Heterosexual Transmission of Subtype C HIV-1 Does Not Require Increased Replicative Capacity or Interferon-α Resistance

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HIV transmission bottleneck: single variants establish infection

Many variants
Quasispecies


(Adapted from Boeras et al. PNAS 2011)
Cohort established by Dr. Susan Allen in 1994
- Couples voluntarily enrolled for HIV testing, counseling and condom provisions, reducing transmission/yr from 22% to 8.5%.
- Negative partner is tested monthly

Zambia-Emory HIV Research Project (ZEHRP)

Table 1. Transmission pair characteristics.

<table>
<thead>
<tr>
<th>Coded ID</th>
<th>Partner Status</th>
<th>Days after EDI</th>
<th>VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z331M</td>
<td>LR</td>
<td>32</td>
<td>2,864,668</td>
</tr>
<tr>
<td>Z331F</td>
<td>D</td>
<td>29</td>
<td>2,620</td>
</tr>
<tr>
<td>Z3576F</td>
<td>LR</td>
<td>22</td>
<td>6,460,200</td>
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<tr>
<td>Z3576M</td>
<td>D</td>
<td>43</td>
<td>54,100</td>
</tr>
<tr>
<td>Z3618M</td>
<td>LR</td>
<td>22</td>
<td>16,600,000</td>
</tr>
<tr>
<td>Z3618F</td>
<td>D</td>
<td>45</td>
<td>20,400</td>
</tr>
<tr>
<td>Z3678M</td>
<td>LR</td>
<td>22</td>
<td>3,017,616</td>
</tr>
<tr>
<td>Z3678F</td>
<td>D</td>
<td>28</td>
<td>269,240</td>
</tr>
<tr>
<td>Z4248M</td>
<td>LR</td>
<td>22</td>
<td>24,993,584</td>
</tr>
<tr>
<td>Z4248F</td>
<td>D</td>
<td>29</td>
<td>119,320</td>
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<td>Z4473M</td>
<td>LR</td>
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<td>16,891,328</td>
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<tr>
<td>Z4473F</td>
<td>D</td>
<td>22</td>
<td>104,427</td>
</tr>
</tbody>
</table>

a Z = Zambia, M = male, F = female
b LR—epidemiologically linked recipient partner, D—donor partner.
HIV sequences from 6 transmission pairs with single variant transmissions

Genotypic and phenotypic correlates of transmission?
Consensus-like relatively neutralization sensitive TF variants

HIV TRANSMISSION

Selection bias at the heterosexual HIV-1 transmission bottleneck

Envelope-Constrained Neutralization-Sensitive HIV-1 After Heterosexual Transmission

(Deymier, Ende et al. PLoS Path 2015)
Replicative capacity (RC) of TF versus source quasispecies
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TF variants are not the highest replicators

(Deymier, Ende et al. PLoS Path 2015)
Replicative capacity (RC) of TF versus source quasispecies

TF variants are not the highest replicators

(Deymier, Ende et al. PLoS Path 2015)
Innate immunity and interferon?
TF variants are not relatively resistant to interferon-alpha.
Caveats on interferon resistance in vitro

IFN resistance can vary based on virus input

(Deymier, Ende et al. PLoS Path 2015)
Summary

In 6 subtype C transmission pairs with genome-length HIV variants:

<table>
<thead>
<tr>
<th>TF is likely...</th>
<th>TF is NOT necessarily...</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑Consensus-like</td>
<td>↑RC</td>
</tr>
<tr>
<td>↑Neutralization Sensitive</td>
<td>↑IFNα resistant</td>
</tr>
<tr>
<td></td>
<td>↑RC in MDDC (not shown)</td>
</tr>
<tr>
<td></td>
<td>↑Particle Infectivity (not shown)</td>
</tr>
</tbody>
</table>

- Findings consistent with the hypothesis that within-host evolution of HIV-1 in response to adaptive immune responses reduces viral transmission potential
- HIV-1 heterosexual transmission is permissive to a range of in vitro fitness phenotypes
- More transmission pairs needed to see more subtle effects
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