HIV Drug Resistance: Implications for Prevention and Therapy

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“Infidelity is one of the most important problems that confront America today”

Jesse Helms, U.S. Senator, 1996
George W Bush, United States President, 2004
These leaders were among the world’s first politicians to attempt to understand the reverse transcriptase enzyme of HIV-1.
Reasons for HIV Drug Resistance

- high viral replication rate
- high reverse transcriptase error rate
  \((5 \times 10^{-5} \text{ mutations per replication event})\)

Therefore, HIV is capable of mutating at every possible locus on a daily basis, creating the potential for selection of resistant viruses.
The female is HIV-infected. She either does not know it or does but chooses to use a microbicide to protect a sexual partner. Will drug resistance be selected? In the case of microbicides, this will depend in large part on whether the microbicide is systemically absorbed and exerts the equivalent of monotherapy. But, inadequate absorption or only very low level absorption may be inadequate to apply antiviral drug pressure and select for drug resistance. e.g. UC-781, TMC-120
Is there enough HIV present and replicating in areas that are exposed to a topically applied microbicide to select for drug resistance? Probably not. But, we do not know for sure. Will there be individual variability in this regard?
The male partner is infected with a drug-resistant variant of HIV-1. Can the presence of transmissible drug-resistant viruses in a population overcome whatever ARV block is in place through use of a microbicide or PREP? There is scant data on this topic.
Will the Development of HIV Drug Resistance due to ARV-Based Microbicides Compromise Future Therapeutic Benefit for People Who Use such a Product?
- e.g. similar to the use of NVP in MTCT
Do Differences Exist among HIV Subtypes in the Development of Drug Resistance?
Silent Mutation at Codon 106 responsible for the V106M mutation in clade C RT with NNRTIs

<table>
<thead>
<tr>
<th>HIV-1 RT</th>
<th>Clade B</th>
<th>Clade C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type codon at position 106</td>
<td>$\text{V(GTA)} \downarrow$</td>
<td>$\text{V(GTG)} \downarrow$</td>
</tr>
<tr>
<td>In clade C, V106M arises</td>
<td>two codon changes</td>
<td>$\text{M(ATG)}$</td>
</tr>
<tr>
<td>In clade B, V106A occurs</td>
<td>$\text{A(GCA)}$</td>
<td>two codon changes</td>
</tr>
<tr>
<td>Description</td>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>No. Patients</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>No. Patients failing</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>No. Patients with K65R</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No. Patients with L74V</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Time (months)</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Selection of RT mutations after sequential passage with ddI and/or d4T

<table>
<thead>
<tr>
<th>*clinical isolate</th>
<th>experiment no</th>
<th>weeks of passage</th>
<th>highest drug concentration achieved</th>
<th>mutations selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>4742</td>
<td>1</td>
<td>28</td>
<td>40 μM ddI</td>
<td>K65R</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24</td>
<td>5 μM d4T</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>17</td>
<td>10 μM ddI; 0.5 μM d4T</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>17</td>
<td>10 μM TDF</td>
<td>K65R</td>
</tr>
<tr>
<td>4761</td>
<td>1</td>
<td>24</td>
<td>10 μM ddI</td>
<td>L74V</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>22</td>
<td>2.5 μM d4T</td>
<td>D67N</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>15</td>
<td>1 μM ddI; 0.1 μM d4T</td>
<td>K65R</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>17</td>
<td>5 μM TDF</td>
<td>none</td>
</tr>
<tr>
<td>BG-05</td>
<td>1</td>
<td>28</td>
<td>30 μM ddI</td>
<td>K65R, D67N</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24</td>
<td>2.5 μM d4T</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>28</td>
<td>10 μM ddI; 0.1 μM d4T</td>
<td>K65R</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>24</td>
<td>10 μM TDF</td>
<td>K65R</td>
</tr>
<tr>
<td>BG-15</td>
<td>1</td>
<td>17</td>
<td>10 μM ddI</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>17</td>
<td>0.5 μM d4T</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>28</td>
<td>10 μM ddI; 0.5 μM d4T</td>
<td>K65R, V75I</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>18</td>
<td>5 μM TDF</td>
<td>none</td>
</tr>
<tr>
<td>Mole 18</td>
<td>1</td>
<td>28</td>
<td>40 μM ddI</td>
<td>L74V</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>22</td>
<td>0.5 μM d4T</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>22</td>
<td>2.5 μM ddI; 0.1 μM d4T</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>28</td>
<td>5 μM TDF</td>
<td>K65R</td>
</tr>
</tbody>
</table>

*Nucleotide accession numbers: 4742 (AF492595), 4761(AF492597), BG-05 (AF492600), BG-15 (AF492601), Mole 18 (AF492607)

The development of K65R resistance to ddI and/or d4T was confirmed by tissue culture selection using 5 HIV-1 subtype C clinical isolates. The K65R mutation arose within 15-28 weeks in 2 of 5 subtype C selections under ddI pressure and 3 of 5 selections conducted using combinations of ddI and d4T. In some cases, ddI also selected for the appearance of the D67N or L74V substitutions in RT.
Are Drug-Resistant Viruses Transmitted with the Same Efficiency as Wild-Type Viruses?
Differential Presence of Select Drug Resistance Mutations in Patient Populations

