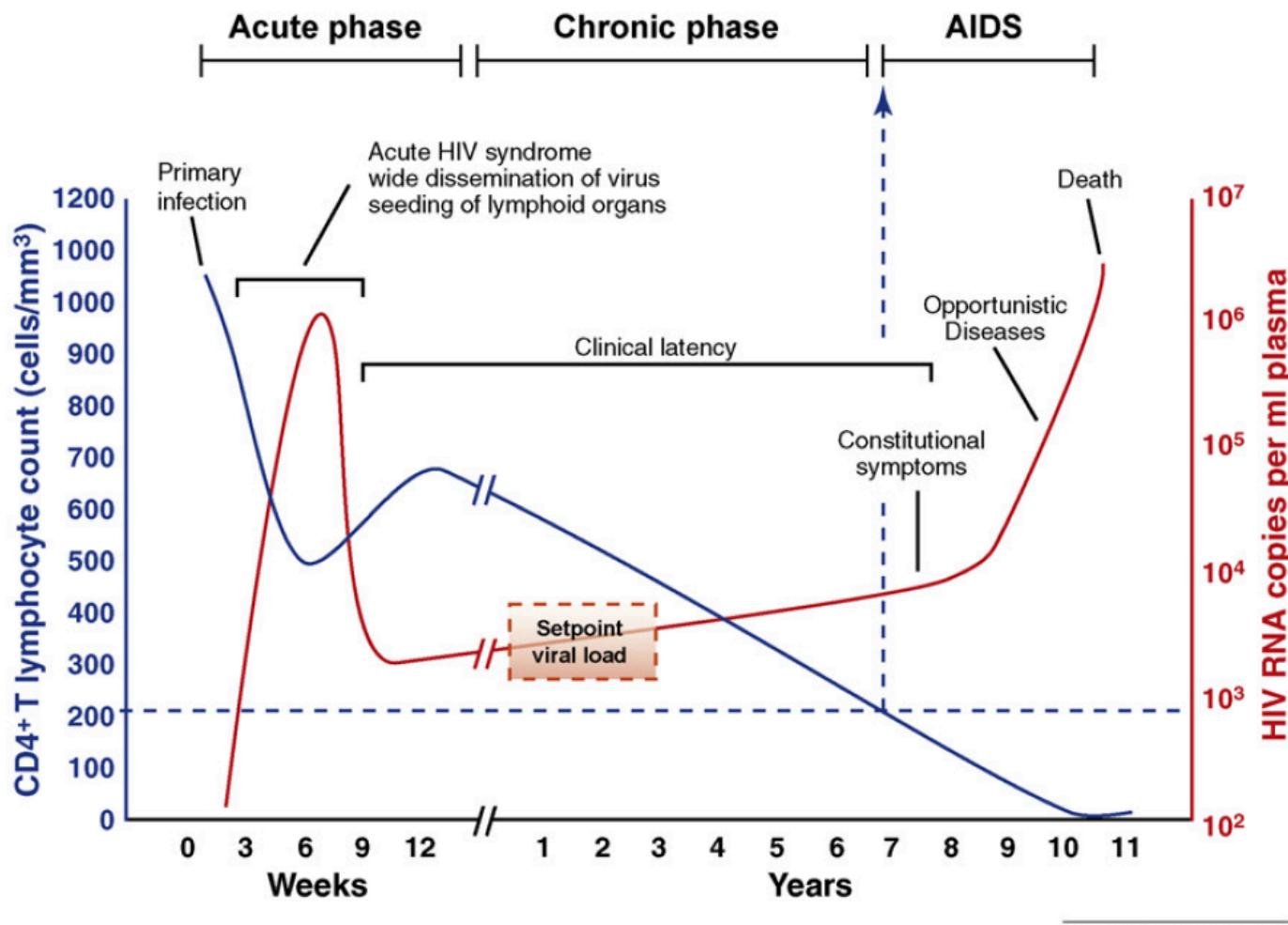


Insects or Pets



Sharing Toilets,
Food, or Drinks

Disease progression



TRENDS in Genetics

HIV1 ‘Cured’

Berlin patient 2009



Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S.,
Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D.,
Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D.,
Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D.,
and Eckhard Thiel, M.D.

Hütter et al. *N Engl J Med* 360:692-698; 2009

London patient 2019

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K. Gupta, Sultan Abdul-Jawad, Laura E. McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M. J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew J. Innes, Luke Muir, Laura Waters, John Frater, Andrew M. L. Lever, Simon G. Edwards, Ian H. Gabriel & Eduardo Olavarria

Gupta et al. *Nature* 568:244-248; 2019

Don't do this

World's first gene-edited babies created in China, claims scientist

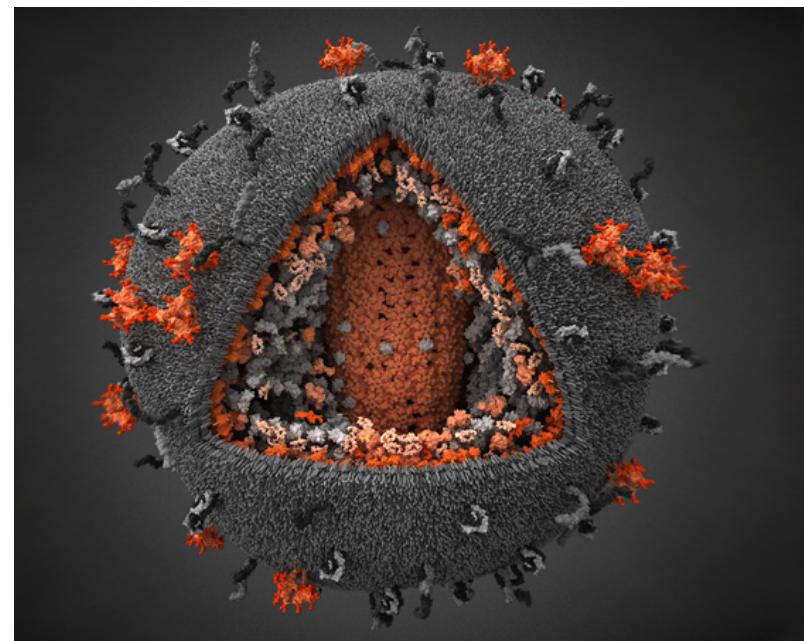
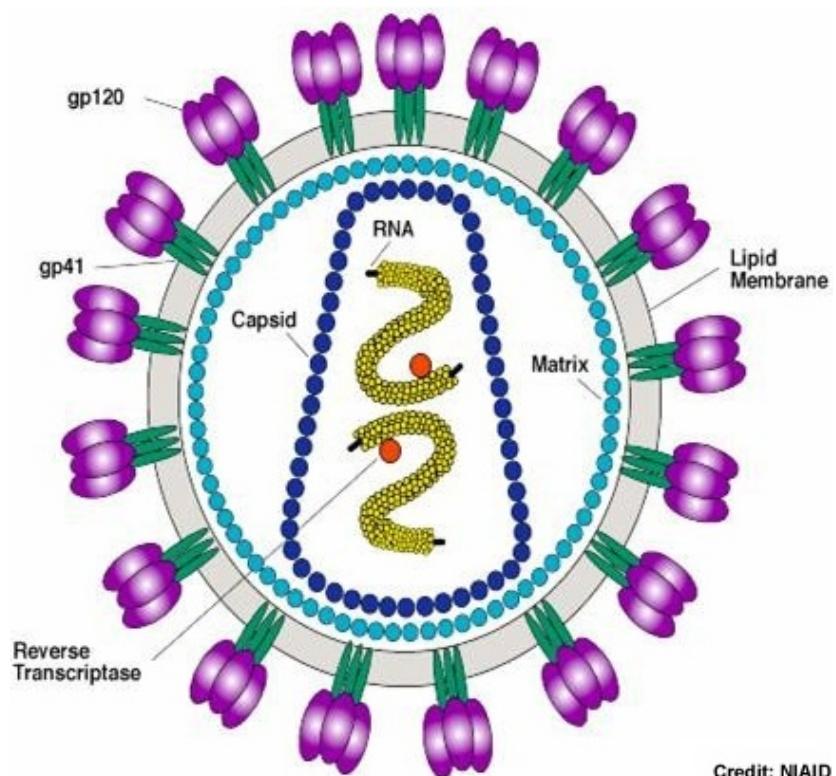
Unconfirmed scientific breakthrough sparks ethical and moral concerns

CRISPR bombshell: Chinese researcher claims to have created gene-edited twins

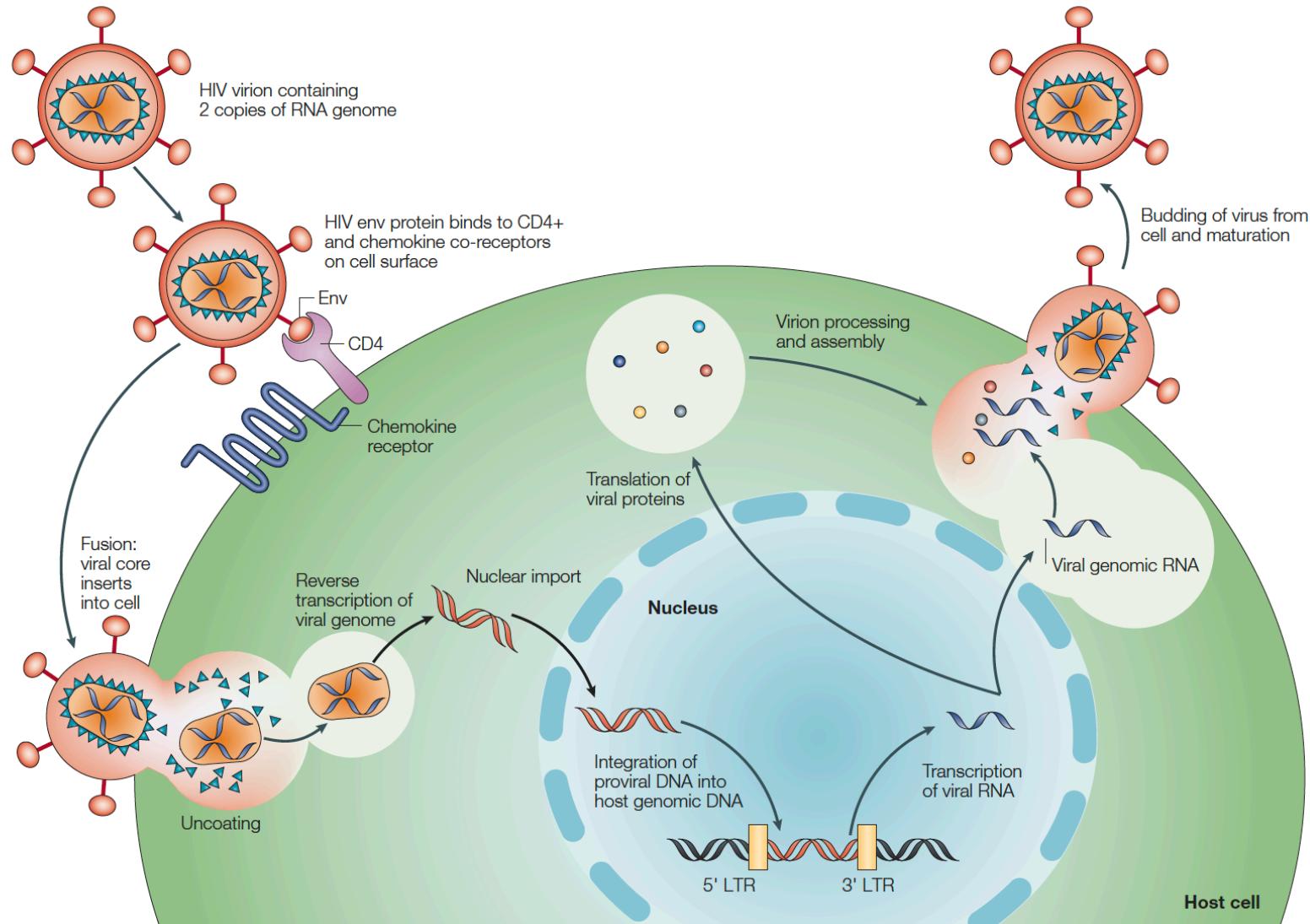
First gene-edited babies born in China, scientist claims

A Chinese researcher has sparked controversy after claiming to have used gene-editing technology known as CRISPR to help make the world's first genetically modified babies.

