

Preferential loss of HIV-1 derived CTL epitopes restricted by protective HLA-B alleles during the HIV-1 epidemic

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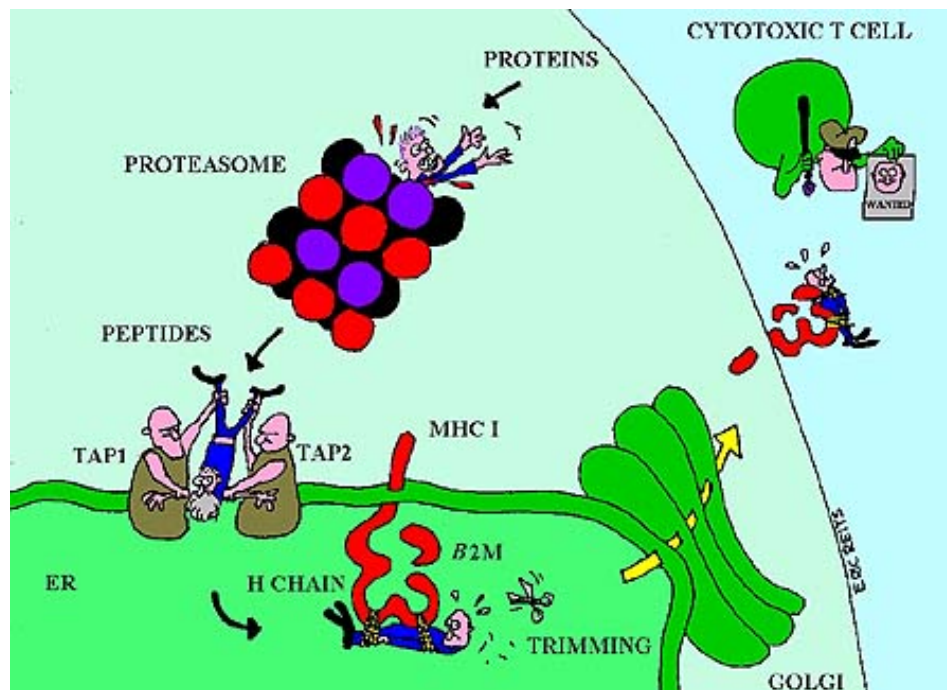


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HIV-1 and Cytotoxic T Lymphocytes



HLA class I molecules present viral peptides to CTL => dictate the repertoire of CTL responses



www.bio.davidson.edu

CTL escape mutations are transmissible

=> can be stable or revert to wild type in a recipient with a different HLA background

Research question



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- i) Is there evidence that current HIV-1 strains contain fewer HLA-binding epitopes than HIV-1 strains from the start of the epidemic?

- ii) Is there a difference between HLA alleles that are common in the population vs. rare alleles?

Study design



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Patients & methods:

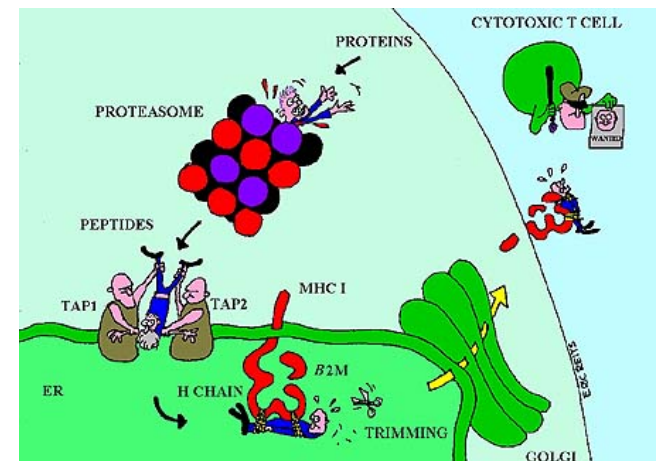
12 HIV infected individuals with sc in 1985

15 HIV infected individuals with sc in 2005/06

All individuals are Subtype B infected Caucasian males, treatment naïve

Sequence data of Gag (P17, P24), Nef, Protease and RT, isolated within one year after seroconversion

