Evolution and transmission in HIV

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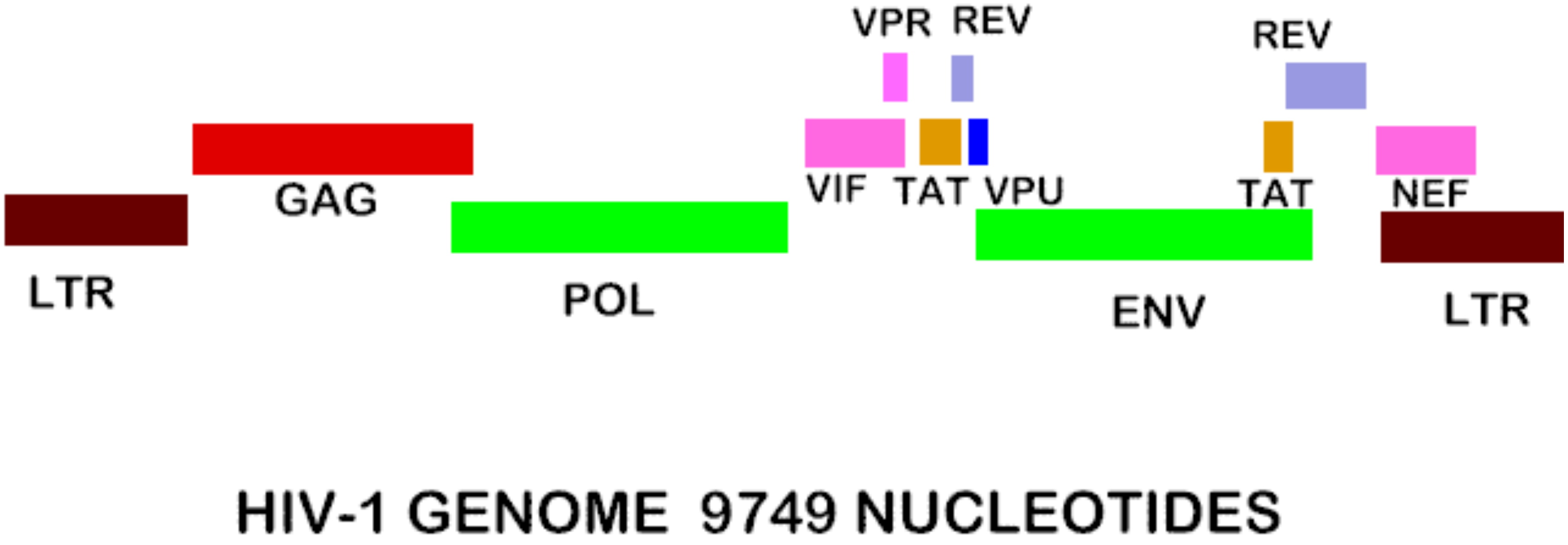
Review; Rambaut 2004 Nature Reviews Genetics 5: 52-61
'The causes and consequences of HIV evolution'

Use phylogenies to follow infection

- HIV is an RNA virus, with a high mutation rate
- mutates over course of infection