HIV Virion

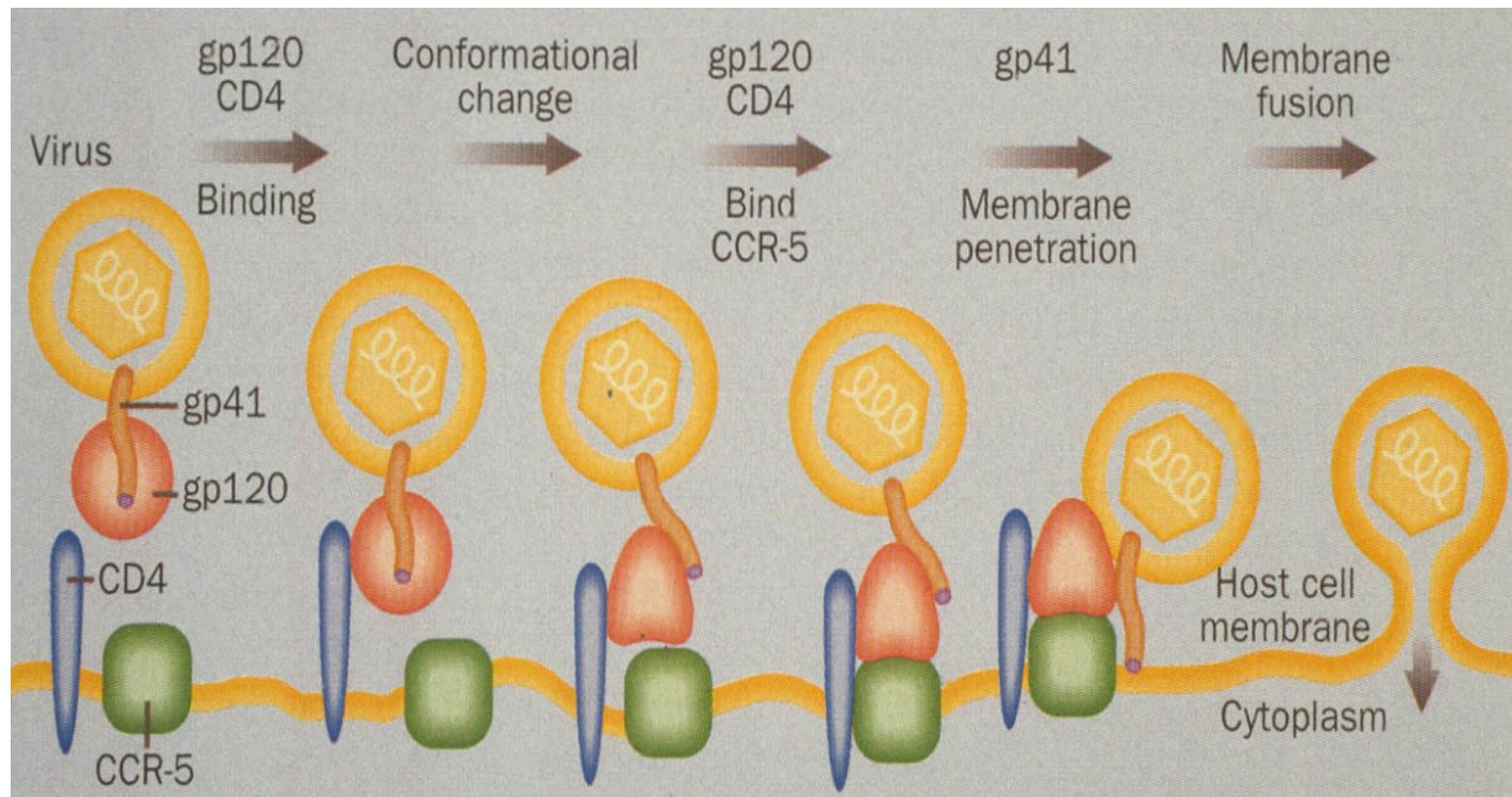


Life Cycle



HIV tropism

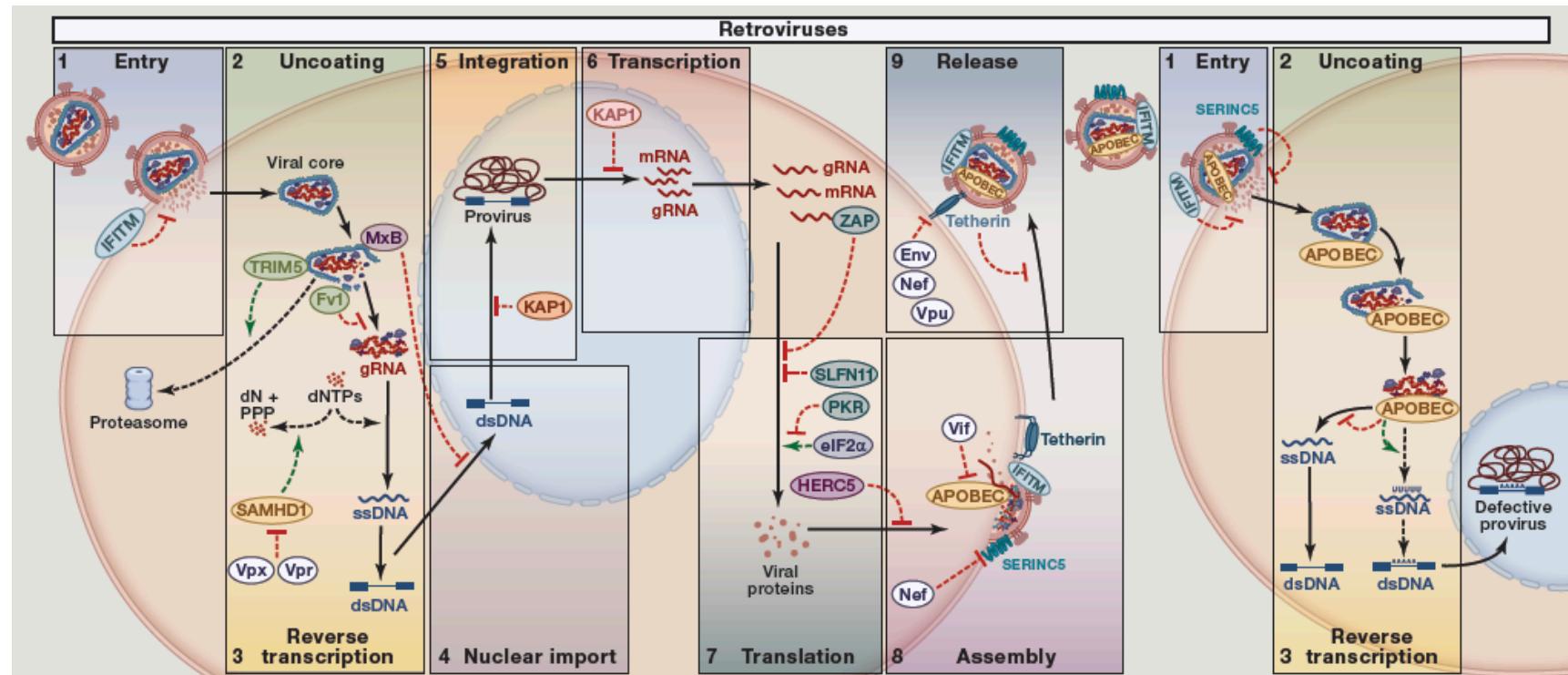
CD4 T cells have both CCR5 and CXCR4 co-receptors
Macrophages & dendritic cells have CCR5 co-receptor



