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
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

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

8 years

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. Polymorphisms attributed to Donor’s HLA

B. Polymorphisms attributed to any HLA

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?

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

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

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.
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).

### Risk of CD4+ Count <350 cells/μl

<table>
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<tr>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*14:01</td>
<td>0.294</td>
<td>0.069</td>
<td>1.247</td>
<td>2.758</td>
<td>0.0968</td>
</tr>
<tr>
<td>HLA-B Sharing</td>
<td>1.393</td>
<td>0.712</td>
<td>2.724</td>
<td>0.937</td>
<td>0.3330</td>
</tr>
<tr>
<td>Replicative Capacity (Lowest Tercile)</td>
<td>0.598</td>
<td>0.312</td>
<td>1.144</td>
<td>2.414</td>
<td>0.1203</td>
</tr>
<tr>
<td>Set-point VL (&gt;5)</td>
<td>1.319</td>
<td>0.575</td>
<td>3.026</td>
<td>0.428</td>
<td>0.5130</td>
</tr>
<tr>
<td>Gag Adapted/Non Adapted Polymorphisms (&gt;Percentile85)</td>
<td>4.404</td>
<td>1.878</td>
<td>10.325</td>
<td>11.627</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

### Risk of CD4+ Count <200 cells/μl

<table>
<thead>
<tr>
<th>Feature</th>
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<th>Wald Chi-Square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*14:01</td>
<td>0.288</td>
<td>0.038</td>
<td>2.183</td>
<td>1.452</td>
<td>0.2283</td>
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<tr>
<td>HLA-B Sharing</td>
<td>0.500</td>
<td>0.220</td>
<td>1.134</td>
<td>2.752</td>
<td>0.0971</td>
</tr>
<tr>
<td>Replicative Capacity (Lowest Tercile)</td>
<td>0.773</td>
<td>0.336</td>
<td>1.782</td>
<td>0.365</td>
<td>0.5459</td>
</tr>
<tr>
<td>Set-point VL (&gt;5)</td>
<td>4.809</td>
<td>1.959</td>
<td>11.803</td>
<td>11.750</td>
<td>0.0006</td>
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<tr>
<td>Gag85-RCLowestTercile Interaction</td>
<td>15.858</td>
<td>1.289</td>
<td>195.155</td>
<td>4.657</td>
<td>0.0309</td>
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<tr>
<td>Gag Adapted/Non Adapted Polymorphisms (&gt;Percentile85)</td>
<td>3.712</td>
<td>1.437</td>
<td>9.587</td>
<td>7.341</td>
<td>0.0067</td>
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</table>
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.
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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