HIV

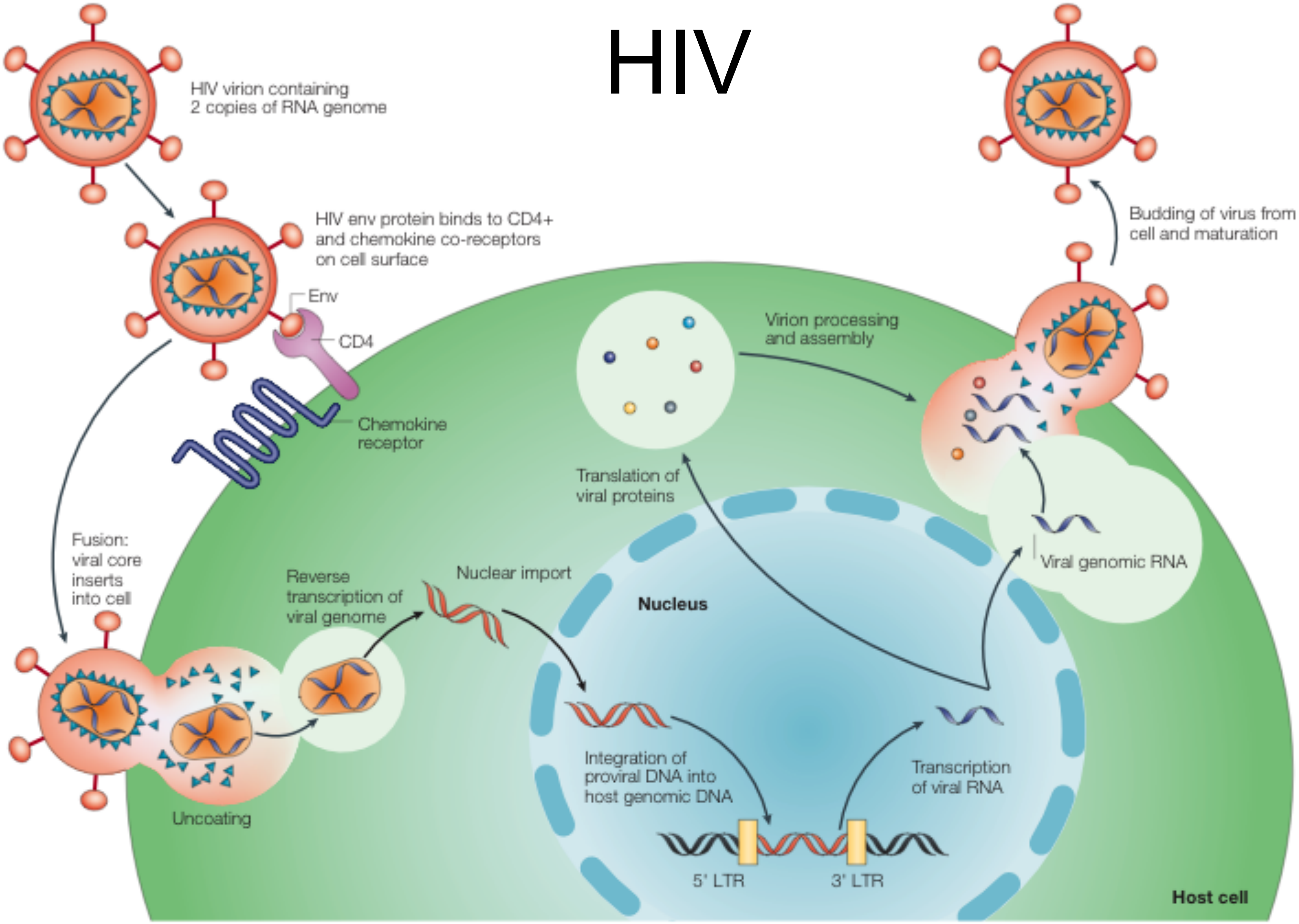
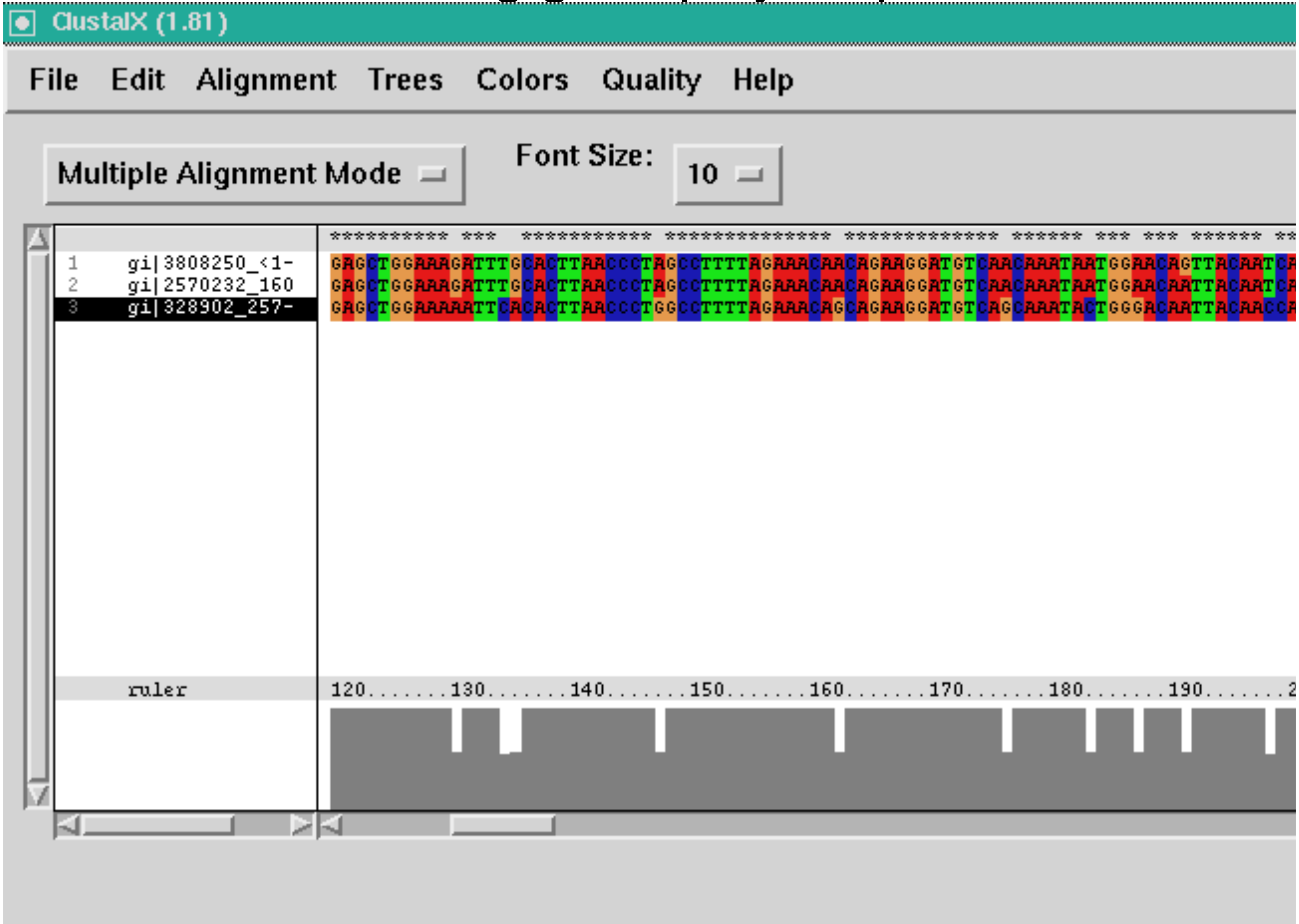


Figure 1 | **Key aspects of the HIV life cycle.** Although the human immunodeficiency virus (HIV) is able to infect a variety of cell types, AIDS results from the depletion of $CD4^+$ T-HELPER LYMPHOCYTE CELLS, a key component of the human immune system. The *env* (*envelope*) gene encodes the proteins of the outer envelope of the virus, the *gag* (*group-specific antigen*) gene encode the components of the inner capsid protein, whereas the *pol* (polymerase) gene codes for the enzymes (such as REVERSE TRANSCRIPTASE) that are used in viral replication.

HIV Gag gene polymorphism



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3      gi|328902_257-      GAGCTGGAAAAATTCACACTTAACCCTGGCCTTTTAGAAACAGCAGAAGGATGTCAGCAAATACTGGGACAATTACAACCA

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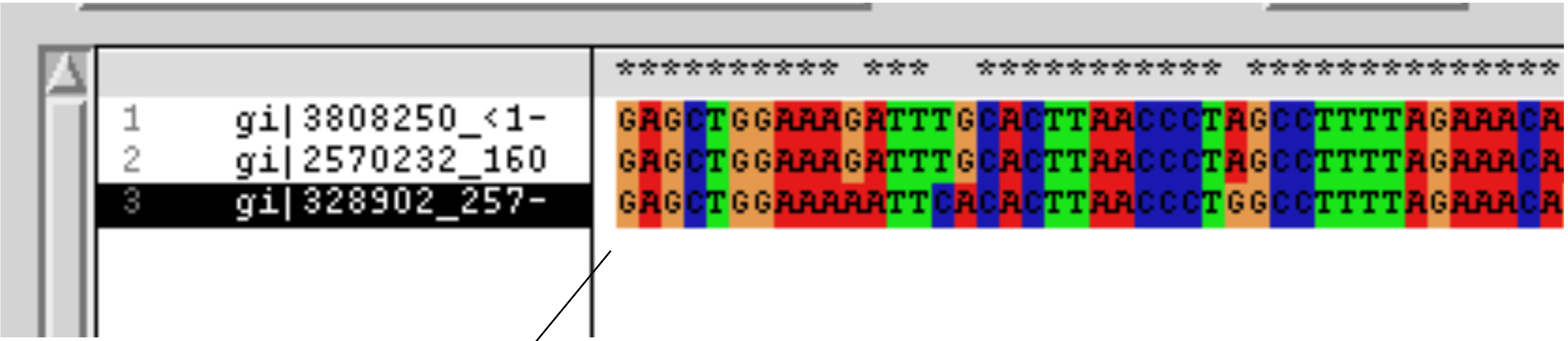