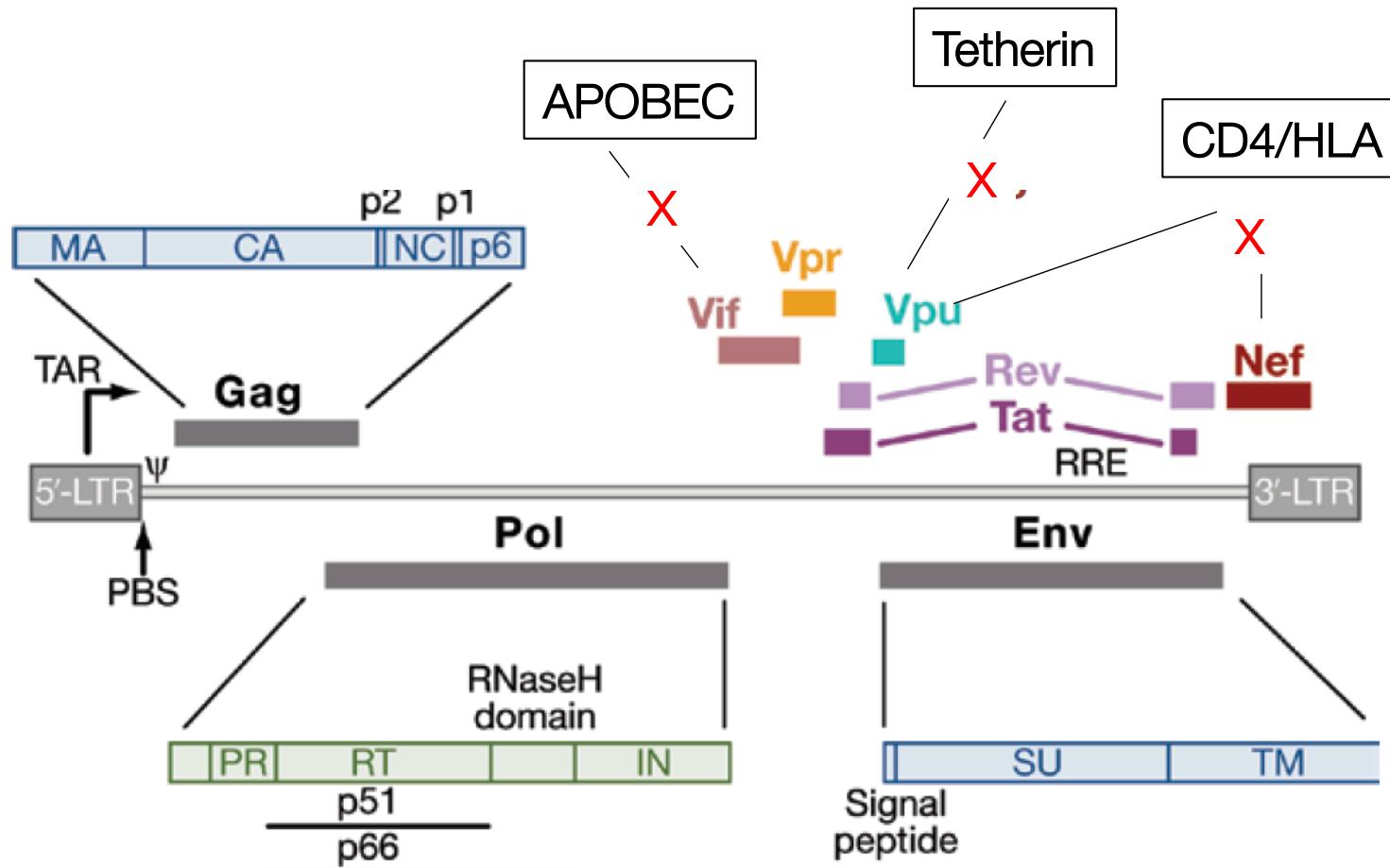
Host defense mechanisms

- Antiviral restriction factors
- Genetic factors - polymorphisms

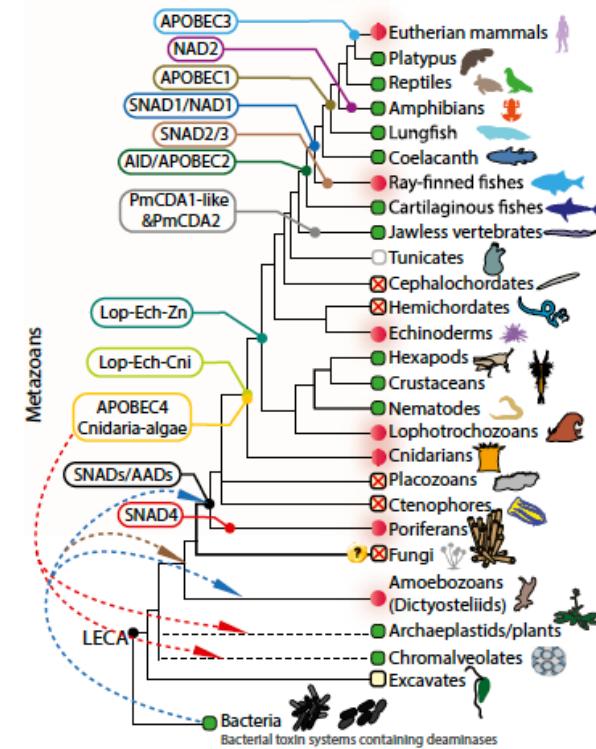
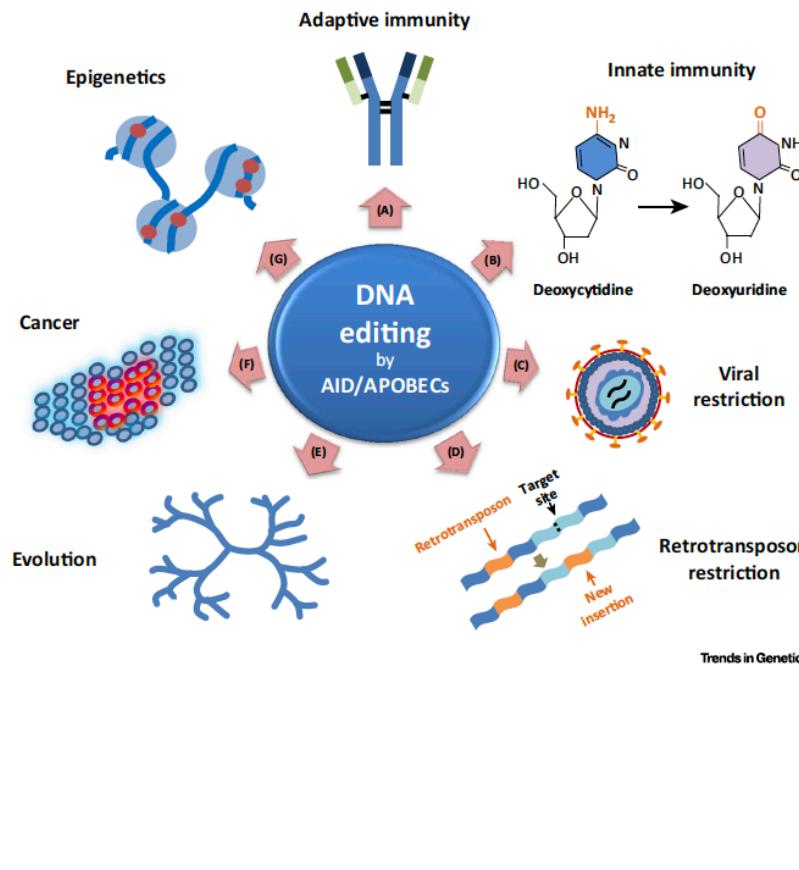
Antiviral restriction factors



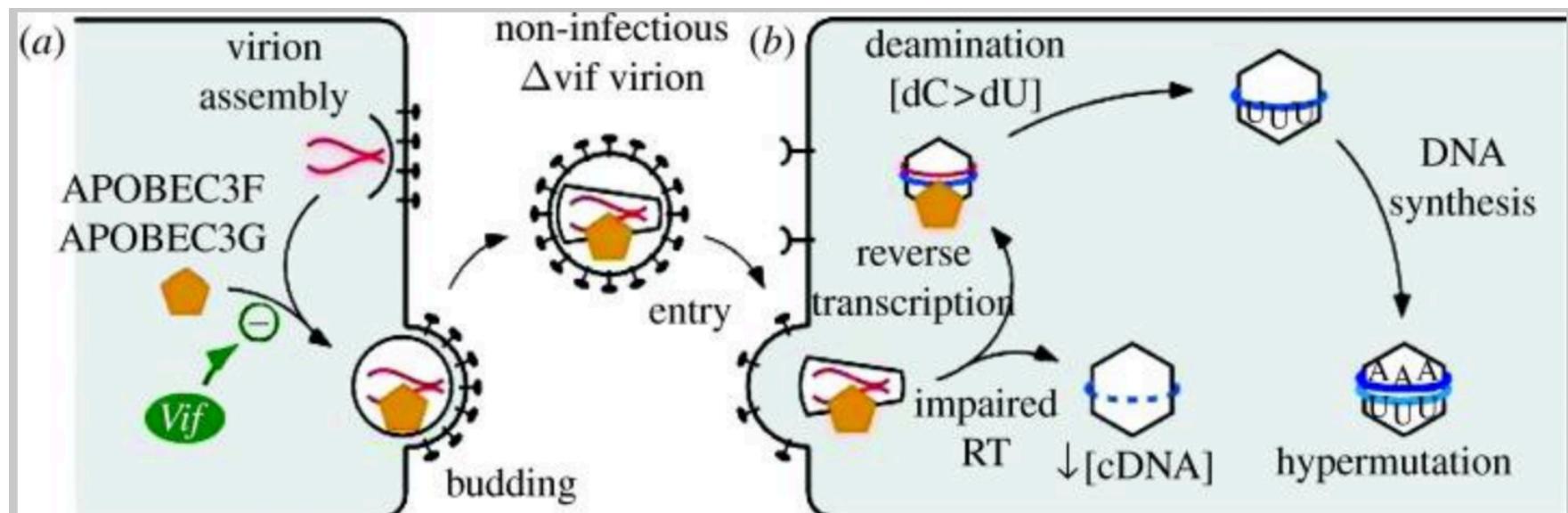
Accessory proteins



APOBEC has many functions



APOBEC3FG target HIV-1



Long-term non progressors

‘Elite-controllers’ that do not develop AIDS

- Robust CD8+ T cell immune response against HIV
- Or a poorly replicative virus
- CD4 > 500 (~ 30 years to AIDS)
- Genetic factors: Human leukocyte antigens (HLA) B57

HLA* B57

- Human major histocompatibility complex
- Crucial for immune system differentiation between ‘self’ and ‘foreign’
- 17,698 different HLA alleles
- ~ 4,950 HLA Class I B alleles
- 1 – 10% of population

HLA* B57 protection in HIV

- People carrying the B57 serotype have a higher risk of developing autoimmune disease
 - Study found that HLA B57 carriers recognise a broader range of antigens
- ‘accept’ more mutations

‘Immune’ individuals

Exposed but uninfected individuals

- Very resistant to HIV infection
- Mutant chemokine receptors (CCR5 delta 32)

CCR5 delta32

- 32 bp deletion leads to non-functional receptor
- Mainly found in European population
- Homozygous individuals are resistant to R5'-tropic HIV (1% in Europe)
- Heterozygous individuals are less susceptible and experience slower disease progression (10% in Europe)

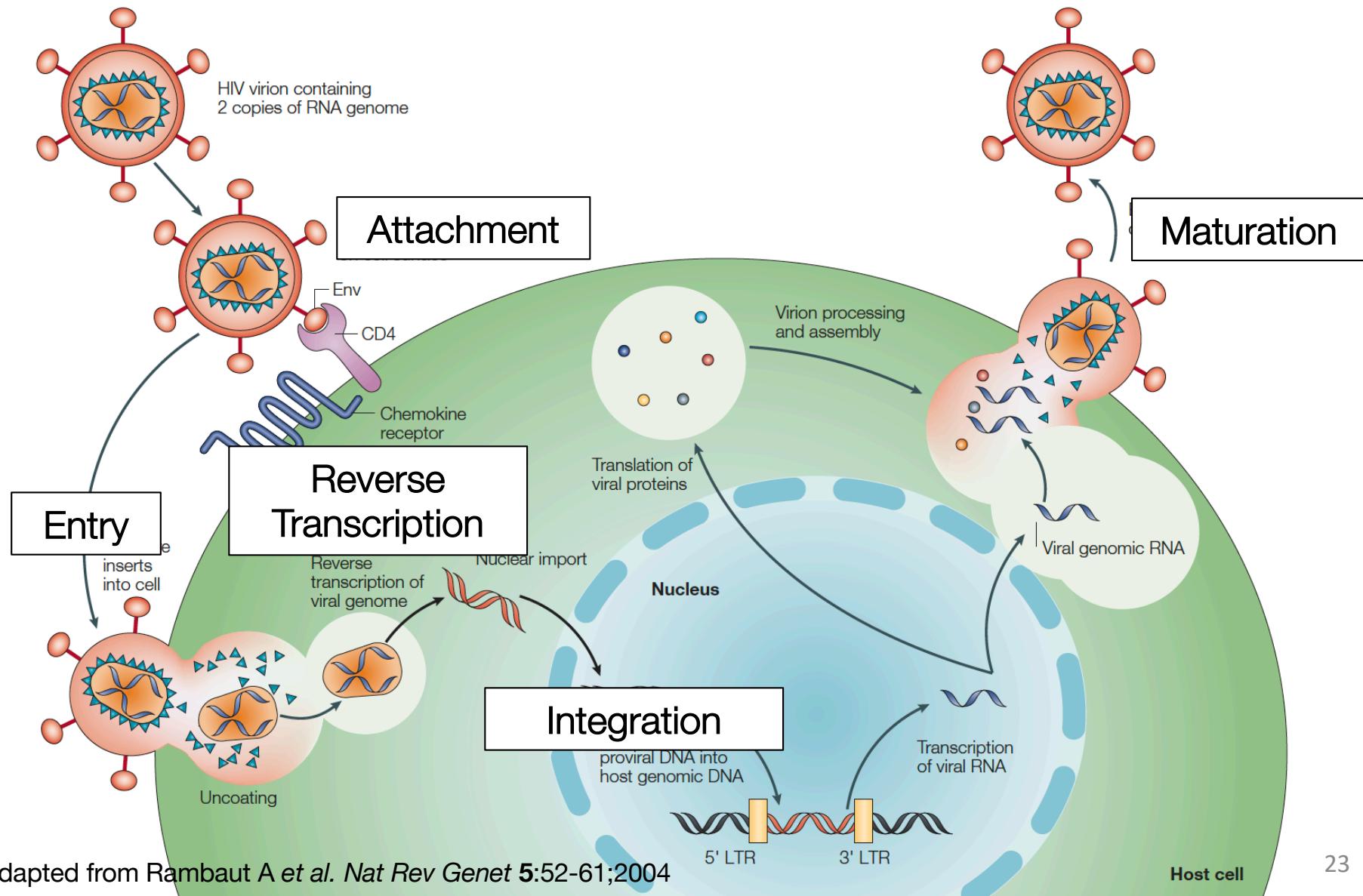
CCR5 delta32

- CCR5 delta32/delta32 transplant not feasible for everyone
- Does not prevent infection from X4-tropic HIV
- Don't fret! There is a pill!