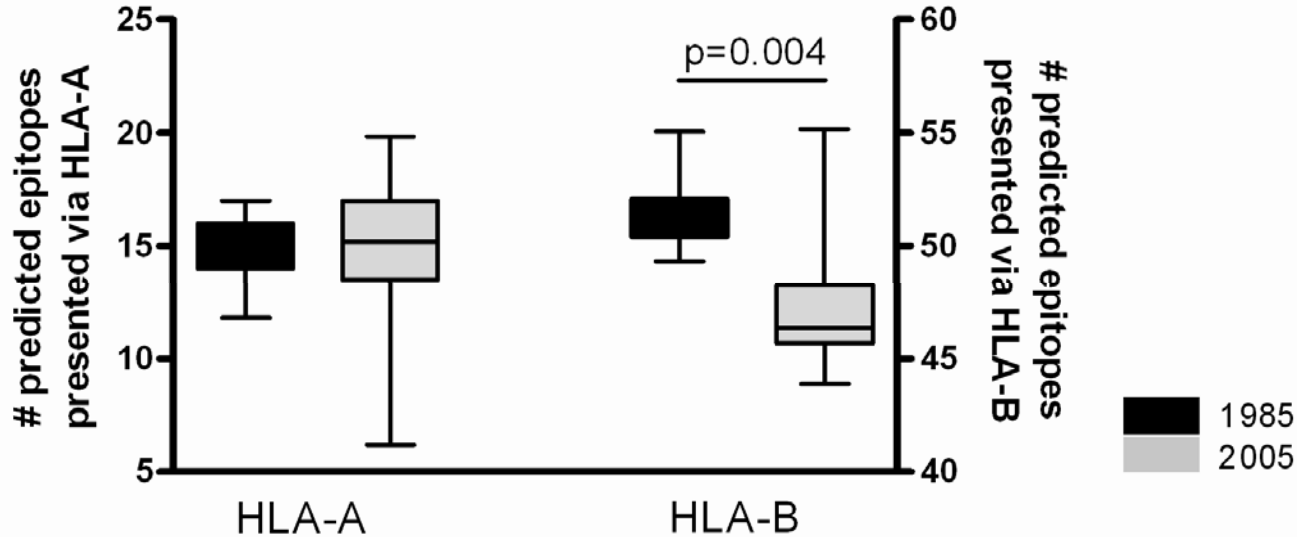
Analysis of the data using peptide prediction programs for proteasomal cleavage, TAP transport and HLA binding



