Transmission of Drug Resistant Variants of HIV-1: Past, Present and Future

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Presented at the 6th Int. Workshop on HIV Transmission, 14 – 15 July 2011, Rome, Italy
Sexual Transmission of Drug Resistance Mutations

• Approximately 5-10% of all new HIV infections in developed countries now include at least one drug-resistance related mutation.

• Transmitted drug resistance is now increasingly being reported in developing countries.

• No information is yet available on whether K65R may be sexually transmitted.

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Early stage infection: The window of opportunity for prevention

- Acute/recent infection: >50% infectivity
- Chronic infection: 10-20% infectivity
- Chronic treated: <<10% infectivity

Viral load & Infectivity

- 1/30-1/200
- 1/100-1/1,000
- 1/500-1/2,000
- 1/100-1/1,000

0 | 6 mo | 2 yrs | 5 yrs | 10 yrs | > 20 yrs

HAART

1/5 HIV+ Untested

CLUSTERING

>50% | 10-20% | <<10%

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Clustering leads to onward transmission of drug resistant subepidemics

Genetic barrier to transmission of M184V and TAM vs. transmission cascades of NNRTIs

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Brenner BG et al, AIDS 2008
ECHO, THRIVE: Treatment Failure, Resistance, and Adverse Events

### Treatment Failure in ECHO and THRIVE

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Rilpivirine</th>
<th>Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF</td>
<td>9.0 (686)</td>
<td>4.8 (682)</td>
</tr>
<tr>
<td>AE</td>
<td>2.0 (686)</td>
<td>6.7 (682)</td>
</tr>
</tbody>
</table>

### Resistance at Virologic Failure

<table>
<thead>
<tr>
<th>Wk 48 Outcome</th>
<th>Rilpivirine (n = 686)</th>
<th>Efavirenz (n = 682)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF with resistance data, n</td>
<td>62</td>
<td>28</td>
</tr>
<tr>
<td>No NNRTI or NRTI RAMs,%</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>≥ 1 Emergent NNRTI RAM,%</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td>Most frequent NNRTI RAM</td>
<td>E138K</td>
<td>K103N</td>
</tr>
<tr>
<td>≥ 1 Emergent NRTI RAMs, %</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>Most frequent NRTI RAM</td>
<td>M184I</td>
<td>M184V</td>
</tr>
</tbody>
</table>

### Adverse Events and Discontinuation

<table>
<thead>
<tr>
<th>Wk 48 Outcome, %</th>
<th>Rilpivirine (n = 686)</th>
<th>Efavirenz (n = 682)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC for AE</td>
<td>3</td>
<td>8</td>
<td>.0005</td>
</tr>
<tr>
<td>Most Common AEs of Interest, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any neurologic AE</td>
<td>17</td>
<td>38</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Any psychiatric AE</td>
<td>15</td>
<td>23</td>
<td>.0002</td>
</tr>
<tr>
<td>Any rash</td>
<td>3</td>
<td>14</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

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M184I vs M184V

M184I usually arises first because it derives from the G to A hypermutation. M184V subsequently arises due to an independent substitution within the same triplet codon. Then, M184V out-competes M184I because of superior replicative capacity.

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Impact of E138K in recombinant HIV-1<sub>NL-4.3</sub> and HIV-1<sub>AG</sub> viruses on NNRTIs susceptibility and replication capacity (RC)

**A: RC in TZM-bl after 48 hrs**

- pNL4.3<sub>E138K</sub>
  - FC = 3.8
- A/G<sub>E138K</sub>
  - FC = 2.7
  - FC = 1.4
  - FC = 3.9
  - FC = 2.2
  - FC = 1.8

**B: RC in TZM-bl after 48 hrs**

**C: Growth curve in CBMCs after 14 days**

The RC of E138K was impaired by 2 to 3-fold compared to WT.


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Compensatory effect of E138K on the replication capacity (RC) of M184I/V.

- The RC of both E138K and M184I are each decreased by 3-fold compared to wild-type and decreased by 2-fold for M184V.
- There is no difference in RC of double mutants E138K/M184I or E138K/M184Vc compared to wild-type.

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Rate of polymerization of HIV-1 RTs with 497nt HIV-1 PBS RNA and 25nt DNA primer (D25) monitored in time-course experiments at high concentration of dNTPs (200 μM)

Under high dNTP concentrations:

- neither M184I nor M184V exhibits deficit in polymerization rate.
- the 138K mutant RT has lower polymerization rate as indicated by the maximum size (~120nt) of extended primers made at 60 sec, while the WT and other mutant RTs reach ~210nt.
- the double mutant RTs 138K/184I and 138K/184V share similar polymerization rate with the WT.

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Selections of M184V Virus with Various NNRTIS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETR</td>
<td>K103N</td>
</tr>
<tr>
<td>DPV</td>
<td>K103N</td>
</tr>
</tbody>
</table>

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Selections of M184I Virus with Various NNRTIS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETR</td>
<td>K103N, V179I</td>
</tr>
<tr>
<td>DPV</td>
<td>Y181C</td>
</tr>
</tbody>
</table>
Selections of E138K Virus with Various NRTIS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>M184I, M184V</td>
</tr>
<tr>
<td>FTC</td>
<td>M184I, M184V</td>
</tr>
</tbody>
</table>
Conclusions

1. The HIV-1 RT E138K mutation has the potential to be an important signature mutation for the second-generation NNRTIs ETR and RPV.

2. The E138K mutation restores RT enzymatic processivity and the viral replication capacity of HIV-1 variants harboring M184I/V.

3. In the ECHO and Thrive clinical trials, we believe that the presence of E138K stabilized viruses containing M184I, thus obviating the need for HIV to develop M184V.

4. This compensatory effect of E138K for M184I/V may have clinical significance in regard to treatment failures involving ETR and other novel NNRTIs as well as on the detectability of these mutations in transmitted resistance.

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Acknowledgements

- Bluma Brenner

- Hongtao Xu (Genetic engineering & enzymatic analysis)

- Eugene L. Asahchop (Relative replication capacity)

- Maureen Oliveira (Phenotyping)

- Funding from the Canadian Institutes of Health Research (CIHR) and by the International Partnership on Microbicides.

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