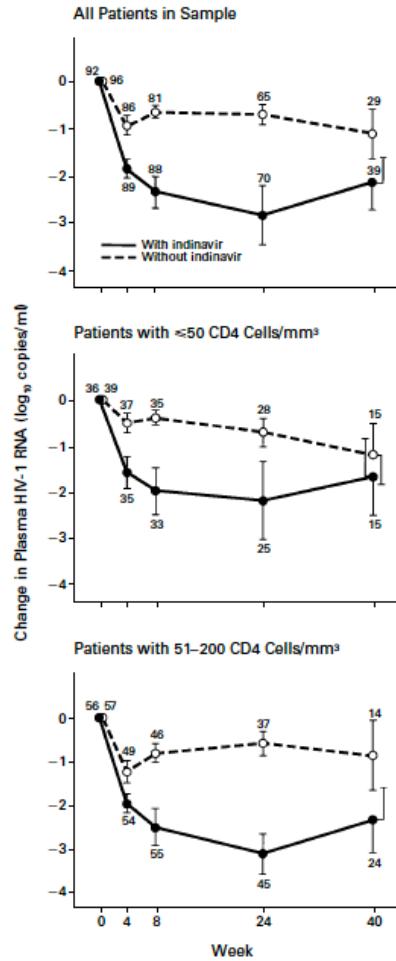
Antiretroviral therapy (ART) past

- First drug approved in 1987 (nucleoside reverse transcriptase inhibitor (NRTI))
- Failed to suppress viral load successfully
- In 1996 the combination of two NRTI with another drug class showed to be effective
- First, and until recently, only effective therapy for a viral infection

Drug targets



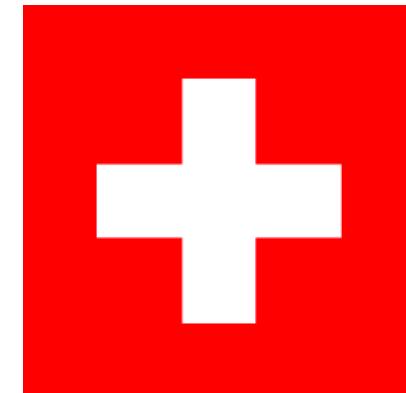
ART present



- Combination therapy successfully suppresses viral load
- CD4 count remains high
- Chronic infection
 - no AIDS
 - no transmission

Swiss statement

- “HIV positive individuals not suffering from any other STD and adhering to an effective antiretroviral treatment do not transmit HIV sexually.”



$$U = U$$

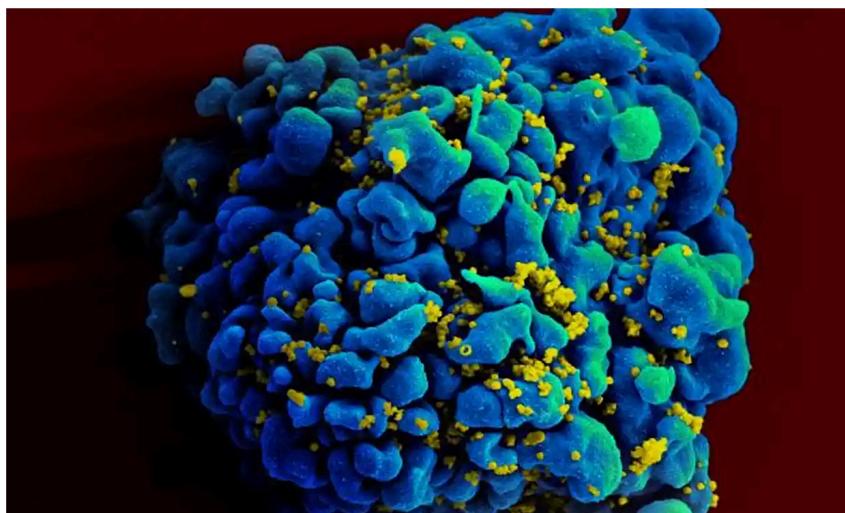
Undetectable viral load equals untransmissible

Aids and HIV

End to Aids in sight as huge study finds drugs stop HIV transmission

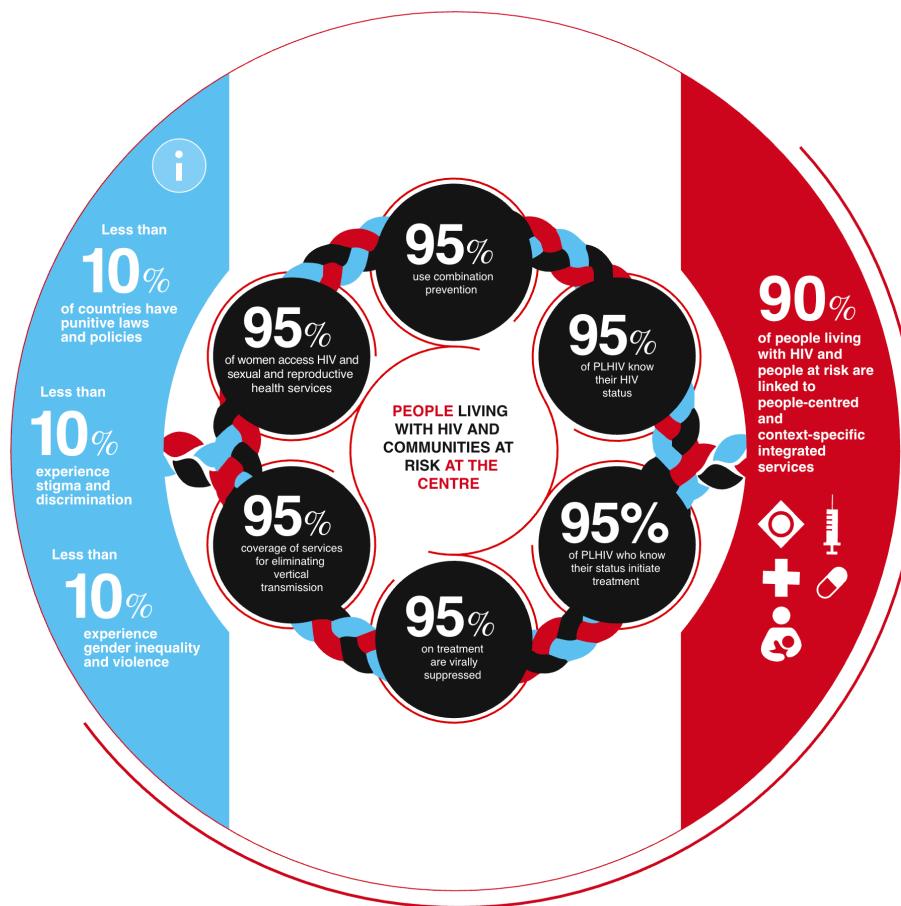
Paper says risk between male partners is zero if virus fully suppressed by antiretrovirals

● [Aids and HIV timeline: from Terry Higgins to PrEP](#)



Over 1,500 zero-discordant couples followed over 2 years. Zero HIV-transmission events occurred.

UNAIDS Target for 2025



Treatment as prevention

- PEP (post-exposure prophylaxis)

3 drug combination

- PrEP (pre-exposure prophylaxis)

2 drug combination

NSW at the forefront

J Int AIDS Soc. 2018 Apr;21(4):e25109. doi: 10.1002/jia2.25109.

The 2016 HIV diagnosis and care cascade in New South Wales, Australia: meeting the UNAIDS 90-90-90 targets.

Keen P¹, Gray RT¹, Telfer B², Guy R¹, Schmidt HM³, Whittaker B³, Holden J³, Holt M⁴, Kelleher A¹, Wilson D⁵, Callander D¹, Cooper DA¹, Prestage G¹, Selvey C², Grulich AE¹; NSW HIV Prevention Partnership Project.

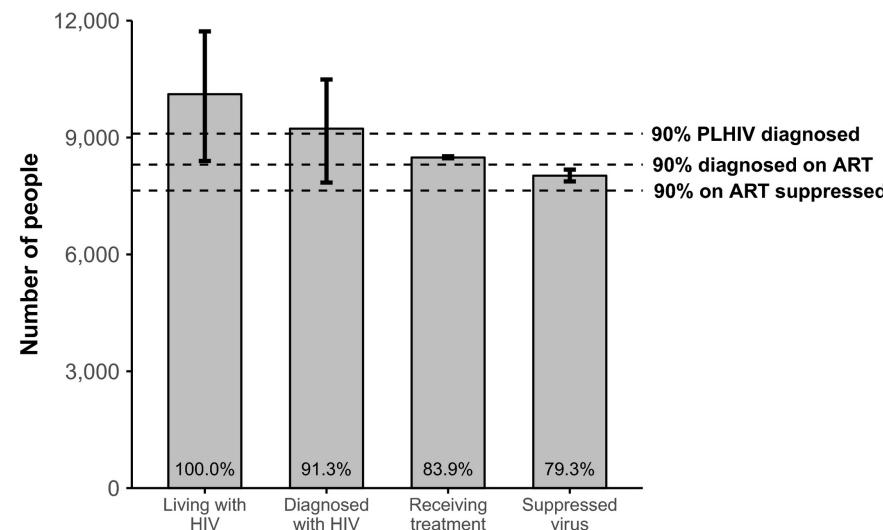
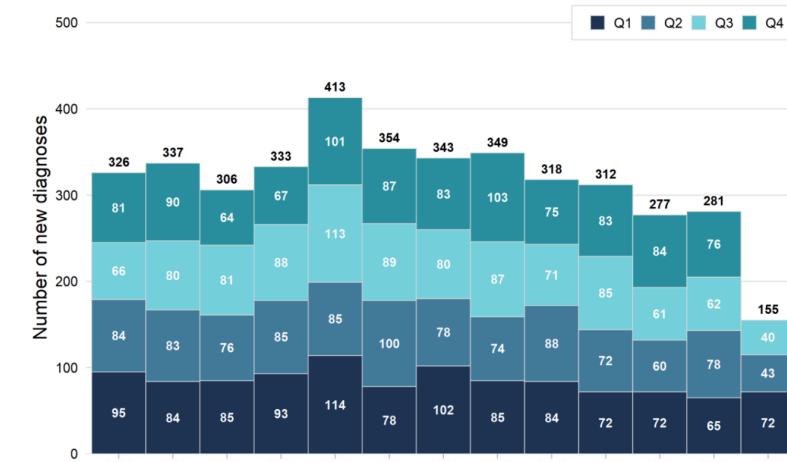
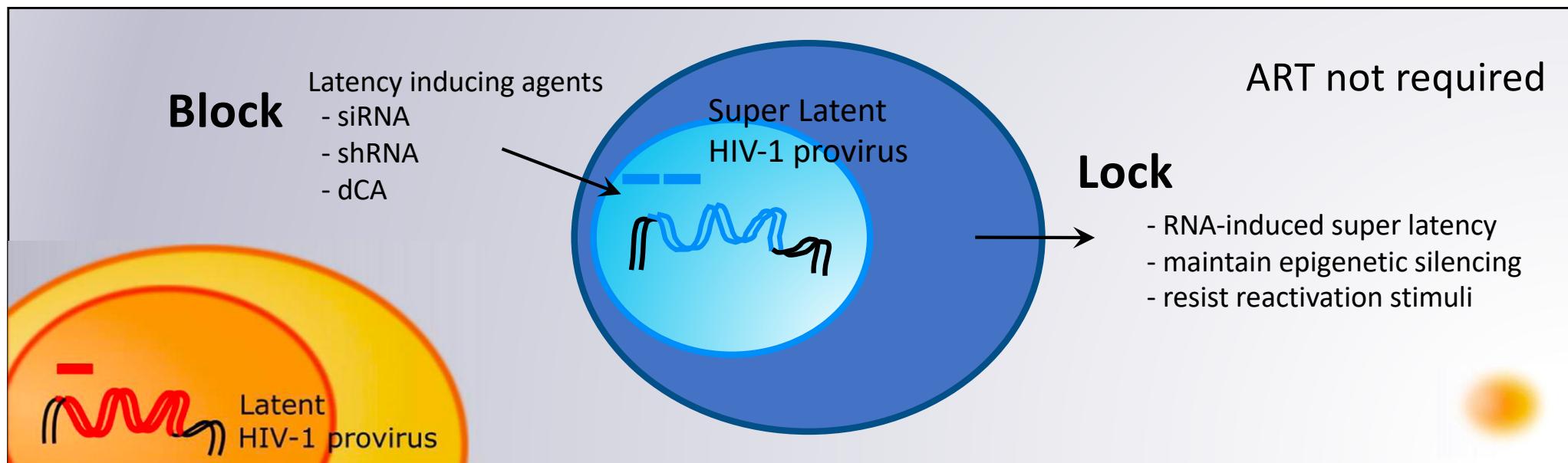
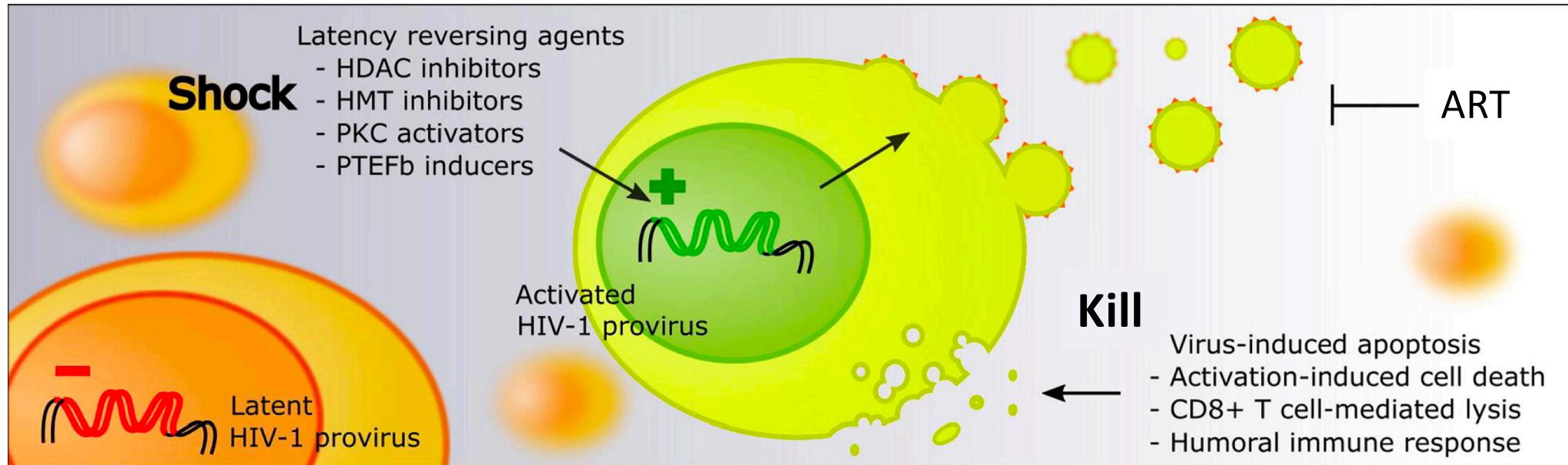