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           ********** ***  *********** **************
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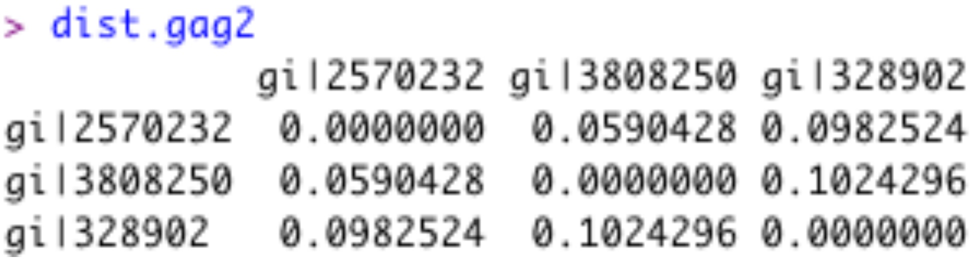

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gi|328902   0.0982524  0.1024296 0.0000000
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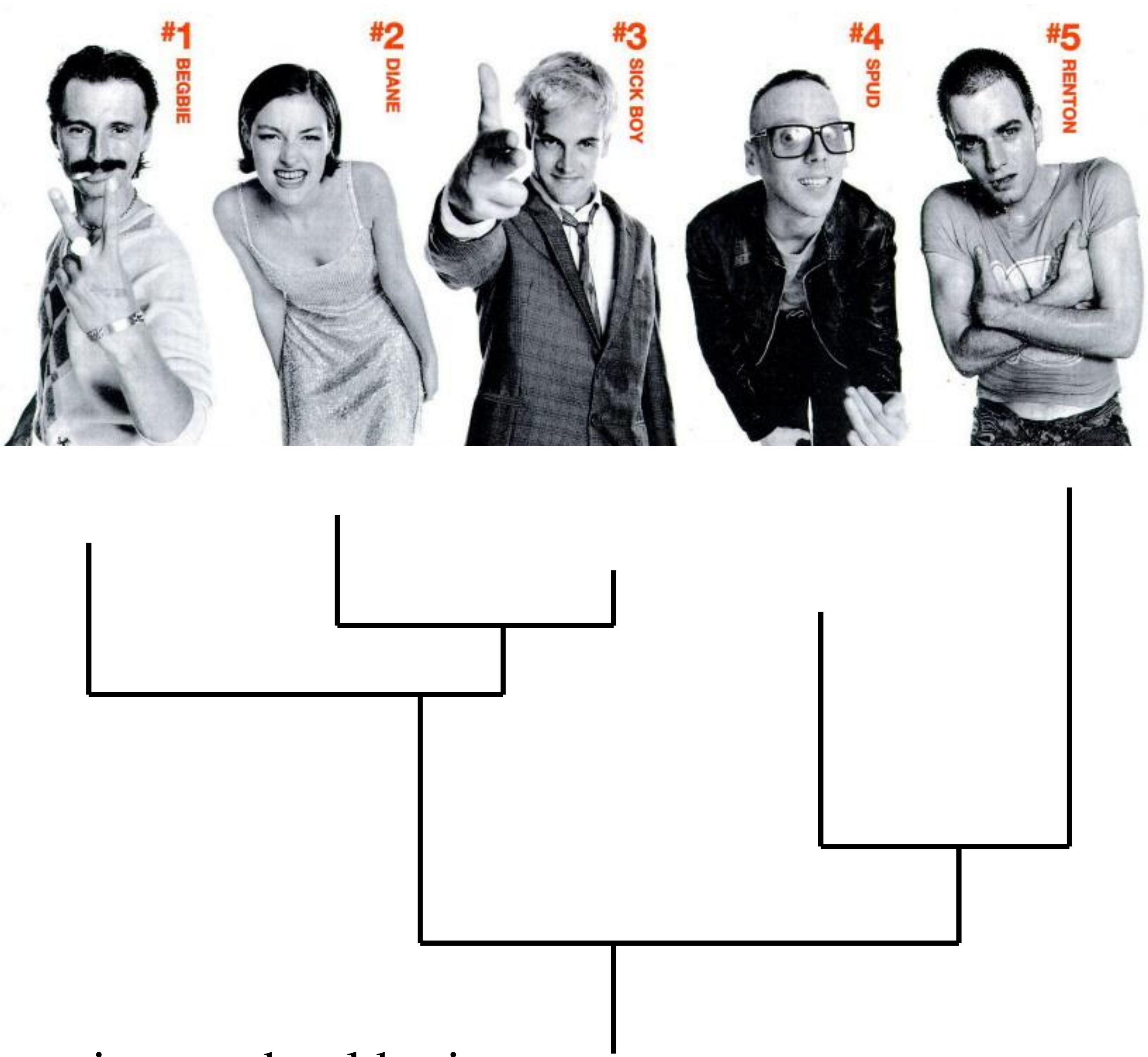
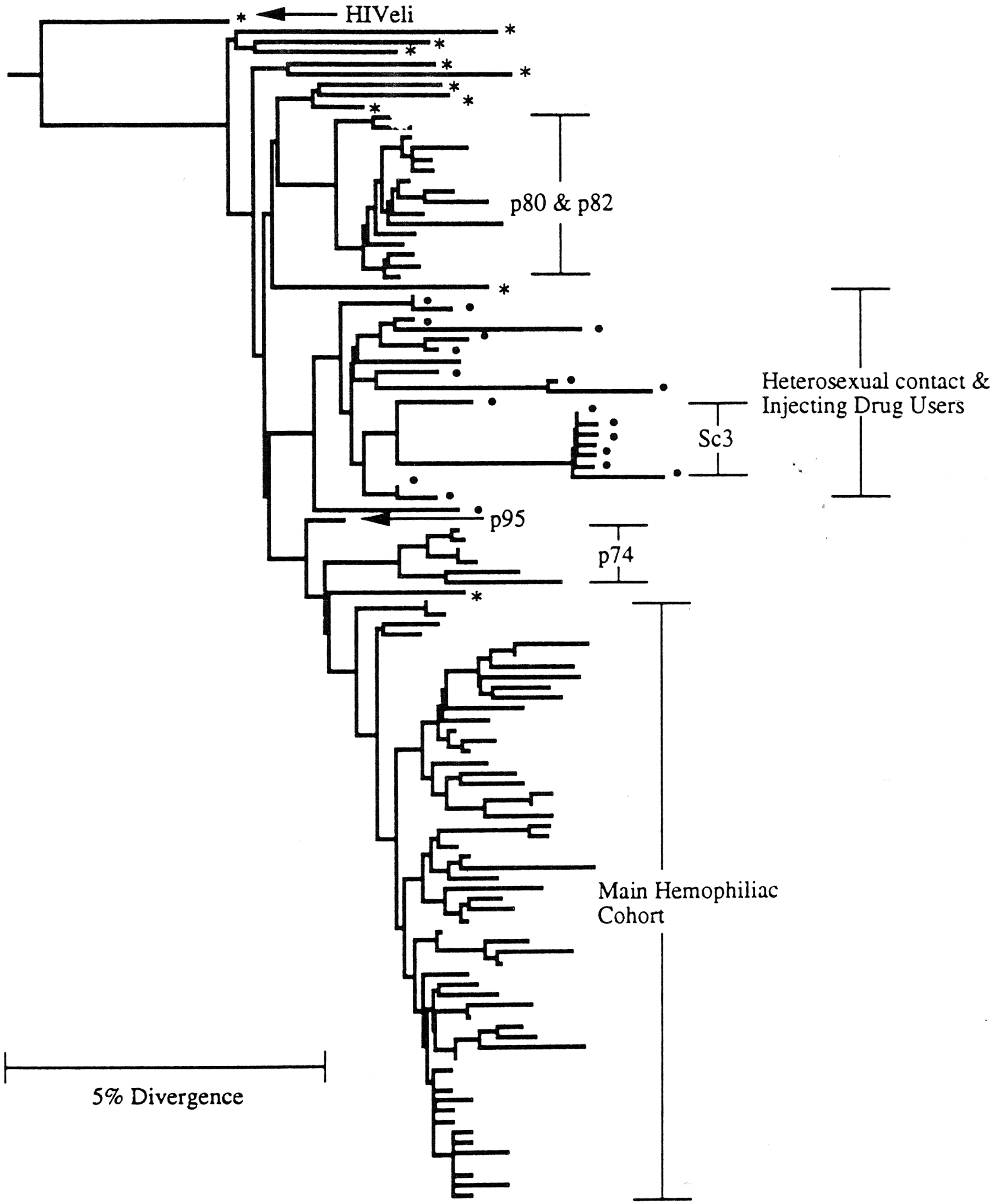


