Global Spread of HIV-1 Drug Resistance: Meeting the Challenge

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Outline

• Refresher on HIV Drug Resistance
  – Principles, types, major vs. minor

• Drivers of HIV resistance
  – PrEP vs ART

• What can we do to minimize resistance?
  – Multiple improvements required

• Take home message
  – We need to meet the challenge!
Principles of Resistance

- HIV-1 can develop resistance to any ARV

HIV Replication + One or Two ARV = RESISTANCE

NO REPLICATION (3 Drug ART) = NO RESISTANCE

- Remove drug, resistance decays, but it depends on mutation and drug
  - M184V (3TC/FTC) = fast
  - K103N (NNRTI) = slow
Types of Resistance

**ACQUIRED**
- Infected with *wildtype* virus
- Resistance selected by sdNVP, ART or PrEP
- Can infect partner with resistant virus

**TRANSMITTED**
- Infected with *resistant* virus
- Never exposed to ARVs
- Partner received ART, sdNVP or PrEP
- Or partner infected with resistant virus (2° transmission)
Major vs. Minor

**MAJOR**
- $\geq 25\%$ of virions in a person are resistant
- Detected by standard population genotype

**MINOR**
- $< 25\%$ of virions in a person are resistant
- Missed by standard genotype
- Detected by sensitive methods (ASPCR, SGS, Deep Sequencing)
What drives drug resistance?
# Resistance in PrEP Trials

## Infected Post-Enrollment

<table>
<thead>
<tr>
<th>Study</th>
<th># Sequenced</th>
<th># Resistant to TDF or FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Active</td>
</tr>
<tr>
<td>Bangkok Tenofovir</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>CAPRISA-004</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPrEX</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>Partners in PrEP</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>TDF2</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>VOICE/MTN-003</td>
<td>128</td>
<td>173</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>665</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Resistance in PrEP Trials

### Enrolled during Acute Seroconversion

<table>
<thead>
<tr>
<th>Study</th>
<th># Infected at Enrollment</th>
<th># Resistant to TDF or FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok Tenofovir</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>iPrEX</td>
<td>10</td>
<td>3 (M184I/V)</td>
</tr>
<tr>
<td>Partners in PrEP</td>
<td>8</td>
<td>2 (1 K65R + 1 M184V)</td>
</tr>
<tr>
<td>TDF2</td>
<td>1</td>
<td>1 (K65R/M184V)</td>
</tr>
<tr>
<td>VOICE</td>
<td>9</td>
<td>2 (M184I/V)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>35</strong></td>
<td><strong>8 (23%)</strong></td>
</tr>
</tbody>
</table>
Drug Resistance in VOICE

355/368 (96%) Successfully Genotyped*

21/22 (95%) Acutely infected at enrollment

301/312 (96%) Seroconverted on study product

33/34 (97%) Seroconverted between PUEV & TV

*No result (n=13) due to:
• No stored plasma (n = 1)
• Insufficient copies of HIV-1 RNA for extraction (n = 11)
• PCR amplification failure (n = 1)
### VOICE Standard Sequencing

<table>
<thead>
<tr>
<th>No resistance to TFV</th>
<th>3 cases of FTC Resistance</th>
<th>8 cases of NNRTI resistance (transmitted)</th>
</tr>
</thead>
</table>
| • TFV oral or gel arms (K65R or K70E)  
  • 0/173 infected after enrollment  
  • 0/18 acutely infected at enrollment | • Oral Truvada arm (M184V/I)  
  • 1/55 infected after 309 days on product  
  • 2/9 acutely infected at enrollment; on product 26 & 29 d | • All arms (K103N/V106M and/or Y181C)  
  • 8/355 (all seroconverters)  
  • 2009 WHO TDR mutations (n=34) |
Drivers of Resistance from PrEP

• Use of product by acutely infected individuals pre-seroconversion
  – Need better point-of-care tests that can detect infection earlier

• Incomplete protection by product
  – Rare so far
  – Resistance may increase with better adherence

• Product does not protect against transmitted resistance from partner
ART in Africa

First line
2 NRTI + 1 NNRTI

Second line
2 different NRTI + PI
Resistance from 1\(^{st}\) Line ART

Virological efficacy and drug-resistance outcomes for 13,288 patients from sub-Saharan Africa on first line ART

How effective was ART?

