Transmission of Pre-adapted Viruses Determines the Rate of CD4^{+} Decline in Seroconvertors from Zambia

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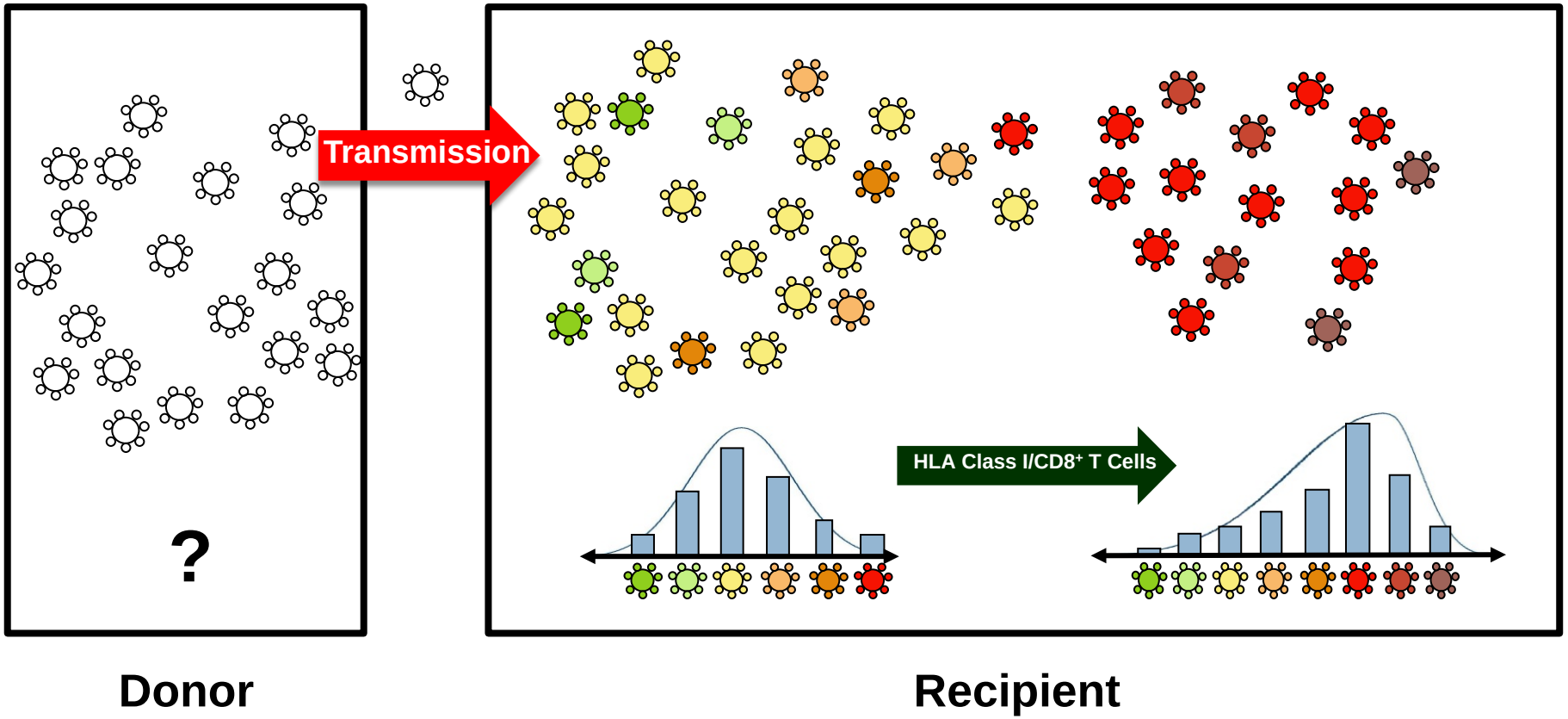
Daniela C. Mónaco, Ph.D.
Emory Vaccine Center, Atlanta, GA, U.S.A.