Phylogenetic tree should mirror
contact structure of infection

Molecular epidemiology of HIV in Edinburgh

- HIV mutates as passes from one individual to next
- Use substitutions to build phylogenies and track pattern of infection

HIV phylogeny



- Holmes et al (1994) J. Inf. Diseases 171:45-53

Last Updated: Thursday, 6 May, 2004, 13:05 GMT 14:05 UK

Libya death sentence for medics

Libya has sentenced five Bulgarian nurses and a Palestinian doctor to death by firing squad for deliberately infecting some 400 children with HIV.

Experts backed the medics' defence that poor hygiene was to blame

Prosecutors demanded the death penalty, claiming the accused gave patients HIV in a bid to find an Aids cure.

The medics, who worked at a children's hospital in the city of Benghazi, were arrested five years ago.

Bulgaria's government, which had been lobbying for their release, condemned the "unfair and absurd" verdicts.

Packed court

The Libyan court found the six health workers guilty of having caused the death of 40 children and of infecting almost 400 others with HIV.

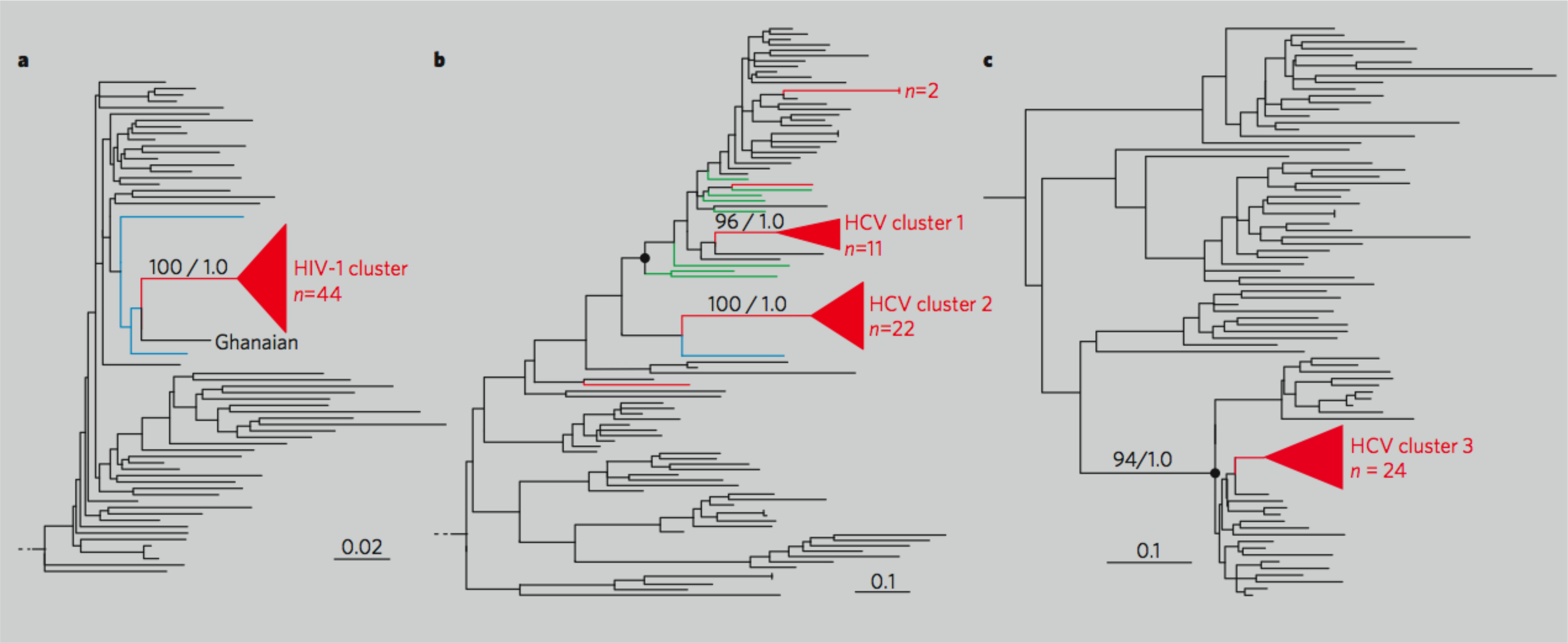


Figure 1 | HIV-1 and HCV sequences from 1998 Al-Fateh Hospital (AFH) outbreak. a–c, Estimated maximum-likelihood phylogenies for HIV-1 CRF02_AG (**a**), HCV genotype 4 (**b**) and HCV genotype 1 (**c**). Source of sequences used for analysis: AFH, red; Egypt, green; Cameroon, blue. Black circles mark the common ancestor of HCV subtype 4a and 1a; numbers above AFH lineages give clade support values using bootstrap and bayesian methods, respectively. Scale bar units are nucleotide substitutions per site. For visual clarity, AFH clusters are represented by triangles and some non-informative reference strains are excluded.