Decreased number of CTL epitopes presented via HLA-B alleles



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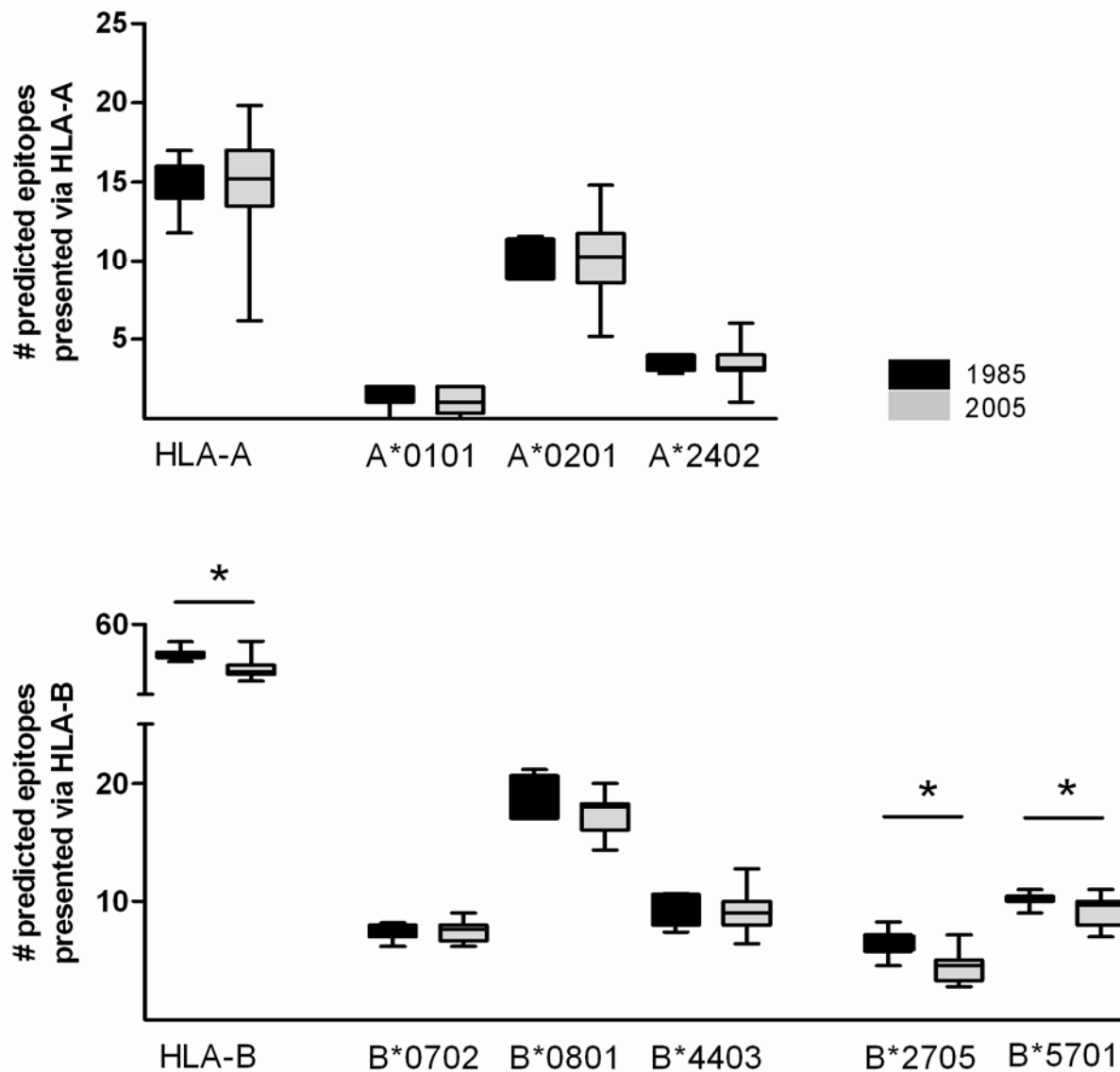


HLA-A*0101
HLA-A*0201
HLA-A*2402

HLA-B*0702
HLA-B*0801
HLA-B*4403

HLA-B*2705
HLA-B*5701

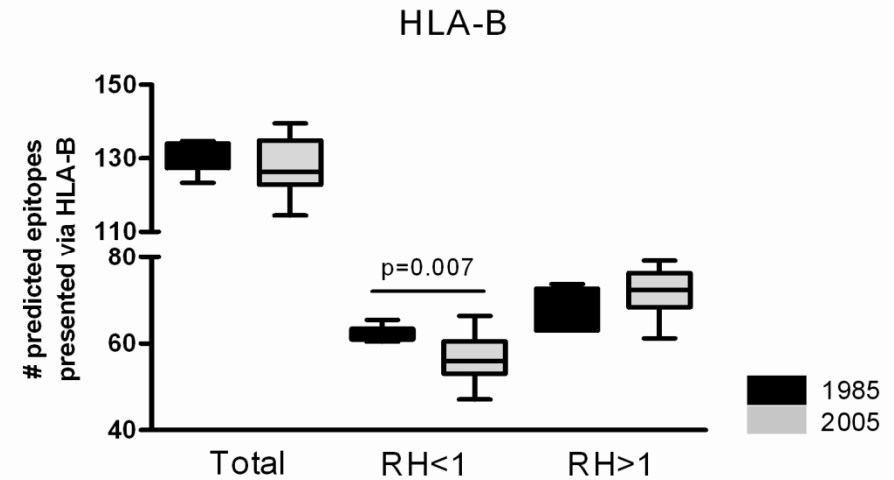
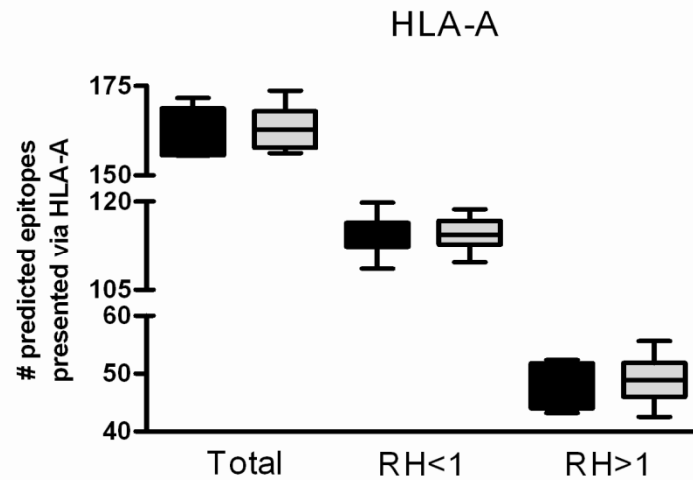
Decrease in the number of CTL epitopes is caused by HLA-B*2705 and B*5701