Transmission of escape mutations to the cytotoxic immune response



Factors that impact early pathogenesis

- ✓ Set-point VL is influenced by a complex interplay of viral and host factors. VL in the donor, gender of the recipient, protective alleles present in the recipient (A*74, B*13 and B*57) and allele B sharing between the donor and the recipient contribute to the set-point VL (Yue *et al*. J. Virol. 2013, 87(2):708)

- ✓ CTL escape mutations present in Gag, but not in Nef, in the donor transmitting sequence correlates with a reduced early VL in the recipient (Goepfert *et al*. J Exp Med. 2008 May 12;205(5):1009-17)

- ✓ Replicative Capacity of the transmitted variant measured on the Gag gene had an independent effect from set-point VL on the rate of $CD4^+$ decline up to 3 years (Prince *et al*. PLoS Pathog. 2012;8(11):e1003041)

- ✓ B*81:01 was associated with higher $CD4^+$ counts in early and chronic infection, even when it showed no effect on set-point VL (Prentice *et al*. J Virol. 2013 Apr;87(7):4043-51)

Objective of the Study

To evaluate the role of transmitted pre-adapted polymorphisms in determining the rate of $CD4^+$ decline in the newly-infected individual

Methodology

Zambia-Emory HIV Research Project (ZHERP), established by Dr. Susan Allen in 1994
Identified 148 epidemiologically-linked couples (median EDI=45.5 days; min=14 days; max=92 days)

Baseline

8 years

Couple is identified as serodiscordant

HIV negative partner is tested once per month

HIV negative partner seroconverts

Plasma collected from **D and LR**

gag, *pol* and *nef* amplified by population PCR and sequenced from **D and LR**

Periodical VL and $CD4^+$ count determinations

Methodology

D polymorphisms
(any position different from the consensus)

LR transmitted polymorphisms
(any position different from the consensus and present in the D sequence)

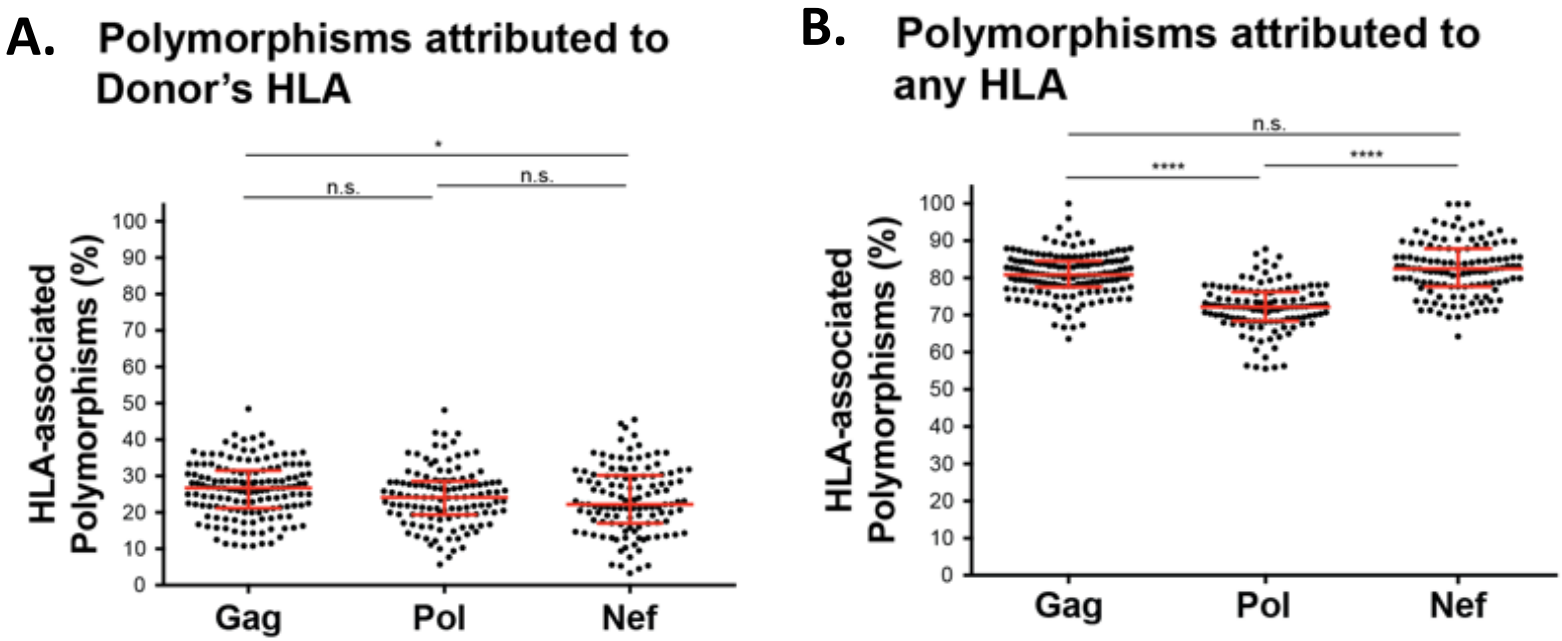
Adaptation
(to the HLA alleles of the D)