<table>
<thead>
<tr>
<th>Time</th>
<th>Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>22%</td>
</tr>
<tr>
<td>12 months</td>
<td>24%</td>
</tr>
<tr>
<td>24 months</td>
<td>33%</td>
</tr>
</tbody>
</table>

Resistance found in failures: M184V (65%), K103N (52%), TAMS (5-20%), K65R (5%)

Barth et al. *Lancet Infect Dis* 2010
PASER

PharmAccess African Studies to Evaluate Resistance

- Multi-country 13-site cohort study
- 70% of patients achieved HIV RNA suppression
- 71% resistance among failures; 21% of all on ART!
  - 96% of cases were acquired resistance
  - 4% of cases were transmitted resistance
  - Predominant mutations: K103N, M184V, TAMS, K65R
Resistance to Second Line Therapy

• 22% fail second-line therapy (HIV RNA not suppressed by 6 months)
  – Major cause: poor adherence
  – PI Resistance is infrequent

• Low level resistance to PI may be caused by mutations in env?

Hosseinipour JID 2013; Stray JV 2013
Transmitted Drug Resistance (TDR)

Stanford Resistance Database HIV-1 Drug Resistance in ARV-naive Populations
Compendium of published virus sequences from 46,765 persons, 264 studies
Increasing TDR!

- Assessment of published studies and WHO surveys of HIV drug resistance in 26,102 untreated persons in 42 countries showed:

<table>
<thead>
<tr>
<th>Region</th>
<th>Rate of Increase of TDR/year since ART roll-out (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Africa</td>
<td>29% (15 – 45)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>14% (0 – 29)</td>
<td>0.054</td>
</tr>
<tr>
<td>West/Central Africa</td>
<td>3% (-0.9 – 16)</td>
<td>0.618</td>
</tr>
</tbody>
</table>

Hamers *Curr Opin HIV AIDS* 2013
Transmitted Resistance in MTN-009 & VOICE

MTN-009 (Women screening for PrEP Trials)

- 26/352 (7.4%) with resistance
  - 62% had single-class NNRTI resistance
  - 19% had dual-class NRTI/NNRTI

VOICE/MTN-003

- 8/355 (2.3%) NNRTI-R (K103N/V106M/Y181C)
- 34/355 (9.6%) WHO TDR mutations
Drivers of resistance from ART

- Lack of viral load monitoring
- Loss to follow-up
- Inconsistent access to ART
- Adherence
- Treatment failure
Drivers of Drug Resistance

PrEP won’t drive resistance – THERAPY will

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Abbas JID 2013
Drivers of Drug Resistance

PrEP

ART
What can we do to minimize resistance from PrEP?

• Earlier detection of HIV infection
  – “Close the window”

• Detect low frequency mutants that can be transmitted or affect response to ART

• Better understand cross-resistance between PrEP and ART – avoid collisions!
  – NNRTI: efavirenz, nevirapine, rilpivirine, dapivirine
Earlier HIV Detection

• 31 acute infections in VOICE were missed by current rapid tests (22 @ enrollment; 9 @ PUEV)

• High rate of resistance (8/28; 29%) in subjects acutely infected at enrollment assigned to active product arms (iPrEx, Partners, TDF2, VOICE)

• Highest risk of resistance for PrEP is from acutely infected persons using active product

HIV Replication + One or Two ARV = RESISTANCE
Close the “Window Period” with New Diagnostic Tests

VIROLOGY CORE GOAL: Evaluate new HIV diagnostic tests and redesign endpoint algorithm for future studies

- Masciotra 2011; Owen 2008; Keren 2008
Detect Low Frequency Mutants

Standard Resistance Testing

Sensitive Resistance testing (ASPCR)

What we see often is only a fractional part of what it really is.
Necessity of AS-PCR

• NVP-resistant mutant frequencies >1% are significantly associated with increased risk of NVP-containing ART failure (A5208/Octane).

• No data on the impact of low frequency NRTI mutations on response to future ART
  – Tenofovir and 3TC/FTC used as 1st line therapy in Sub-Saharan Africa

• Will seroconverting on product select for low-frequency resistance mutations?
  – In ASPIRE?
What can we do to minimize resistance from ART?

- Individual monitoring of ART for viral breakthrough/treatment failure
  - POC HIV-1 RNA assays
- Differentiate non-adherence from HIV-1 drug resistance as cause of breakthrough/failure
  - POC tests for ARV levels or common drug resistance mutations
- Better access to 2nd line therapy for first-line resistance
  - 2nd line may become first-line in specific regions
- Real-time global surveillance for HIV-1 drug resistance
  - When to switch first-line regimen?
- Strengthen ARV supply chain
  - Prevent stock outs
Global Threat of Resistance

Cross-Resistance

ART Failure

>>> Resistance

PrEP Failure

Transmitted Resistance
We can meet the challenge by...

• Improved individual and epidemiological monitoring for ART failure and drug resistance using standard and sensitive methods for detection

• Simplified single tablet regimens for 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} ART with a strong supply chain

• Improving HIV diagnostic tests to close the window period during which PrEP could cause resistance

• Gaining a better understanding of cross-resistance between ART and PrEP through analysis of patient-derived viruses, thus avoiding collisions!
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