Adaptation of HIV-1 is driven by HLA-B alleles associated with slow disease progression



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Conclusions



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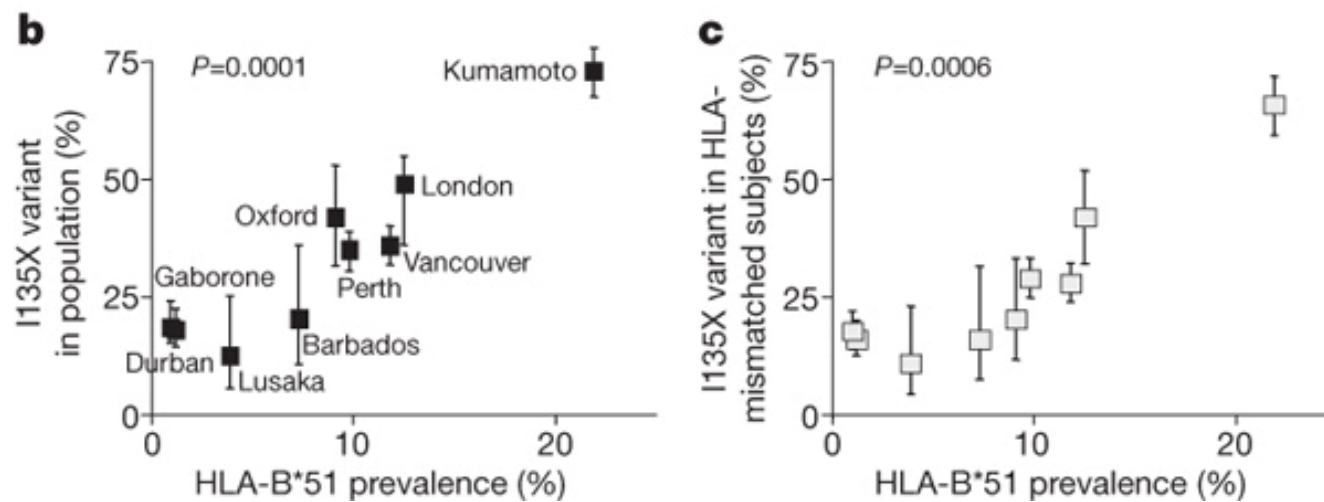
Even within 20 years of HIV-1 evolution, HIV-1 has significantly adapted to the human immune system by decreasing the number of CTL epitopes

Adaptations are not driven by the most common HLA molecules in the human population, but by HLA-B molecules associated with a low relative hazard of HIV-1 disease progression