Pre-adaptation
(to the HLA alleles of the LR)

- ✓ **HLA-linked**: any polymorphism located on a position statistically-linked to a certain HLA allele present in the individual (using a cut-off of $q<0.2$ or $q<0.01$)
- ✓ **Epitope-located**: any polymorphism located in a well-defined epitope (A-list epitopes from http://www.hiv.lanl.gov/) restricted by the HLA alleles present in the individual
- ✓ **HLA-associated**: HLA-linked + Epitope-located

1. What is the level of adaptation of the viral population in the chronically-infected individuals?

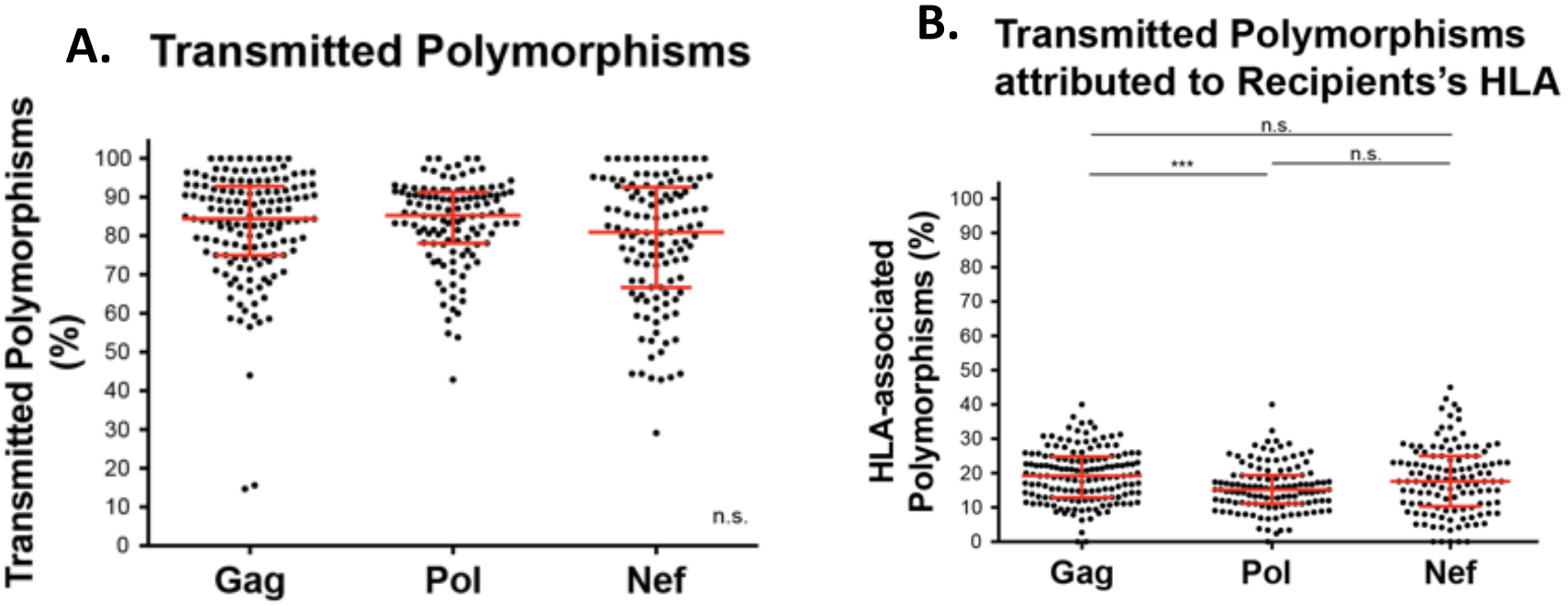
HLA-associated (q<0.2)



A small fraction of polymorphisms in a chronically-infected individual is associated with immune selection in the same individual. Most of these polymorphisms can be associated with other HLA alleles.