Oliveira et al (2006) Nature. 444, 836-837

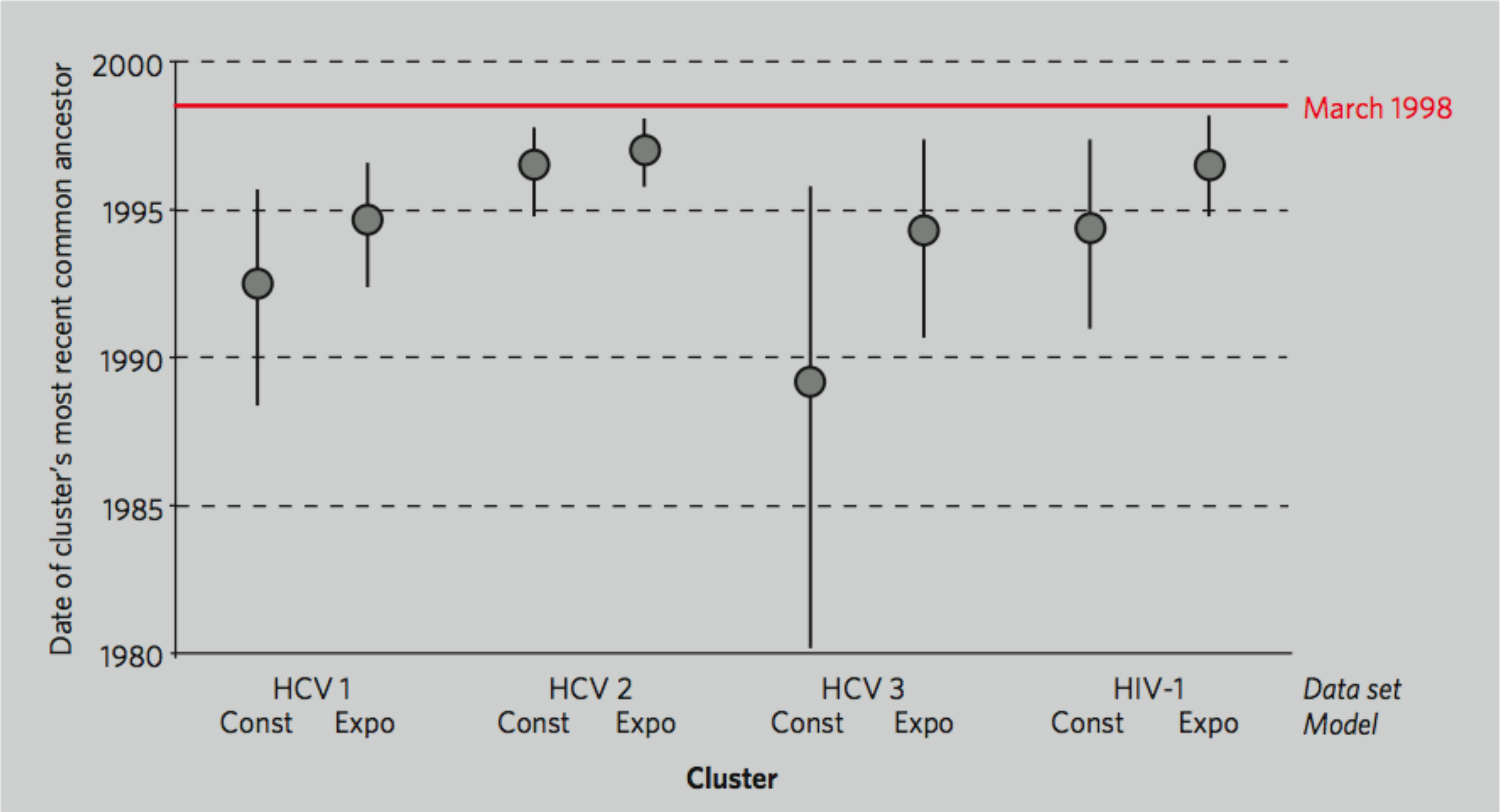


Figure 2 | Estimated dates of the most recent common ancestor for each cluster. Results obtained by using different evolutionary models. Vertical lines show the 95% highest posterior density intervals. Red line shows time of arrival of Bulgarian staff in March 1998. For further details, see supplementary information. 'Const', constant size; 'Expo', exponential growth.

Page last updated at 14:29 GMT, Tuesday, 24 July 2007 15:29 UK

HIV medics released to Bulgaria

Six Bulgarian medical workers who were imprisoned in Libya for deliberately infecting children with HIV have arrived in Bulgaria after being freed.

The five nurses and a Palestinian-born doctor, who served eight years of the life sentences they received, had always maintained they were innocent.