Figure 1: Number of NSW residents with newly diagnosed HIV infection, January 2008 to September 2020



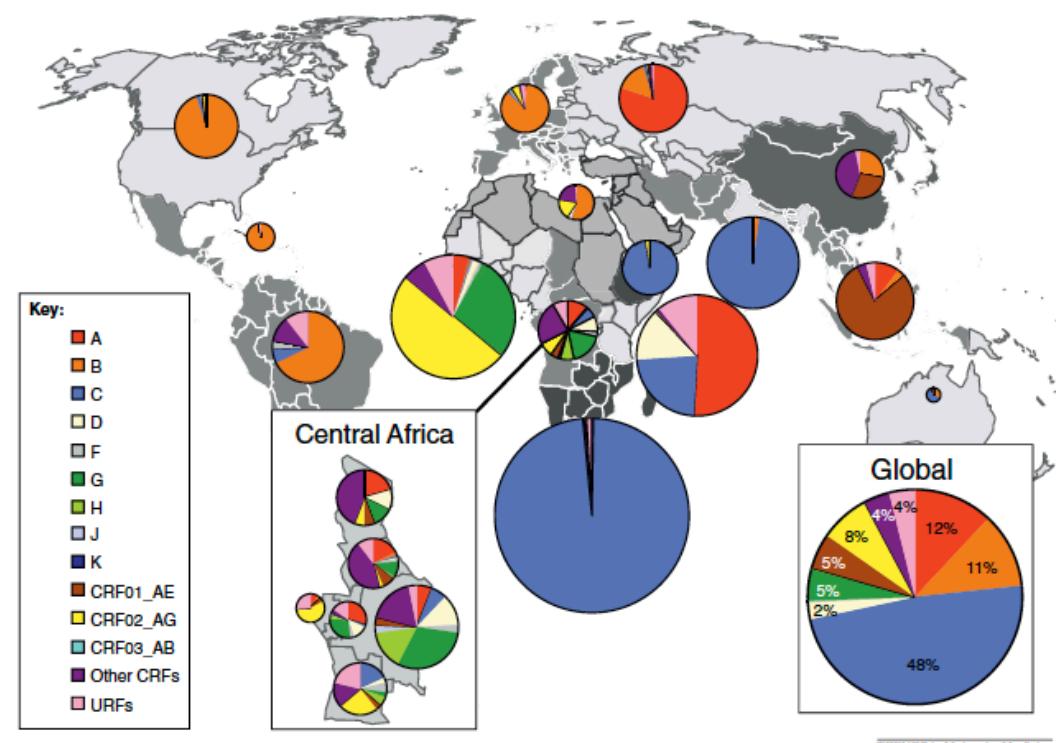
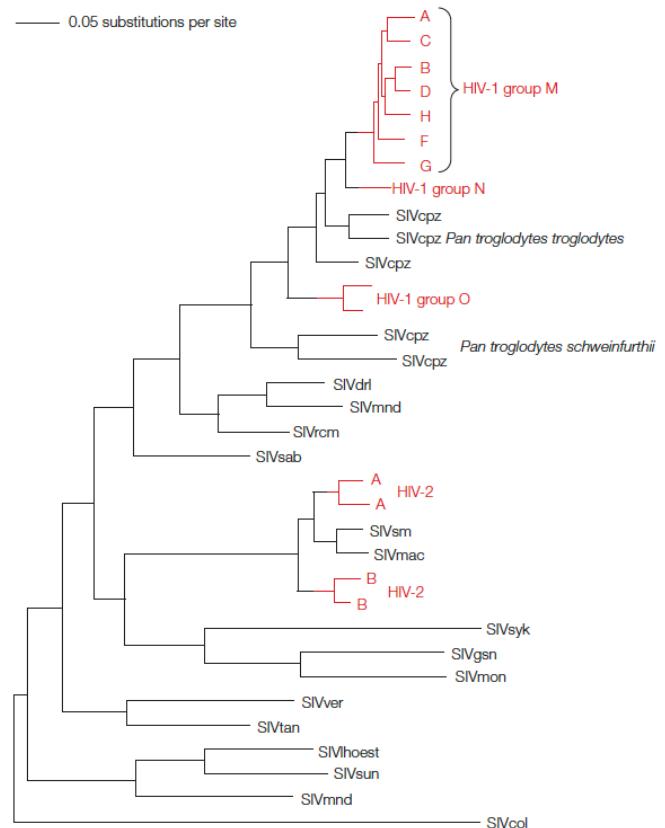
Source: Notifiable Conditions Information Management System, Health Protection NSW, 9 November 2020

