The New News on ARV Resistance

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Top 3 PrEP (and Resistance) Candidates

**Oral PrEP**
Truvada (TDF-FTC)

**Vaginal Ring**
Dapivirine (DPV)

**Injectable**
TMC-278LA (RPV)
PrEP Resistance Concerns

• Breakthrough infection and subsequent selection of resistance with continued use of PrEP during acute infection could compromise the effectiveness of first-line ART

• Efficacy of PrEP could be reduced if the transmitted variant is from a partner failing an ART regimen with virus that is cross-resistant to PrEP
The Latest News on...

1. TDF-FTC Resistance
2. Dapivirine Resistance
3. Rilpivirine Resistance
Should we fear resistance from TDF/FTC PrEP?
## TDF/FTC PrEP Resistance Occurs Infrequently in Seroconverters

Seroconverted on TDF/FTC Arm during follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Seroconverters in TDF/FTC Arm</th>
<th>TFV Resistance</th>
<th>FTC Resistance</th>
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<tbody>
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<td></td>
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<td>Sensitive</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
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</tr>
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<td>TDF2</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
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- Parikh and Mellors, Current Opinions in HIV/AIDS, 2015 (in press)
TDF/FTC PrEP Resistance Occurs Infrequently in Seroconverters

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# 5 Cases of FTC Resistance

**TDF/FTC Arm; Standard Genotyping**

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<th>FEM-PrEP</th>
<th>CASE 1</th>
<th>intracellular TNV-DP equivalent to 4 tablets/week</th>
</tr>
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<tr>
<td>CASE 2 &amp; 3</td>
<td><em>acute infection at enrollment could not be ruled out</em></td>
<td></td>
</tr>
<tr>
<td>CASE 4</td>
<td><em>seroconverted 48 weeks after discontinuing study product</em></td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td>CASE 5</td>
<td>Detectable tenofovir</td>
</tr>
</tbody>
</table>

*van Damme, NEJM, 2012 & Parikh CROI 2014*
10 Cases of Low Frequency FTC Resistance

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Percentage</th>
</tr>
</thead>
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<tr>
<td>FEM-PrEP</td>
<td>Case 1</td>
<td>0.66%</td>
</tr>
<tr>
<td>iPrEX</td>
<td>Cases 2-3</td>
<td>0.53 &amp; 0.75%</td>
</tr>
<tr>
<td>VOICE</td>
<td>Cases 4-5</td>
<td>0.7 &amp; 5%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Cases 6-10</td>
<td>All &gt;1%</td>
</tr>
</tbody>
</table>

- Detection of these low frequency mutants may be intermittent
- No proof that they were selected by TDF/FTC
- Clinical significance of these low frequency drug-resistant variants is unknown.

-Grant AIDS 2015; Leigler JID 2014; Panousis CROI 2015; Lehman JID 2015
NO Cases of TDF Resistance

• No cases of TDF resistance detected by standard genotyping.

• One participant in Partners PrEP with low frequency K65R from the TDF/FTC arm > 1%.
  – Clinical significance **unknown**

-Parikh CROI 2014; Lehman JID 2015
### Resistance to TDF/FTC PrEP Common in Acute Infection

#### Acutely Infected at Enrollment

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</tr>
<tr>
<td>iPrEX</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>TDF2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
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<td>VOICE</td>
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<td>0</td>
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</tr>
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<td><strong>TOTAL</strong></td>
<td><strong>17</strong></td>
<td><strong>1 (6%)</strong></td>
<td><strong>7 (41%)</strong></td>
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- Parikh and Mellors, Current Opinions in HIV/AIDS, 2015 (in press)
TDF/FTC PrEP Resistance

Resistance is infrequent (3%) from use of oral TDF/FTC PrEP if HIV-1 infection is not present at the time PrEP is started.

Resistance is more common (41%) if TDF/FTC PrEP is started during undiagnosed acute HIV-1 infection.

Acute HIV-1 infections should be excluded before starting PrEP!
Should we fear resistance from DAPIVIRINE RING?
Mutations Important for DPV Resistance

- Minimal resistance data available because dapivirine is not used therapeutically.