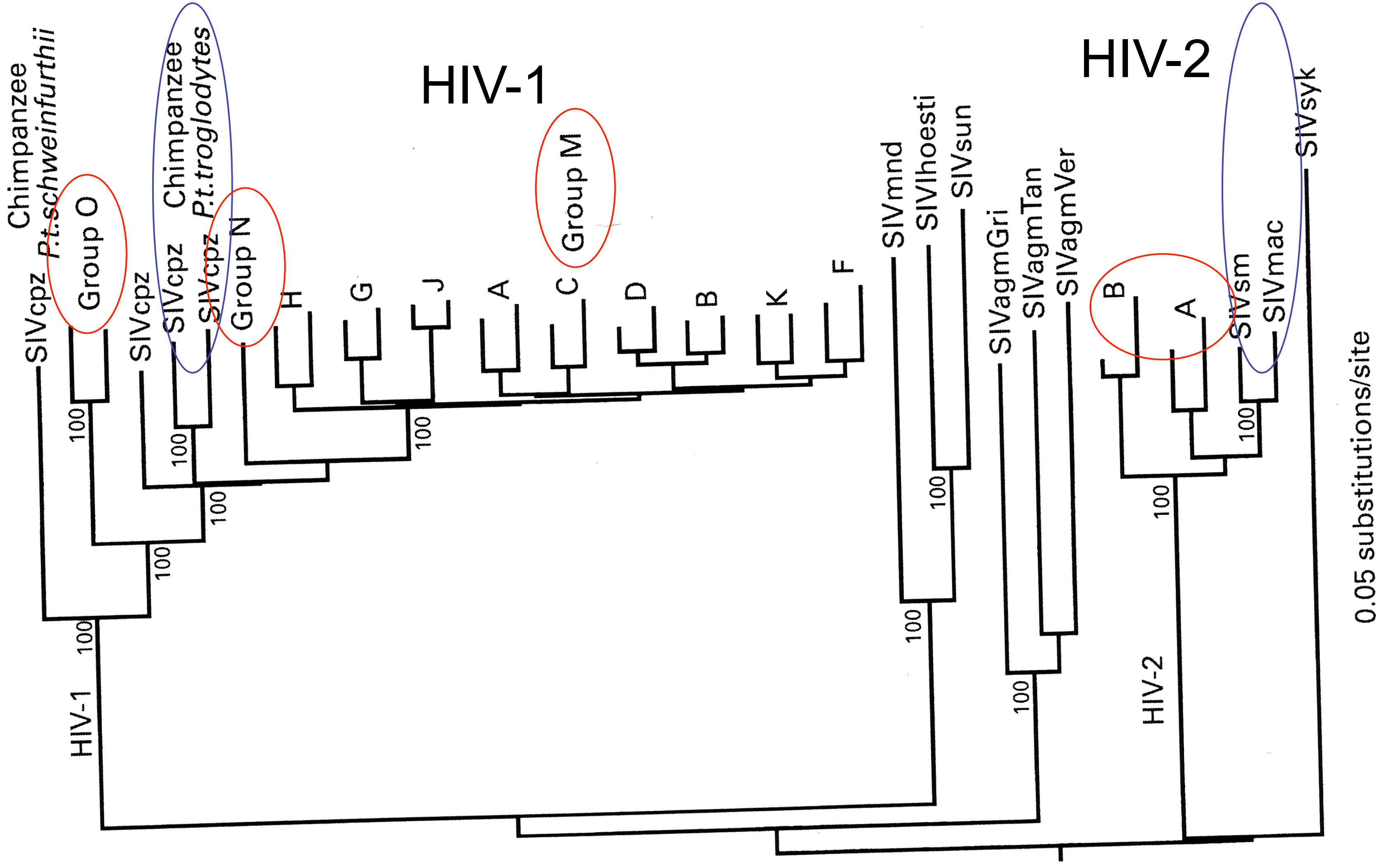
The medics were greeted by tearful relatives and well-wishers

All six were pardoned on their arrival by Bulgarian President Georgi Parvanov.

The release was made possible by a deal struck in Tripoli on improving Libya-EU ties, following years of negotiations.

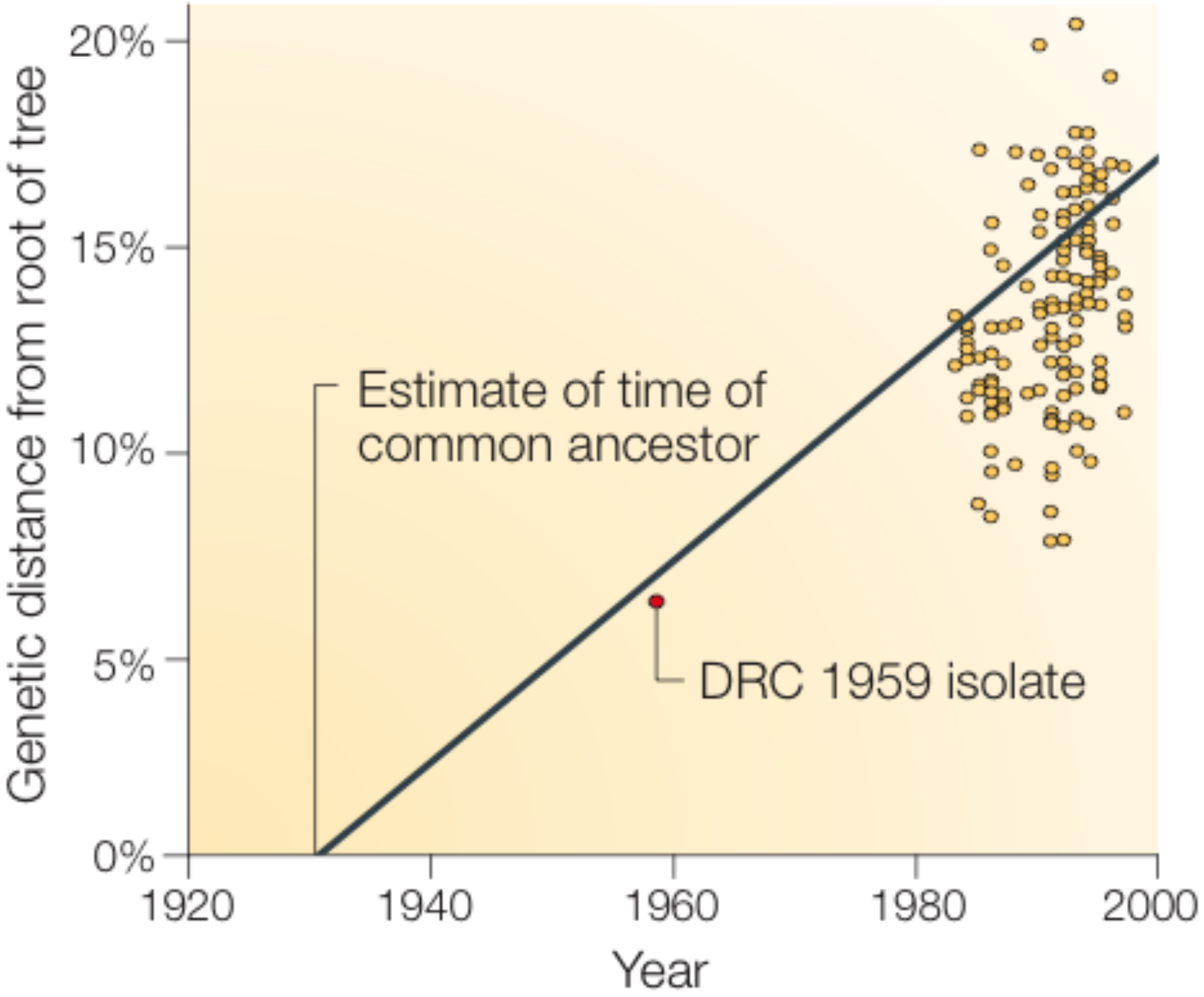
The EU's External Affairs Commissioner, Benita Ferrero-Waldner, made many trips to Libya, meeting the prisoners and working to improve conditions for children infected with HIV/Aids.