- TAMs: 70.7%
- NNMs: 61.3%
- M184V: 61.5%
- PRAMs: 37.2%

Long-term treated patients (n=380)

- TAMs: 66.1%
- NNMs: 10.1%
- M184V: 23.7%
- PRAMs: 23.7%

PHI (Untreated n=59)
HIV-1 Transmission Dynamics in an Urban North American Setting
Evolving trends in the HIV-1 Epidemic in Canada

Integrating surveillance, prevention & treatment initiatives fundamental to control HIV/AIDS

Quebec Genotyping Program (2001-2006) n ~ 4000
PHI Cohort (1997-2006) n = 318


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PHI Cohort (1997-2006) n = 318

Potential Transmitter Populations

- PHI (<6 mo) n = 891
  - 4.64 ± 0.83
- CI-Naïve
  - 4.71 ± 0.70
- CI-Treatment Failure
  - 4.14 ± 0.76

Undiagnosed
- 25-30%

Non-genotyped CI
- ~2.58 n=2328
Genotypic surveillance of HIV transmission

- **Pol** gene sufficient to reconstruct transmission events
  - RT and protease sequences are conserved
  - A single dominant viral species is transmitted & persists

- Sequence clustering infers viral inter-relationships
  - Hué S, AIDS 2004

- **Non-subjective surveillance**
  - **Caveats**: Cannot identify time or direction of transmission

- PHI cohort data can establish risk correlates
Clustering of PHI transmission events

Non-B Subtypes (n=17)

Clustered PHIs
n=293

Non-B Subtypes (n=53)

Nonclustered PHIs
n=300

Chronic infections rarely co-cluster

5 year follow-up of 54 HIV-infected individuals
Mutation reversal: PI: 30,50,54,82,84 and 90
RT: 41,65,67,69,70,74,103,106,151,181,184,215

CI: PHI
5.8% → 14.4%
Co-Clustering of PHI and Chronic Infections

2.5 ± 0.7

8.4 ± 3.9 PHI/cluster

Small

Large

Cluster size

# Infections

PHI:PHI

Cl:PHI

# Infections

UNIQUE
Time intervals for onward PHI:PHI transmission

<table>
<thead>
<tr>
<th>Cluster Size</th>
<th>Cluster Interval (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 PHI / Cluster</td>
<td>12 ± 6 months</td>
</tr>
<tr>
<td>&gt;5 PHI / Cluster</td>
<td>15 ± 9 months</td>
</tr>
</tbody>
</table>

- 64 clusters (n=158)
- 20 clusters (n=168)
# Drug resistance in clustered transmissions

<table>
<thead>
<tr>
<th>Resistance profiles of CI within PHI clusters</th>
<th>Resistance Profiles in PHI</th>
<th>PHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>wt (n=15)</td>
<td>wt</td>
<td>7</td>
</tr>
<tr>
<td>184V (n=6)</td>
<td>wt</td>
<td>6</td>
</tr>
<tr>
<td><strong>67N,69R,70R,184V</strong> PI (n=1)</td>
<td><strong>67N, 69N, 219Q</strong></td>
<td>1</td>
</tr>
<tr>
<td>103N /PI (n=1)</td>
<td>103N, 103N/PI</td>
<td>2, 2</td>
</tr>
<tr>
<td>103N (n=1)</td>
<td>103N</td>
<td>2</td>
</tr>
<tr>
<td>190A (n=1)</td>
<td>190A</td>
<td>-</td>
</tr>
</tbody>
</table>
Conclusions

• Population-based genotypic surveillance complements epidemiological & behavioural cohort data

• Early/PHI disease stages linked to 50% of HIV transmissions

• Onward transmission of drug resistance may occur through transmission cascades

• Prevention initiatives should target early infection
  – Enhanced behavioural approaches to reduce transmission
  – Increased sensitivity to early clinical diagnosis
  – Optimizing HIV testing methods for early detection
  – Earlier treatment initiation
Quebec PHI Study Group

Actuel
R. Thomas, B Trottier, F Asselin, M Boissonnault, L Chareste, H Dion, S Lavoie, D Legault, D Longpré, PJ Maziade, ME Morin, D Murphy, VK Nguyen, R O’Brien, S Vézina

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Daniela Moisi
Michel Roger
Jean Pierre Routy
Hugues Chareste
Joseph Cox

Jean-Guy Baril

PHI Cohort Participants
ACKNOWLEDGEMENTS

The patients
The Ministry of Health of Botswana
The Infectious Diseases Service at the IDCC clinic

Ava Avalos
Diana Dickinson
Tendani Gaolathe
Simani Gaseitsiwe
Madisa Mine
Mr Moyo
Musetsanagepe Modukanele
Howard Moffat
Ndwapi Ndwapi
Trevor Peter
Enoch Sepako
Ibou Thior
Mpho Zwinila

Florence Doualla-Bell
Bluma Brenner
Maureen Oliveira
Daniella Moisi
Bonnie Spira
Max Essex
Ric Marlink
THANK YOU