Block & Lock versus Shock & Kill: The good, the bad and the ugly

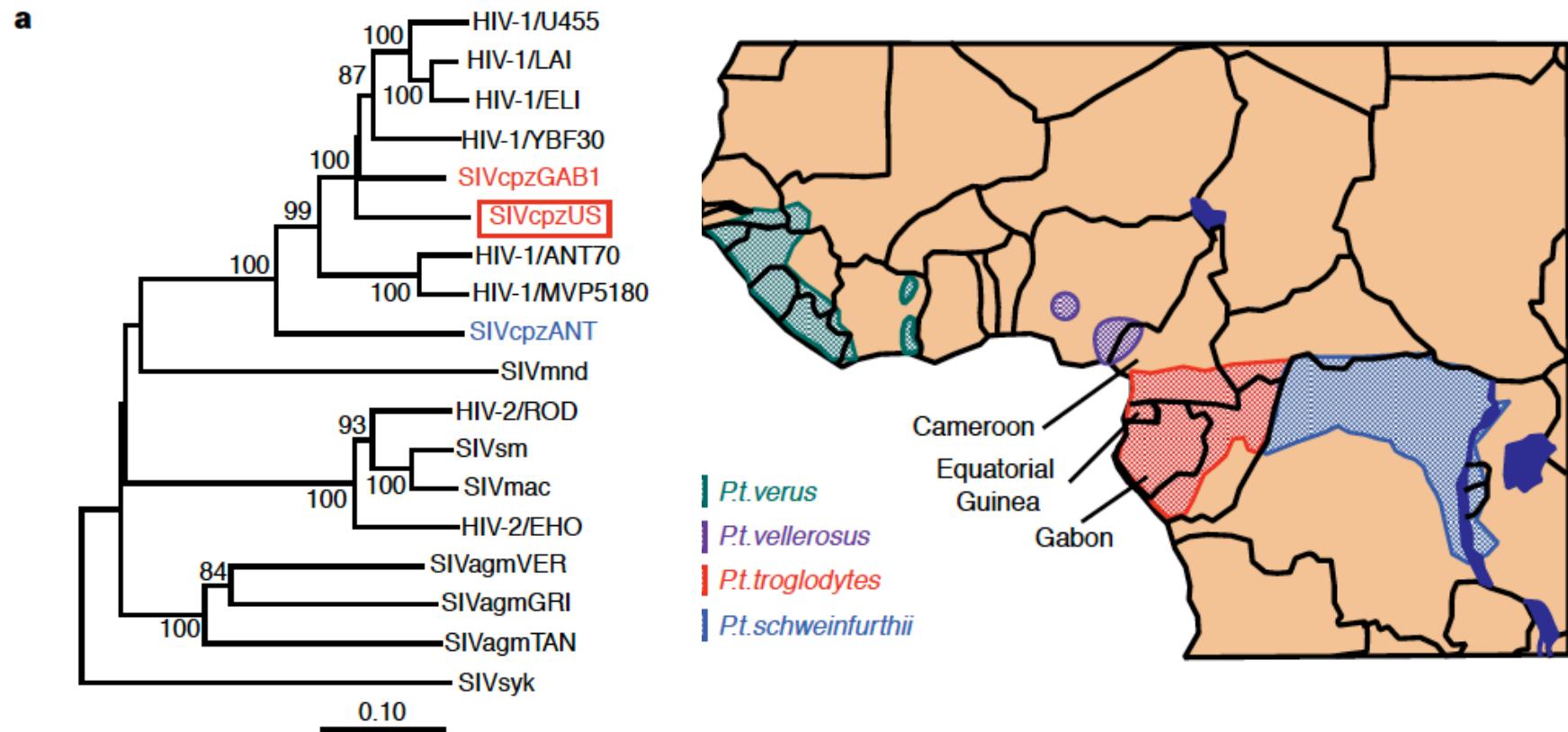


The Origin

Genetic diversity



HIV-1 from chimpanzee



HIV-2 from Sooty Mangabeys

gag

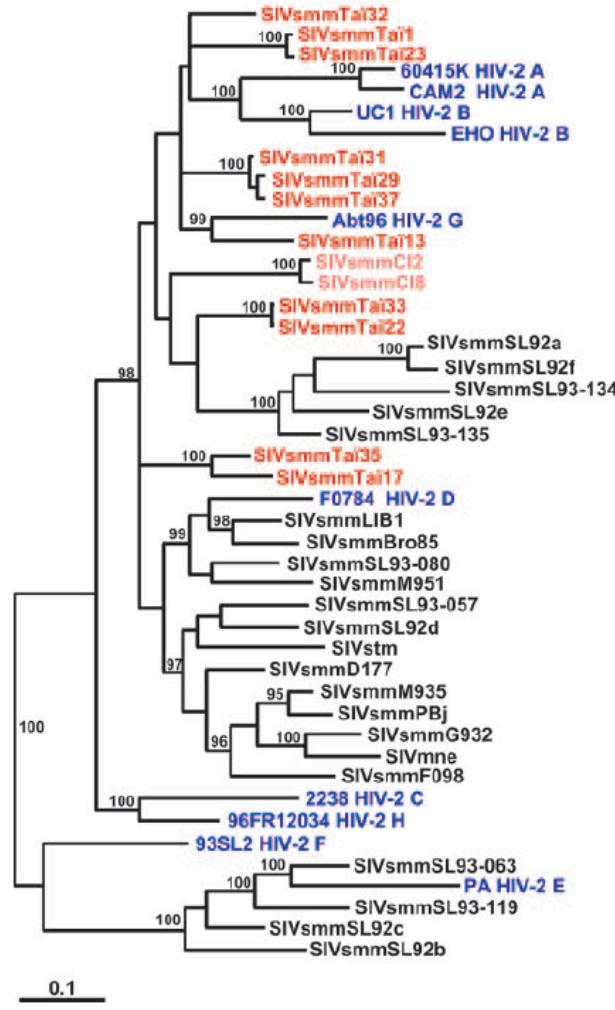
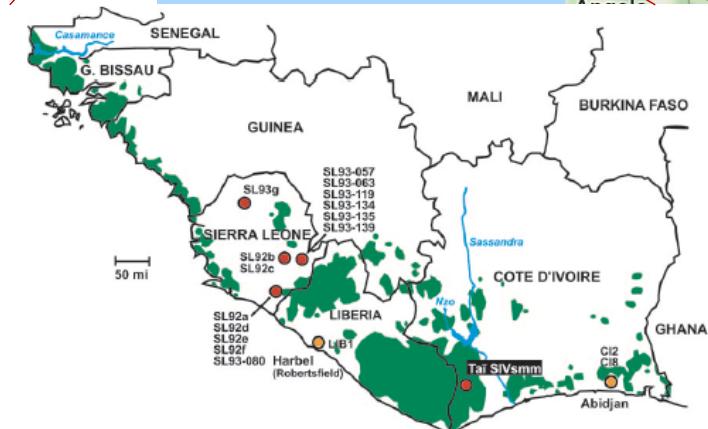
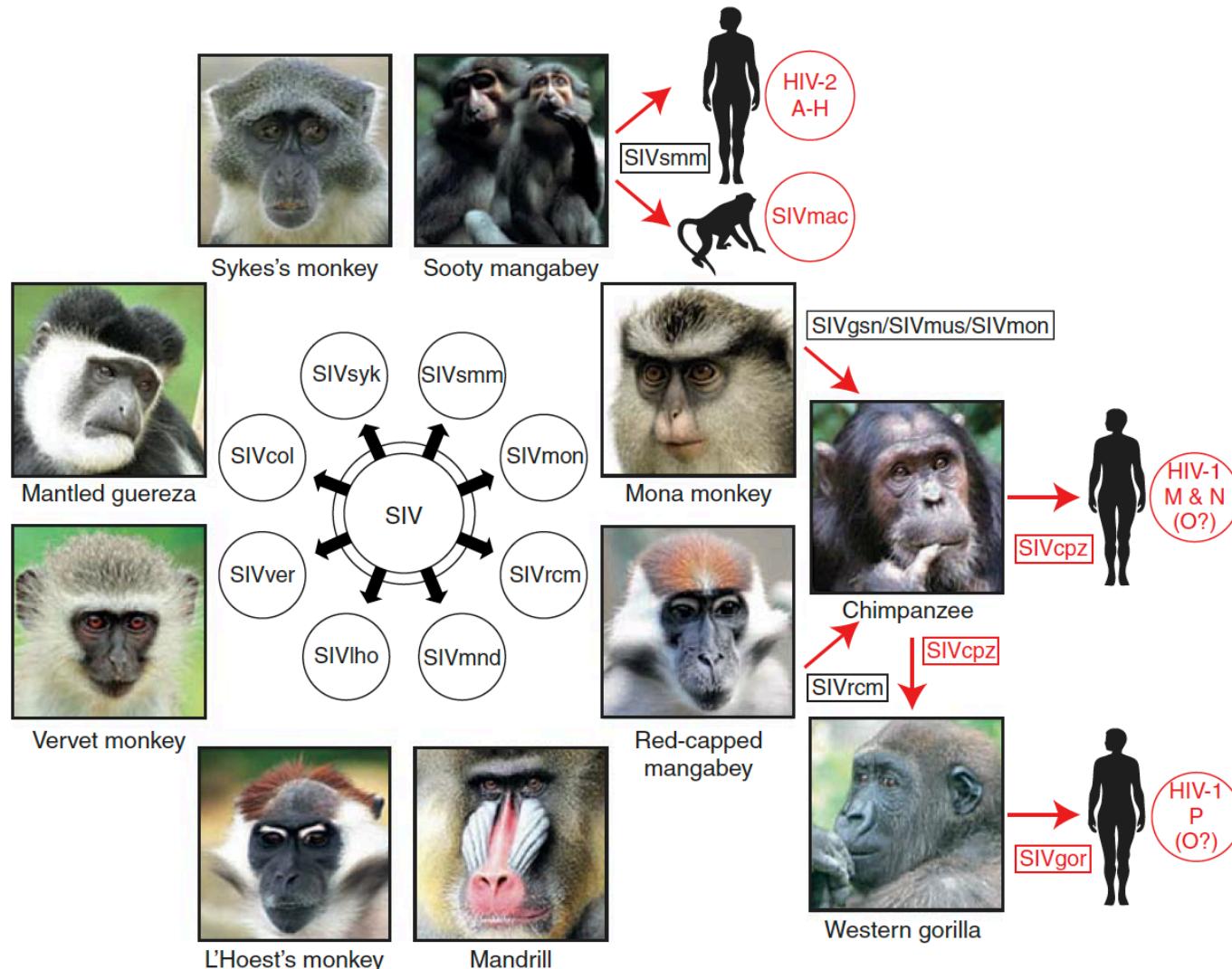


Fig. 2 Phylogenetic relationships of SIVsmm from the Tai Forest to

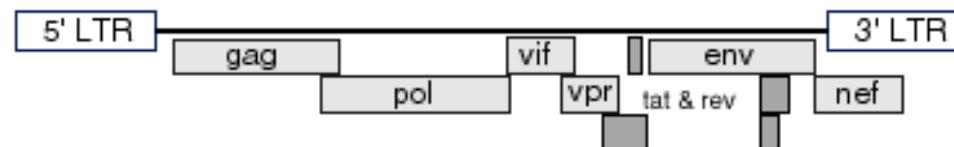


Multiple Species Jumps

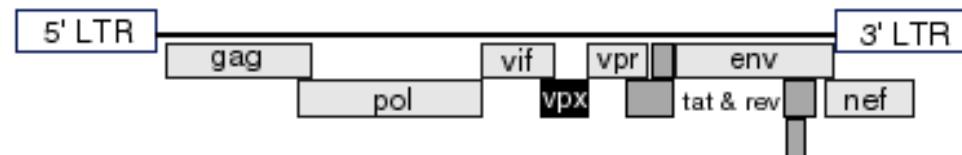


Different genomic structure

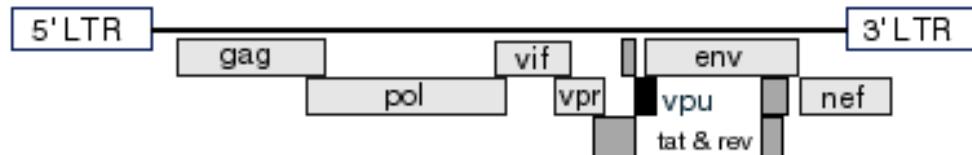
SIVagm, SIVsyk, SIVmnd, SIVhoest, SIVsun