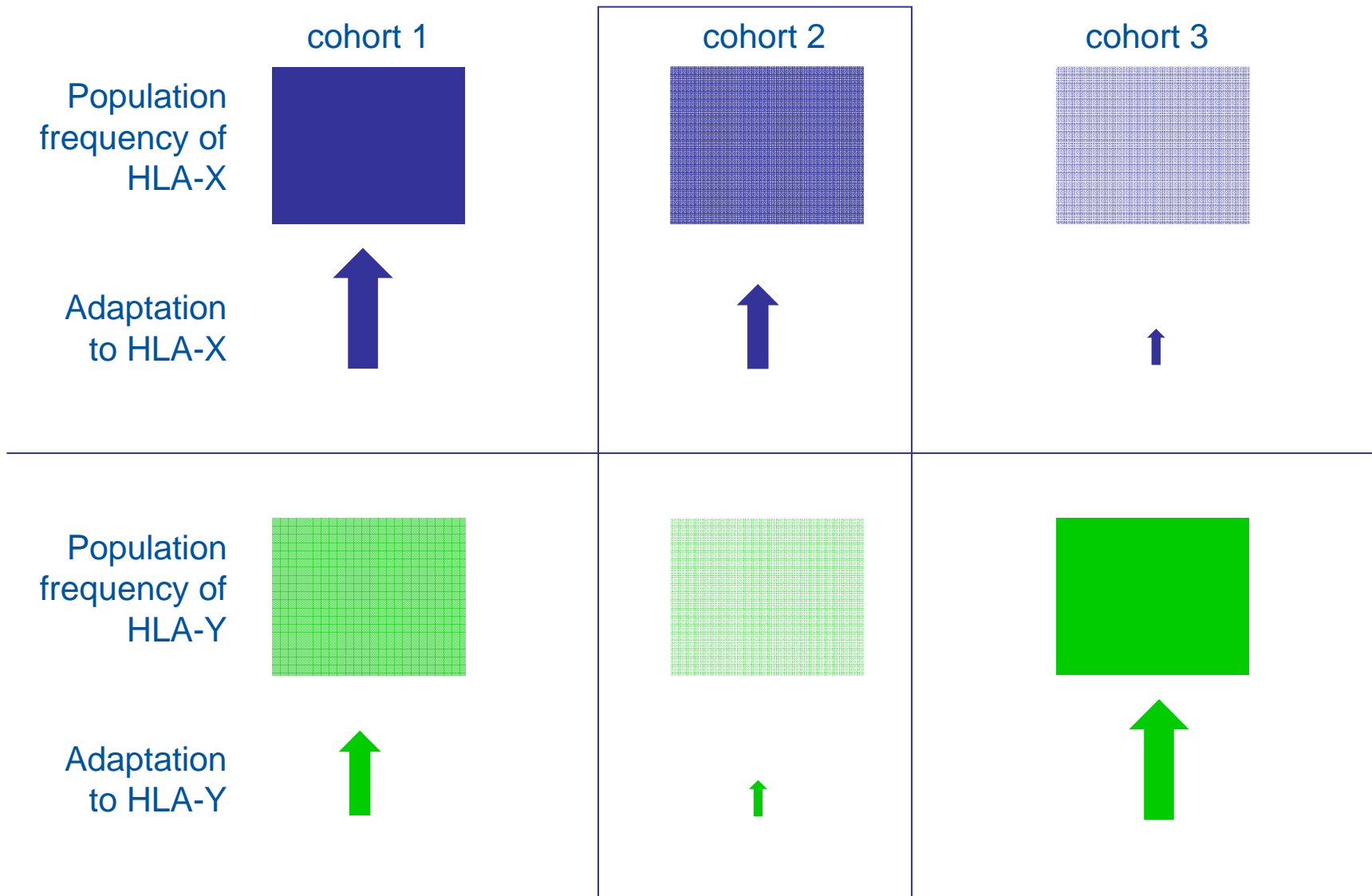
Correlation between HIV variant frequency and HLA prevalence in study cohorts