2. What is the level of pre-adaptation of the transmitted variant in the newly-infected individual?

HLA-associated (q<0.2)



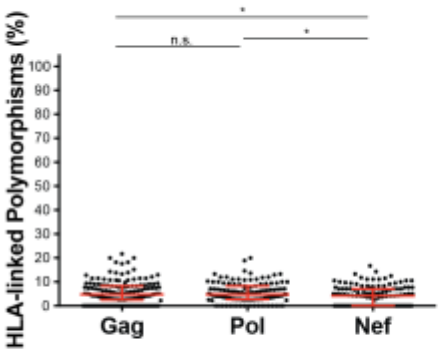
Most donor polymorphisms are transmitted to the newly-infected individual (approximately 80%) and a 20% of them are already adapted to the HLA alleles of the recipient.

3. What is the role of transmitted pre-adapted polymorphisms in determining the rate of CD4$^+$ decline in the newly-infected individual?

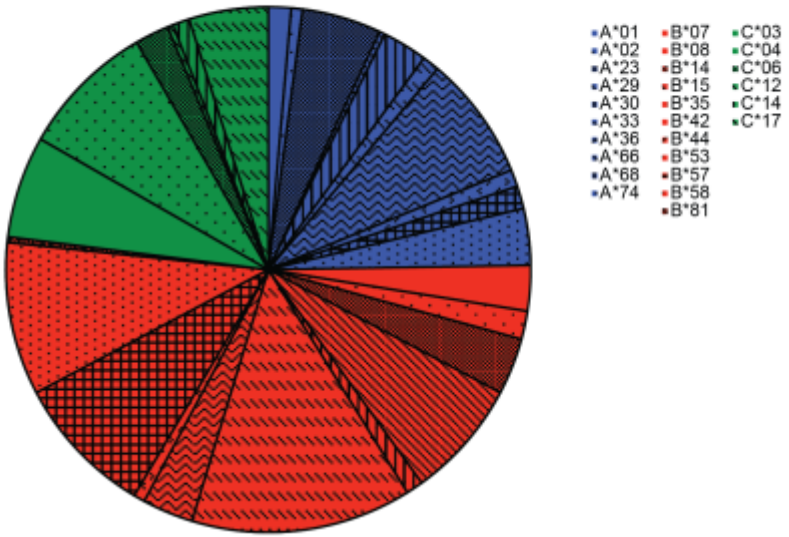
Ratio of Pre-adapted/Non-adapted Polymorphisms in Gag:

- HLA-linked polymorphisms (q<0.01)

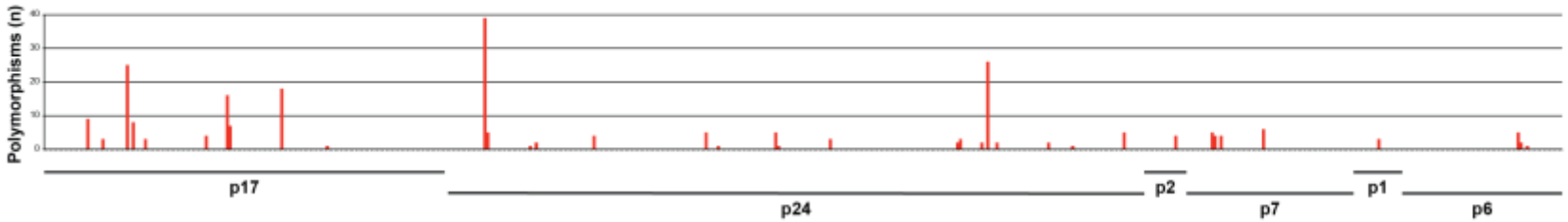
A. Transmitted HLA-linked Polymorphisms (*q*=0.01) attributed to Recipients's HLA