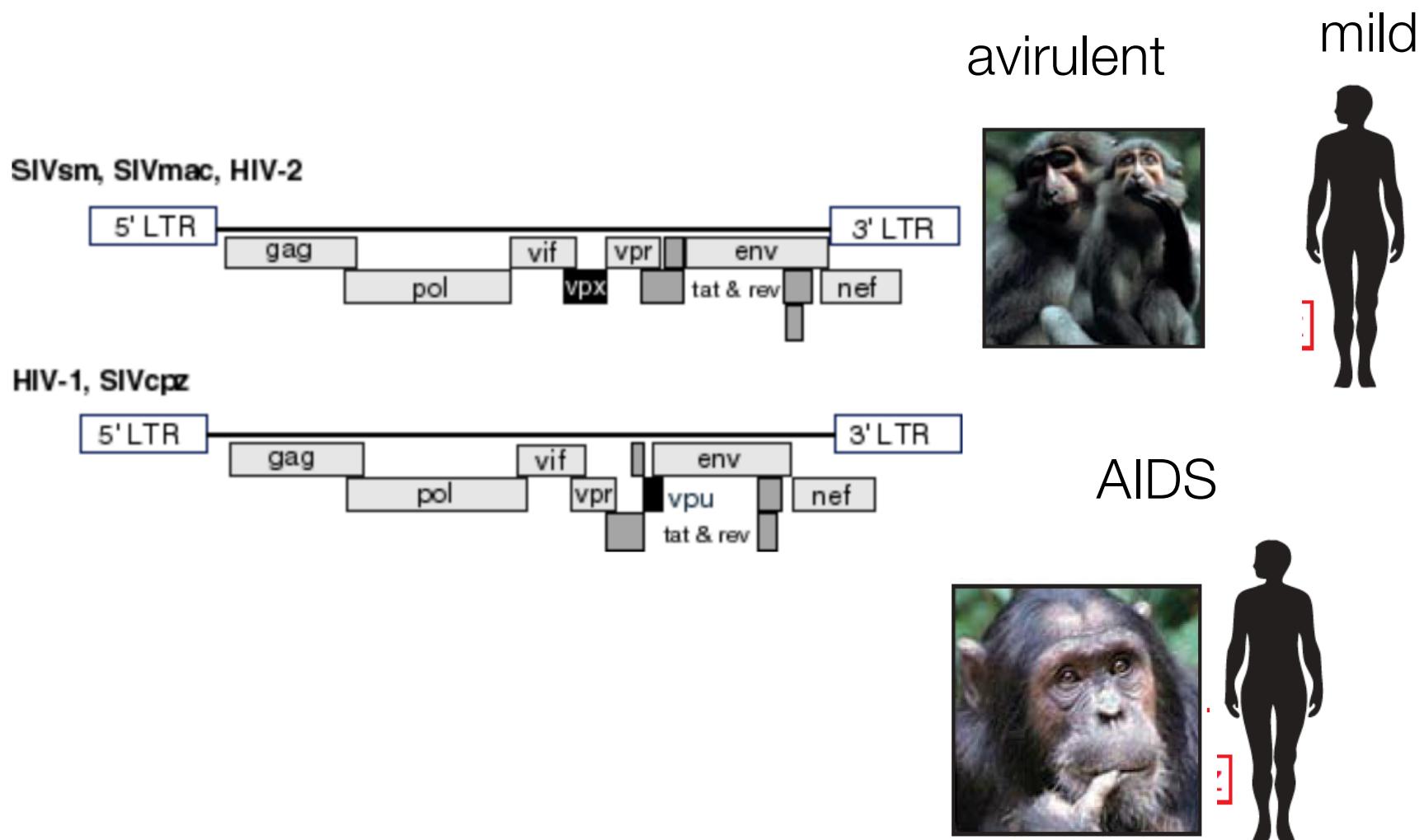
SIVsm, SIVmac, HIV-2



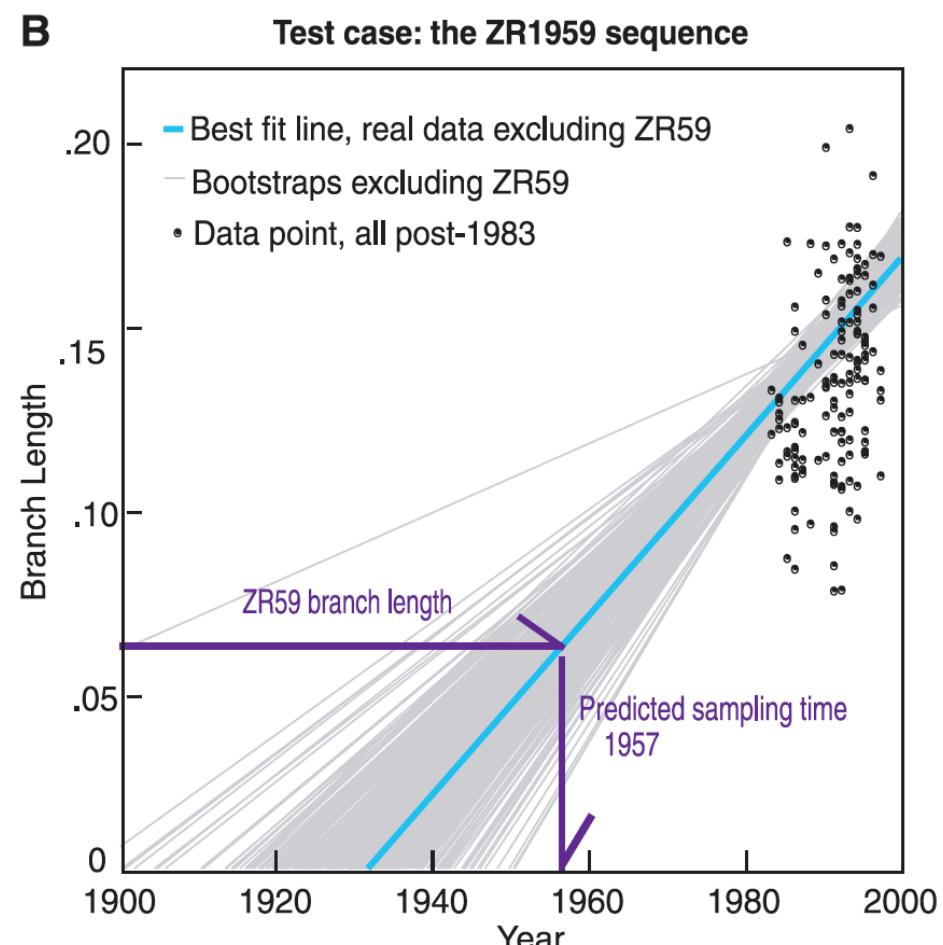
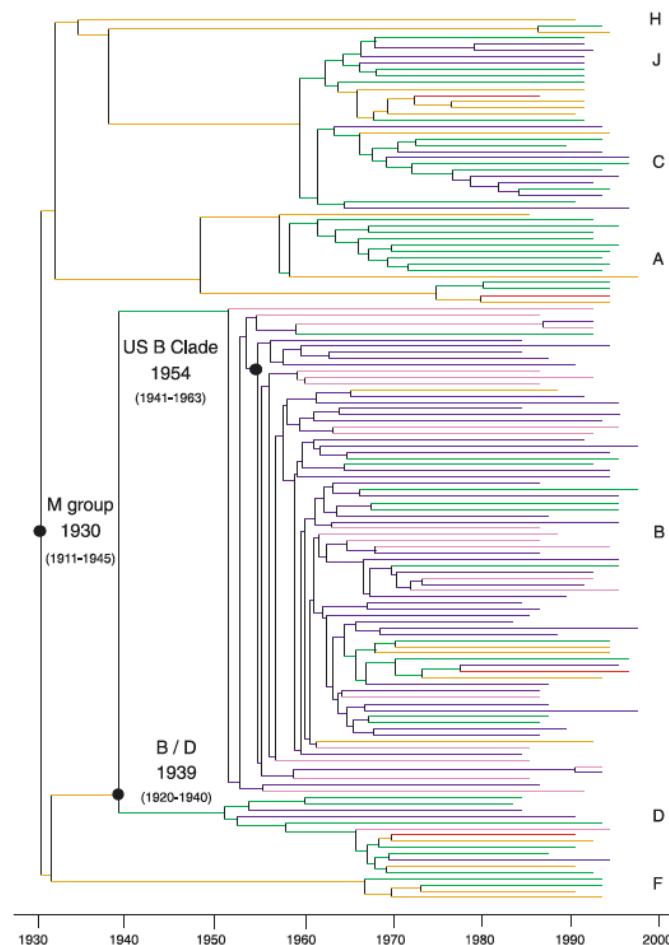
HIV-1, SIVcpz



Difference in Virulence

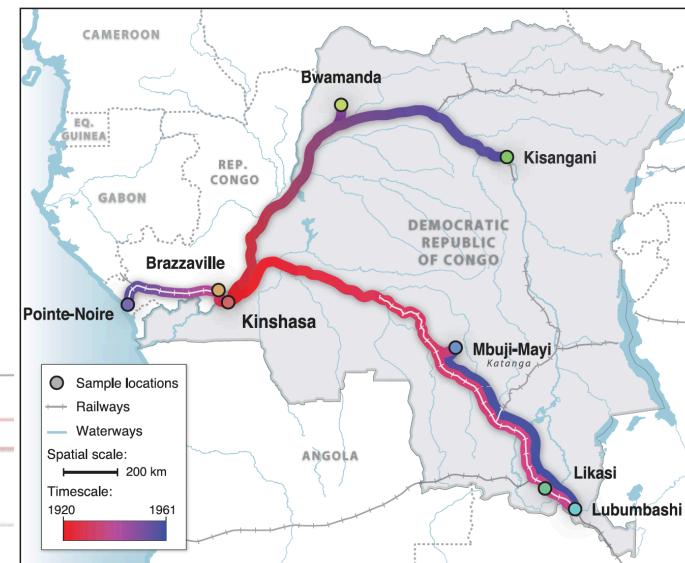
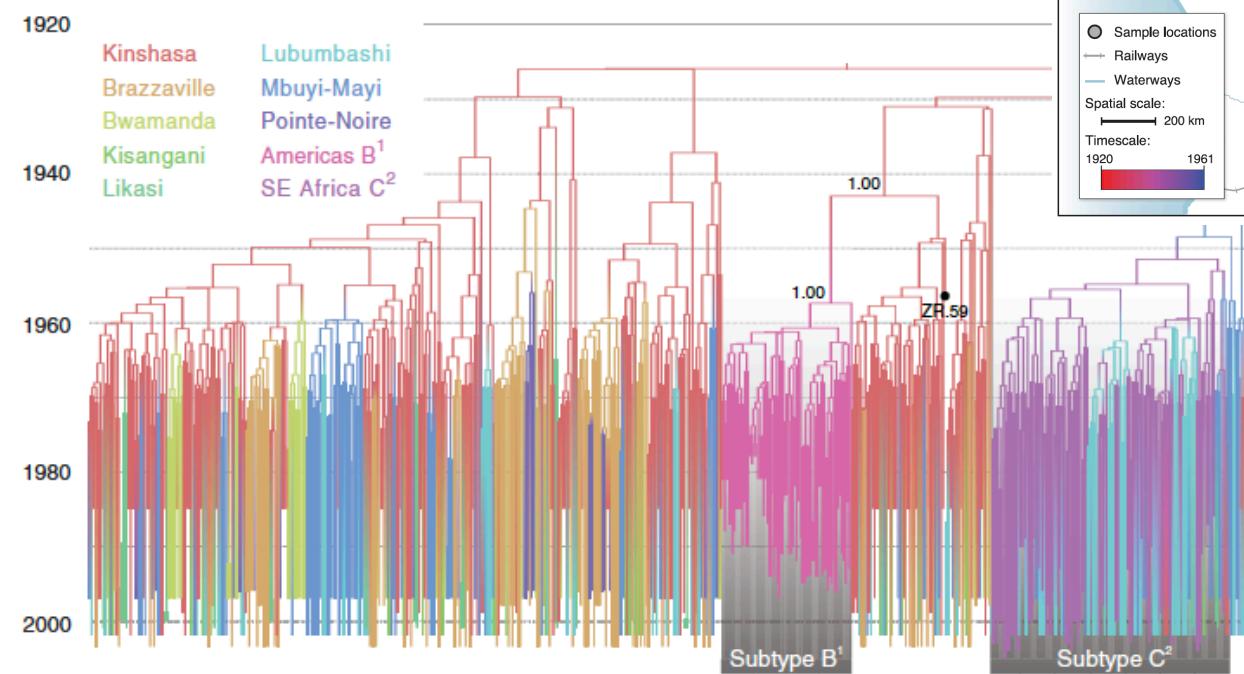