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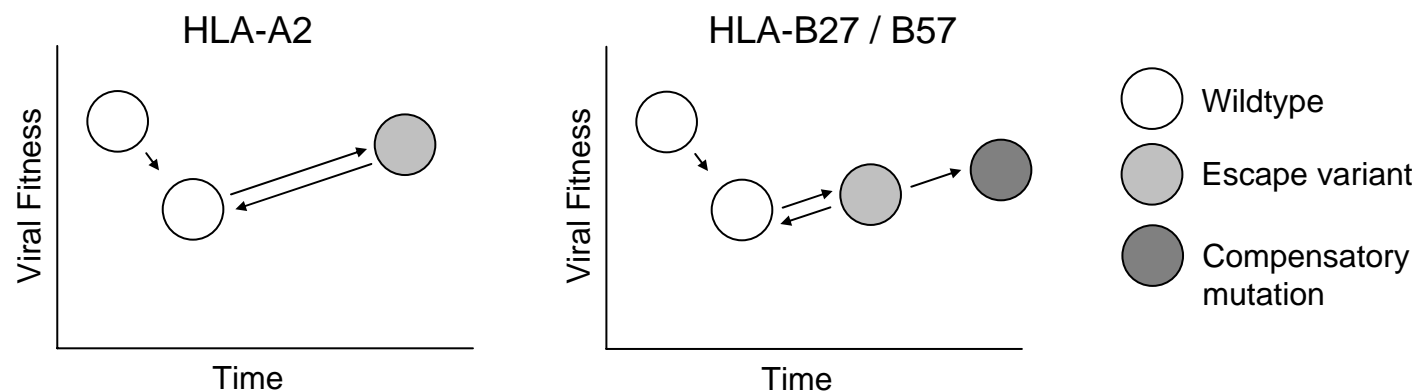
Population frequency & adaptation



Discussion



- The HLA alleles for which we observed significant adaptation are not common in the Caucasian population
- Mutations in epitopes restricted by HLA-B27 and B57 have been shown to be associated with reduced viral fitness
=> such escape mutations are expected to revert to wildtype upon transmission to a host that does not express this allele



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HLA alleles grouped based on RH

- HLA-A alleles with a $RH < 1$ are:
A*0201, A*0301, A*1101, A*2601, A*3101, A*3201 (not available when using NetMHC), and A*6901.
- HLA-A alleles with a $RH > 1$ are:
A*0101, A*2301, A*2402, A*2902, A*3002, A*3301 and A*6801.
- HLA-B alleles with a $RH < 1$ are:
B*0801, B*1801, B*2705, B*4001, B*5101, B*5701 and B*5801.
- HLA-B alleles with a $RH > 1$ are:
B*0702, B*1501, B*3501, B*4403, B*4501 and B*5301.



HLA alleles grouped based on frequency

- HLA-A alleles with a frequency $> 5\%$ are:
A*0101, A*0201, A*0301, A*1101 and A*2402.
- HLA-A alleles with a frequency $< 5\%$ are:
A*2301, A*2601, A*2902, A*3002, A*3101, A*3201 (not available when using NetMHC), A*3301, A*6801 and A*6901.
- HLA-B alleles with a frequency $> 5\%$ are:
B*0702, B*0801, B*1501, B*2705, B*3501, B*4001, B*4403 and B*5101.
- HLA-B alleles with a frequency $< 5\%$ are:
B*1801, B*4501, B*5301, B*5701 and B*5801.