B. HLA Alleles associated to Gag HLA-linked Polymorphisms (*q*=0.01)



C. Distribution of Gag HLA-linked Polymorphisms (*q*=0.01)



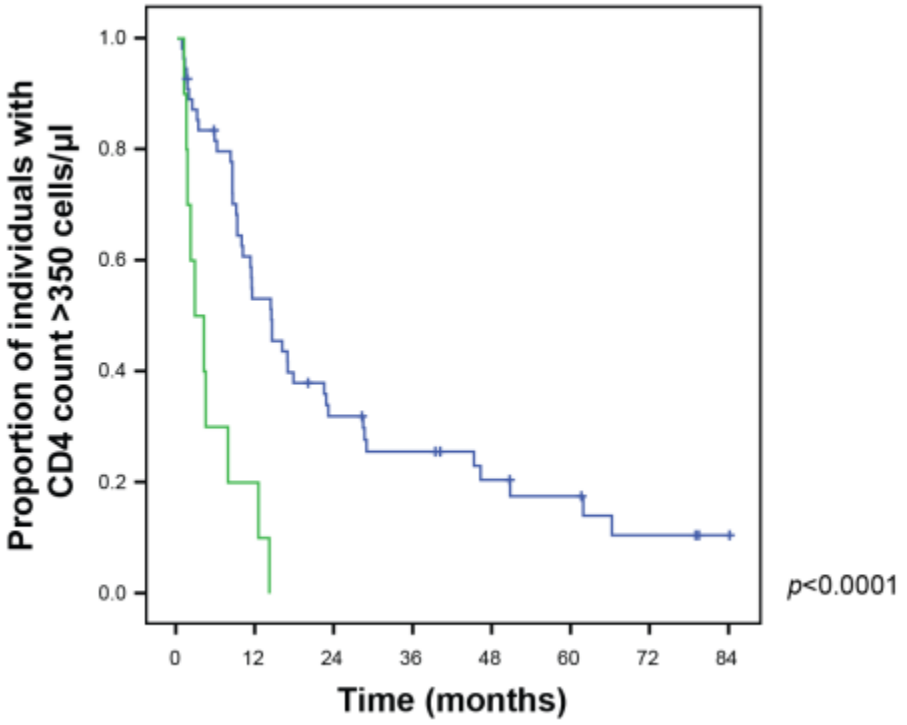
3. What is the role of transmitted pre-adapted polymorphisms in determining the rate of CD4$^+$ decline in the newly-infected individual?

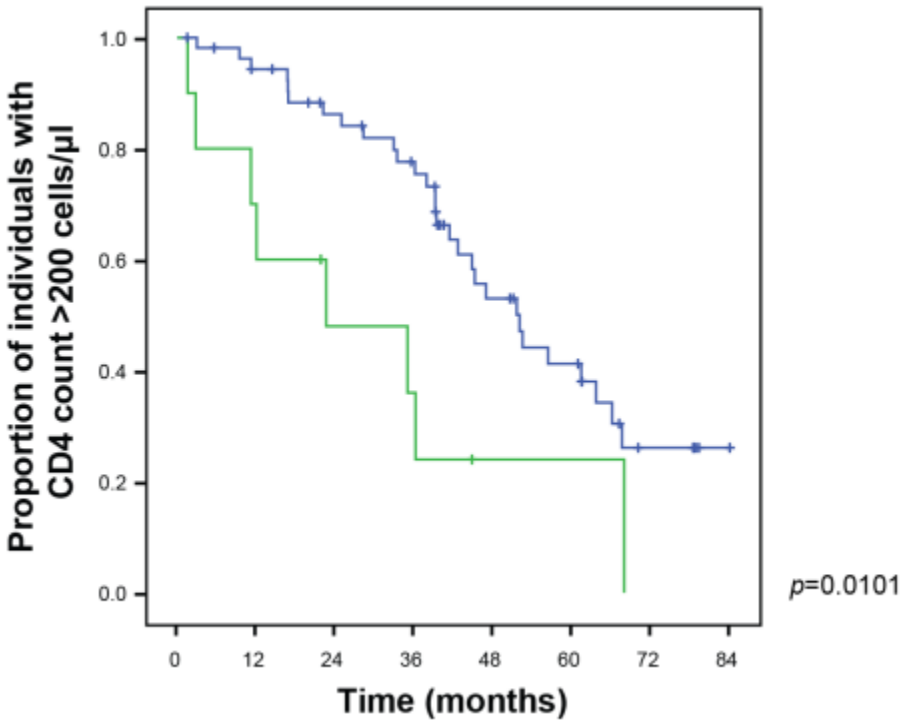
Risk of CD4+ Count <350 cells/µl		95% Confidence Interval			
Feature	HR	Lower	Upper	Wald Chi-Square	*p*-value
B*14:01	0.274	0.065	1.157	3.103	0.0782
HLA-B Sharing	**11.306**	**2.014**	**63.478**	**7.591**	**0.0059**
Replicative Capacity	**1.813**	**1.104**	**2.978**	**5.530**	**0.0187**
Set-point VL	1.000	0.685	1.459	0.000	0.9989
B Sharing-RC Interaction	**0.320**	**0.130**	**0.787**	**6.160**	**0.0131**
Gag Adapted/Non Adapted Polymorphisms	**1.065**	**1.015**	**1.119**	**6.491**	**0.0108**