The start of the epidemic in humans

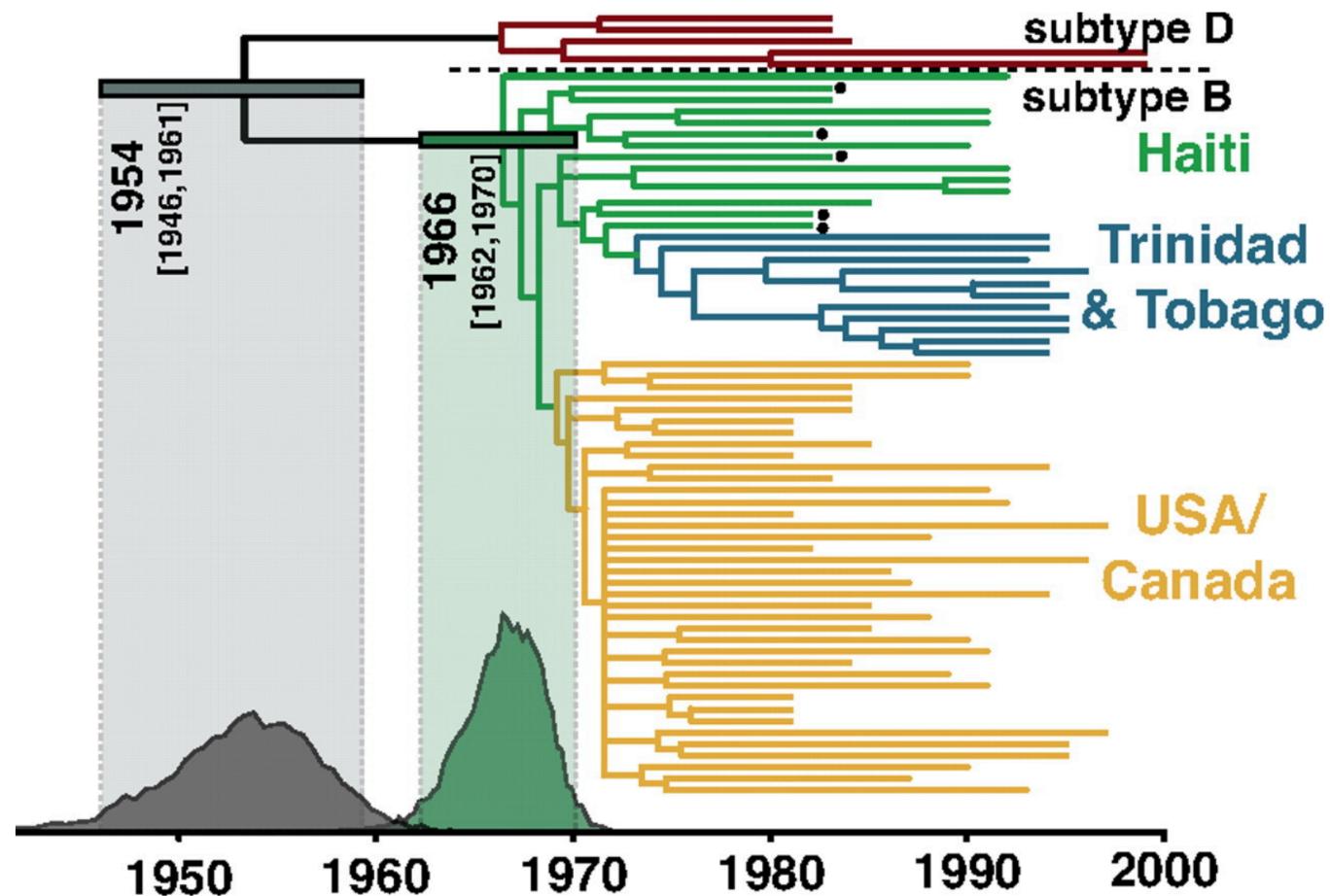


The start of the epidemic in humans

1920 Kinshasa

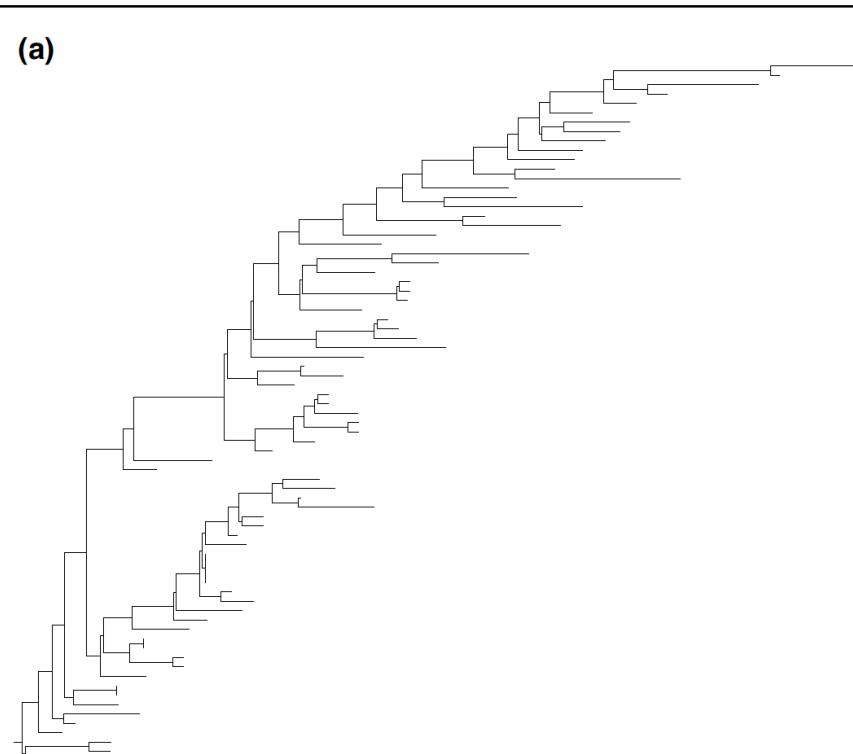


Emergence in the Americas

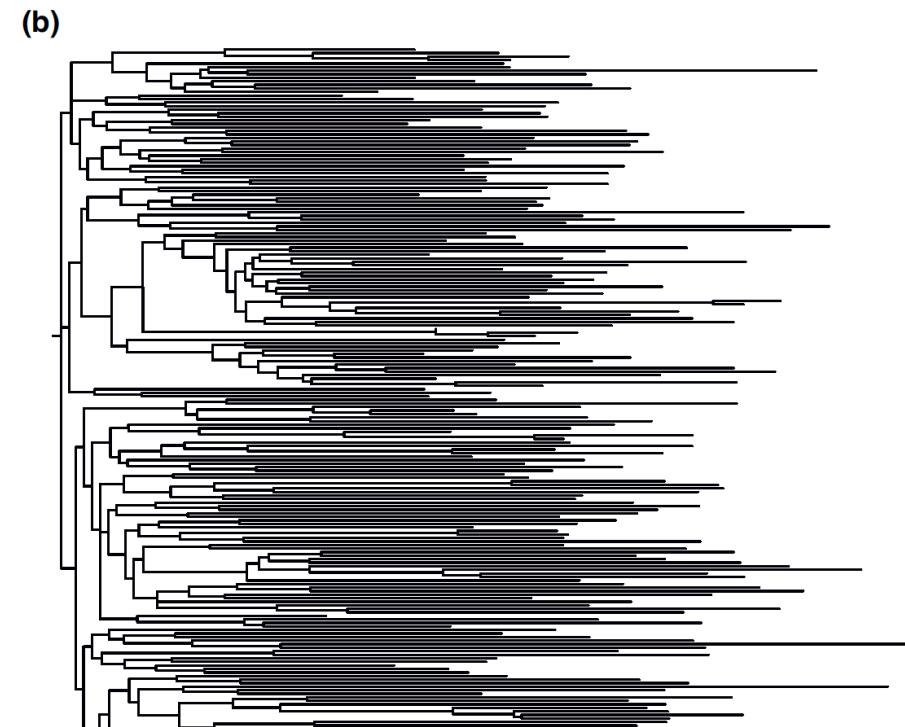


Phylogenetic Dynamics of HIV

Intra-patient

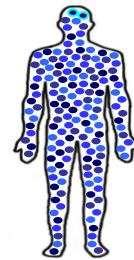
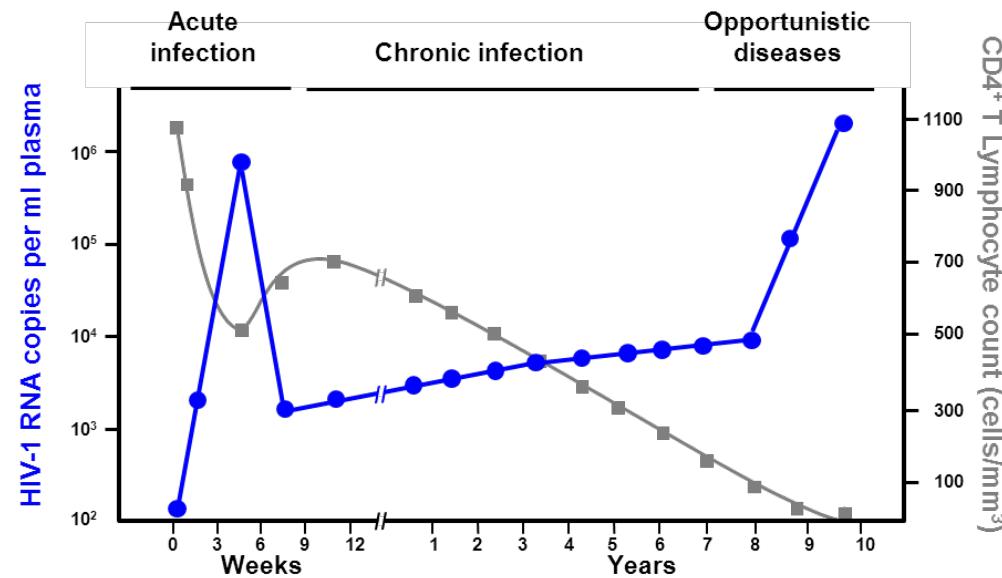


Inter-patient

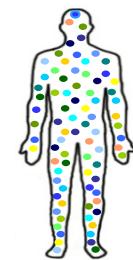


Current Opinion in Virology

Founder effect

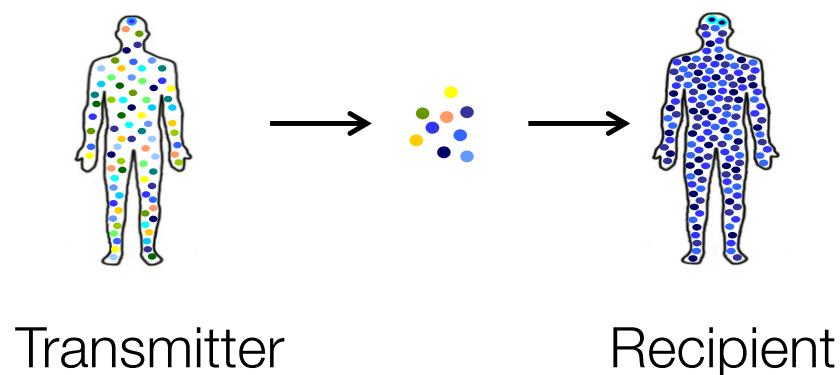
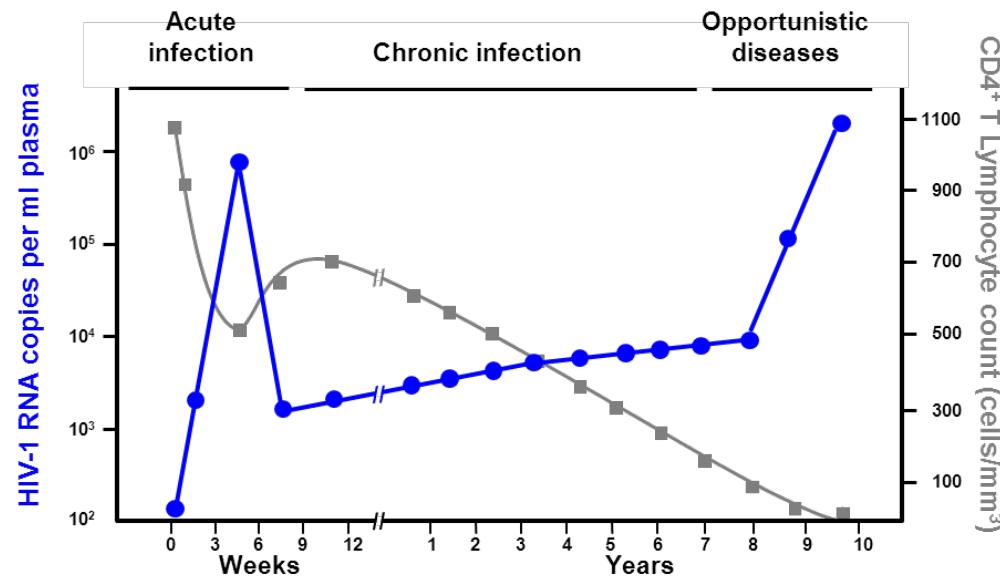


Low diversity



High diversity

Founder effect



Take Home Message

- No cure but if treated HIV positive people can live a normal life
- No transmission with undetectable viral load
- HIV-1 (at least 3) cross-species transmission from SIVcpz in the early 20ths century
- HIV-2 (at least 4) cross-species transmission from SIVsm
- No positive selection in inter-patient evolution