HIV-1 polymorphisms identified by phylogenetic correction

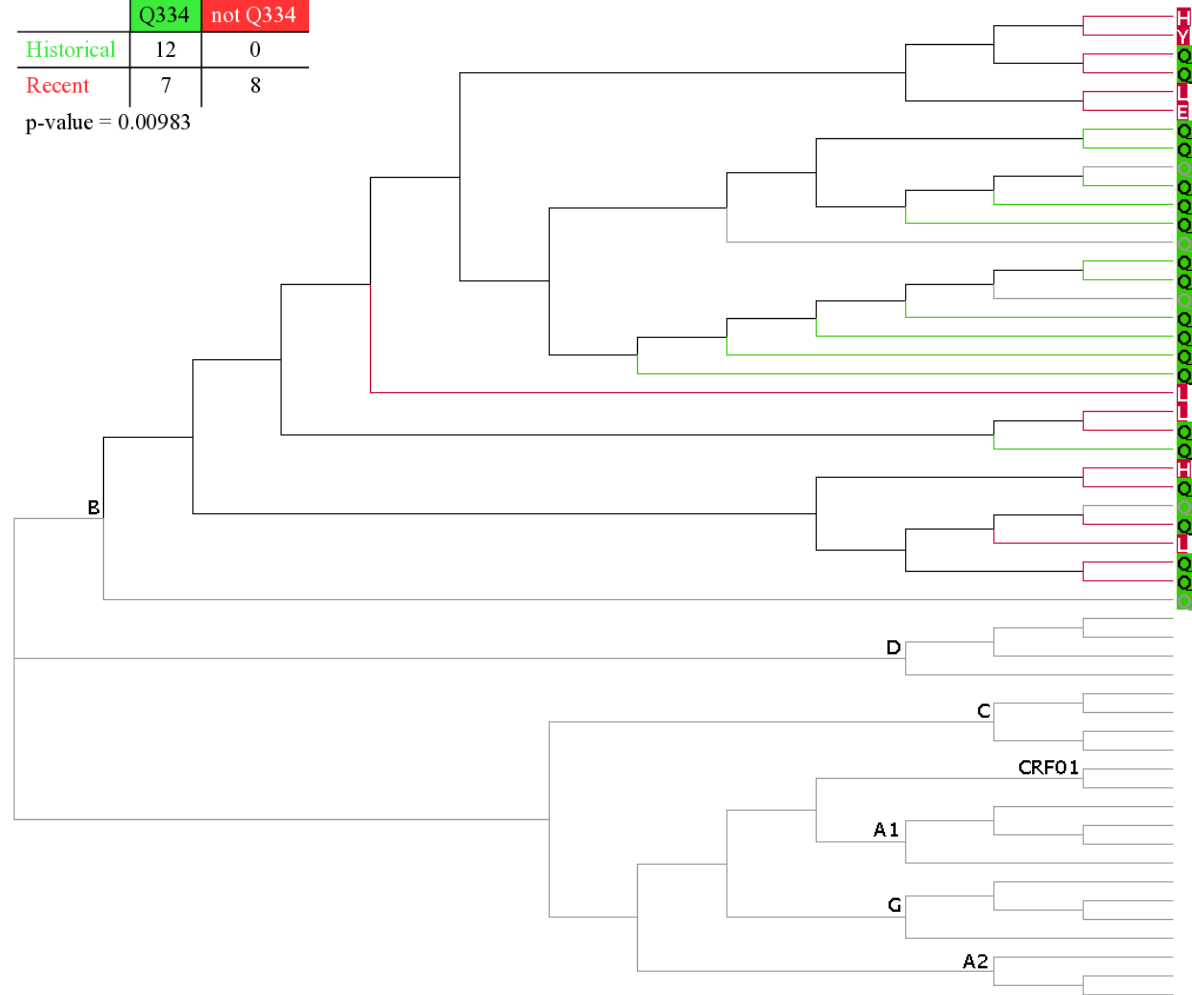


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Protein	Position	Uncorrected p-value
protease	X10L	0.0209
protease	L63X	0.0319
RT	Q334X	0.0098
P17	A10X	0.0397
P17	E12X	0.0029
P17	R76X	0.0330
P17	K91X	0.0312
P17	E93X	0.0279
P17	V94X	0.0397
P17	E102X*	0.0093
P24	G116X	0.0028
P24	N120X	0.0410
Nef	G11X	0.0170
Nef	X39R	0.0423
Nef	T50X	0.0134
Nef	N80X	0.0475
Nef	R105X	0.0475
Nef	E174X	0.0405
Nef	T176X	0.0475
Nef	X185Q	0.0474
Nef	R188X	0.0337
Nef	M194X	0.0399
Nef	L198X	0.0197

	Q334	not Q334
Historical	12	0
Recent	7	8

p-value = 0.00983



Escape mutations can either revert or be stable after transmission