Origins of HIV



Rambaut 2004 Nature Reviews Genetics 5: 52-61

Origins of HIV-1



Within host evolution of HIV

- high rate of mutation
  - (0.2 errors/genome)
- high rate of replication
  - (gen. time = 2.5 days, 10^{10} - 10^{12} virions/ day)
- natural selection
  - immune selection
  - genetic drift

Genetic diversity of HIV

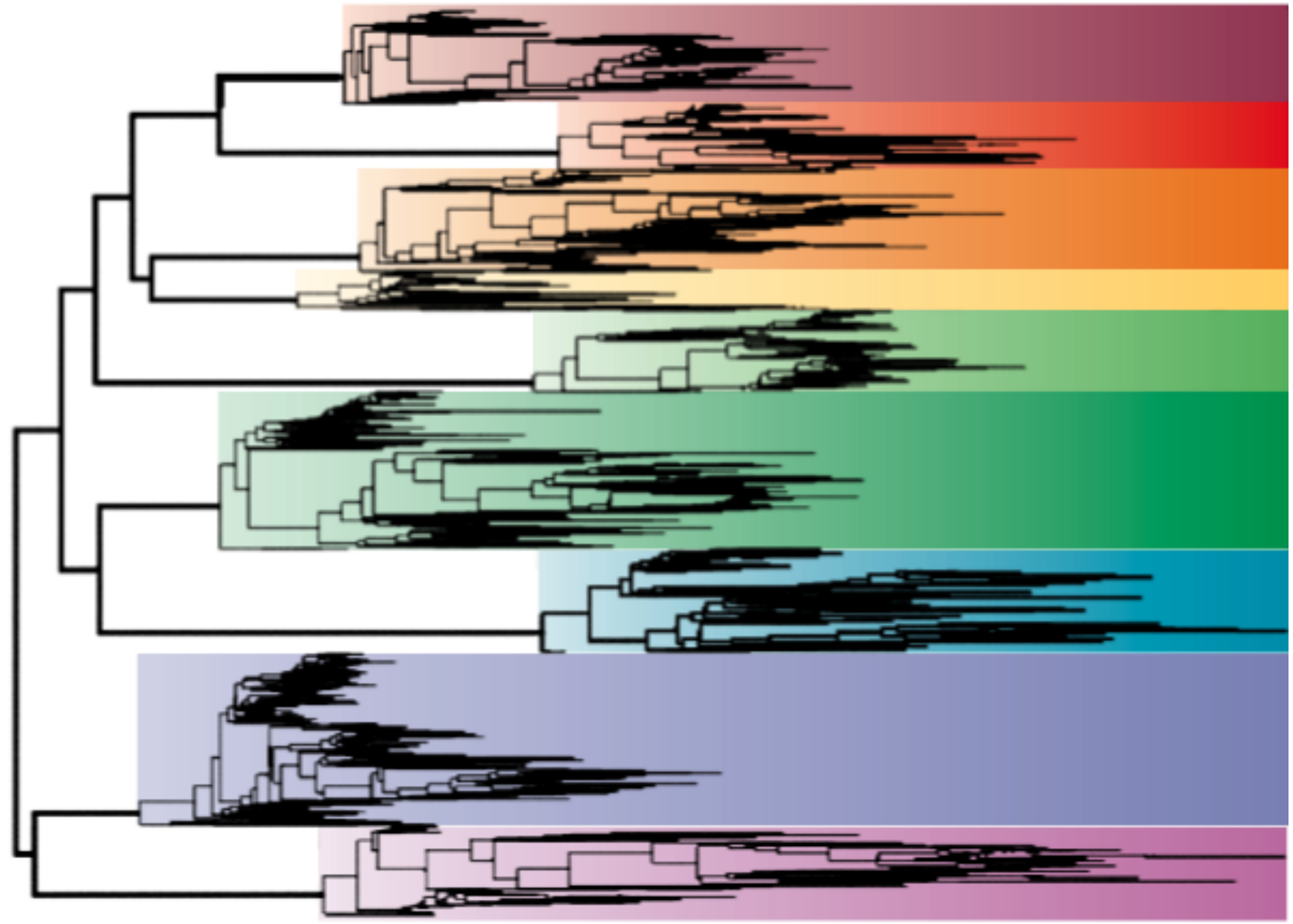


Figure 4 | **Contrasting patterns of intra- and inter-host evolution of HIV.** The tree was constructed using the NEIGHBOUR-JOINING METHOD on *envelope* gene-sequence data that was taken from nine HIV-infected patients[48] (a total of 1,195 sequences, 822 base pairs in length), with those viruses sampled from each patient depicted by a different colour. In each case, intra-host HIV evolution is characterized by continual immune-driven selection, such that there is a successive selective replacement of strains through time, with relatively little genetic diversity at any time point. By contrast, there is little evidence for positive selection at the population level (bold lines connecting patients), so that multiple lineages are able to coexist at any time point. A major BOTTLENECK is also likely to occur when the virus is transmitted to new hosts.