The ratio of pre-adapted/non-adapted transmitted polymorphisms in Gag has an independent effect on determining the rate of CD4$^+$ decline to 350 cells/µl.

3. What is the role of transmitted pre-adapted polymorphisms in determining the rate of CD4$^+$ decline in the newly-infected individual?

Individuals receiving the highest ratios of Pre-adapted/Non-adapted Polymorphisms in Gag have the highest rate of CD4$^+$ decline





>Percentile 85
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3. What is the role of transmitted pre-adapted polymorphisms in determining the rate of CD4$^+$ decline in the newly-infected individual?

Risk of CD4+ Count <350 cells/µl		95% Confidence Interval			
Feature	HR	Lower	Upper	Wald Chi-Square	*p*-value
B*14:01	0.294	0.069	1.247	2.758	0.0968
HLA-B Sharing	1.393	0.712	2.724	0.937	0.3330
Replicative Capacity (Lowest Tercile)	0.598	0.312	1.144	2.414	0.1203
Set-point VL (>5)	1.319	0.575	3.026	0.428	0.5130
Gag Adapted/Non Adapted Polymorphisms (>Percentile85)	**4.404**	**1.878**	**10.325**	**11.627**	**0.0007**

Risk of CD4+ Count <200 cells/µl		95% Confidence terval			
Feature	HR	Lower	Upper	Wald Chi-Square	*p*-value
B*14:01	0.288	0.038	2.183	1.452	0.2283
HLA-B Sharing	0.500	0.220	1.134	2.752	0.0971
Replicative Capacity (Lowest Tercile)	0.773	0.336	1.782	0.365	0.5459
Set-point VL (>5)	**4.809**	**1.959**	**11.803**	**11.750**	**0.0006**
Gag85-RCLowestTercile Interaction	**15.858**	**1.289**	**195.155**	**4.657**	**0.0309**
Gag Adapted/Non Adapted Polymorphisms (>Percentile85)	**3.712**	**1.437**	**9.587**	**7.341**	**0.0067**

A high ratio of pre-adapted to non-adapted transmitted polymorphisms in Gag is the single predictor for a fast CD4$^+$ decline to an early stage (350 cells/µl) but set-point VL and RC also play a role in determining the rate of CD4$^+$ decline to a disease stage (200 cells/µl).

Conclusions I

In the chronic Zambian HIV^{+} population, we found that only a small proportion of polymorphisms in Gag, Pol and Nef proteins can be associated with the individual's own HLA-I alleles. This could be explained by the polymorphism's:

(1) high rate of transmission, even when a bias for transmission of consensus residues is observed (Carlson *et al.*, Science. 2014 Jul 11;345(6193):1254031);

(2) low rate of reversion, approximately 10% in the first 2 years after transmission, even in the absence of the selecting HLA in the newly-infected individual (data not shown).

These observations would also explain the high numbers of pre-adapted HLA-linked polymorphisms transmitted to the newly-infected individual.

Conclusions II

In the newly-infected individual, transmission of pre-adapted polymorphisms is associated with an accelerated $CD4^+$ decline, independently of other factors such as protective alleles, allele sharing, replicative capacity or set-point VL.

In contrast these pre-adapted polymorphisms didn't have any significant effect on early set-point VL (data not shown).

This results show that, even when selection of polymorphisms is usually associated with a less pathogenic virus due to the impact of these polymorphisms in replicative capacity, the release from immune pressure driven by these polymorphisms may be of greater advantage for the virus.

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