Rambaut (2004) *Nature Reviews Genetics* **5**, 52-61

Evolution of drug resistance in HIV

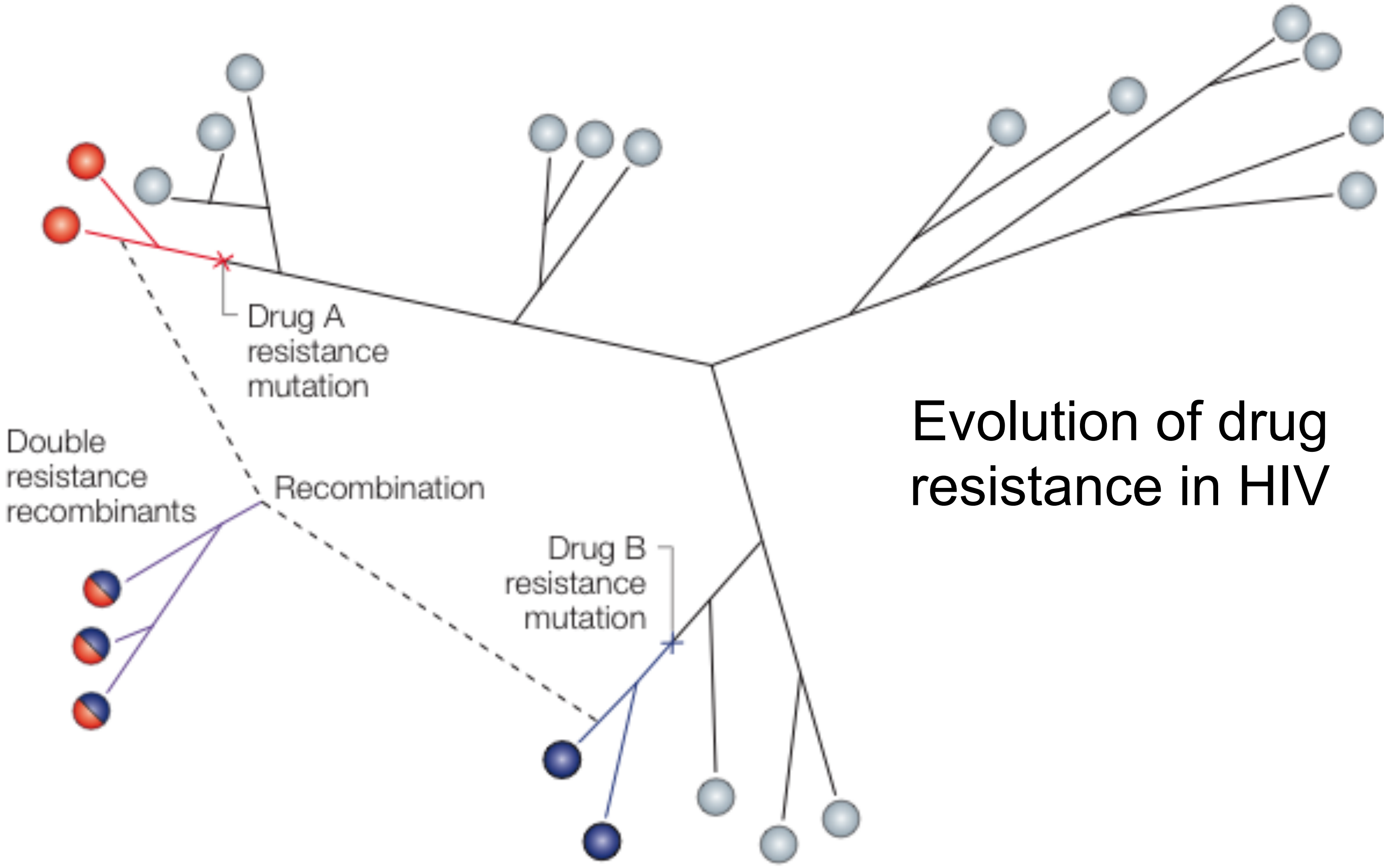
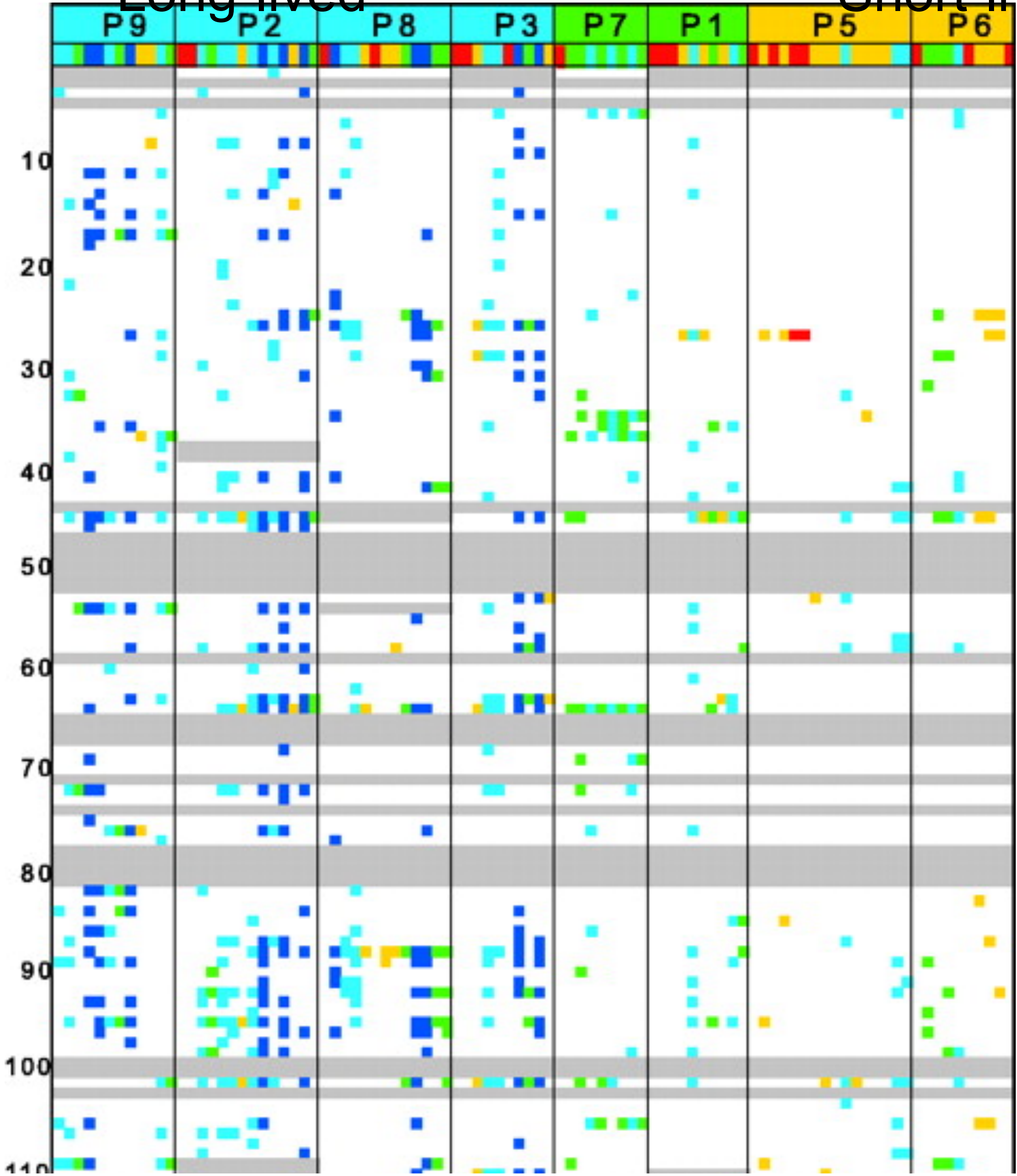


Figure 5 | **Multiple drug resistance induced by recombination.** Hypothetical example showing how recombination will be an important mechanism to generate drug resistance in HIV. In this figure, two different HIV strains that are resistant to drug A (in red) and drug B (in blue) recombine to produce a new strain that is resistant to both drugs.

env gene

Long-lived Short-lived



CTL escape

blue sites = +ve seln.
Ross (2002) J. Virol.
76 : 11715-20

Immune pressure, effective at driving amino-acid change in long-lived patients?