- Mutations associated with dapivirine resistance:
  - In vitro selection with sub C-HIV-1: E138K & Y181C (Schrader 2012)
  - Cross-resistance: Y181C, K103N, L100I, Y188L (Fletcher 2009)

- In ASPIRE, standard resistance testing and next generation sequencing (NGS) will determine the frequency of NNRTI/DPV resistance mutations in active vs placebo arms.
## Dapivirine Cross-Resistance

<table>
<thead>
<tr>
<th>Level of DPV Resistance*</th>
<th># of Samples (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (≥ 10-fold)</td>
<td>79 (77%)</td>
</tr>
<tr>
<td>Intermediate (3 to 9-fold)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Susceptible (≤ 2-fold)</td>
<td>9 (9%)</td>
</tr>
</tbody>
</table>

* All virus were >10-fold resistant to NVP and EFV

- Patient viruses derived from 1st line ART failures with ≥ 1 ARV mutation & RNA >10,000 c/ml
- K103N and L100I significantly associated with maximum DPV resistance
Risk of DPV Breakthrough Infection?

- Vaginal $C_{day 28}$ exceeds adjusted IC$_{90}$ of all samples by >23-fold

- Risk of breakthrough is seen in a short window following ring removal; 32/102 (31%) viruses exceed $C_3$ days following ring removal
DPV Resistance Summary

- NNRTI-resistant virus from 1st line treatment failures are usually resistant to dapivirine

- Local [dapivirine] >> IC$_{90}$ of NNRTI-resistant virus
  - May be sufficient to block both wild type and resistant virus
  - Critically important to continue to evaluate both selected and transmitted resistance with dapivirine ring use

- Plasma [dapivirine] from monthly ring use are low
  - But may be too low to select resistance with wild type infection

- Critically important to continue to evaluate both selected and transmitted resistance with dapivirine ring use
Should we fear resistance from injectable **TMC-278LA**?
RPV Resistance

• 47 HIV+ ARV-naïve participants on RPV monotherapy for 7 days → no resistance (Cohen JAIDS 2012)

• Prevalence of RPV-associated mutations:
  – 5% in treatment-naïve
  – 59% in NNRTI-containing 1st-line ART failures

• 17 mutations associated with RPV resistance:

• ECHO and THRIVE: E138K with M184I most commonly emerged in virologic failures
PK evaluation of the exposure and distribution of TMC278LA (RPV), for use as PrEP, in plasma and genital tract/rectal compartments, following a single IM injection at different doses

Study Population
• 60 HIV-negative female volunteers
• Received single IM dose of RPV:
  • 300, 600 or 1200 mg

Unexpected seroconverter in 300 mg arm
Case History

- Patient received single 300 mg IM injection
- Exposure is believed to have occurred
- First detectable viral load (370 copies/ml)
- Seropositive (HIV-1/2 Ag/Ab EIA)
- ART with TFV/FTC and DRV/r started
Residual RPV Led to Resistance Selection

Days post RPV injection vs. [plasma RPV] ng/ml

- 50 ng/ml therapeutic RPV target
Residual RPV Led to Resistance Selection

HIV RNA copies/ml

Days post RPV injection

ART initiation

Viral Load

plasma [RPV]

50 ng/ml therapeutic RPV target

644,925 c/ml Day 115

769 c/ml Day 226

HIV Exposure

[plasma RPV] ng/ml
Residual RPV Led to Resistance Selection

HIV RNA copies/ml

Days post RPV injection

50 ng/ml therapeutic RPV target

644,925c/ml Day 115

769 c/ml Day 226

- Penrose R4P 2014
## K101E Selected After Transmission

<table>
<thead>
<tr>
<th>Days post injection</th>
<th>84</th>
<th>115</th>
<th>151</th>
<th>199</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard</strong></td>
<td>K101</td>
<td>K101E/K</td>
<td>K101E/K</td>
<td>K101</td>
</tr>
<tr>
<td><strong>ASPCR (%K101E)</strong></td>
<td>0</td>
<td><strong>19.4</strong></td>
<td>Sample not available</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>HIV RNA (c/mL)</strong></td>
<td>175,060</td>
<td>644,925</td>
<td>6,204</td>
<td>3,558</td>
</tr>
</tbody>
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Risk of Breakthrough Infection with 1200 or 600 mg monthly injectable RPV

No/Low Risk for Breakthrough

High Risk for Breakthrough

- 600 mg RPV: 39%
- 1200 mg RPV: 30%
RPV Resistance Summary

• The lowest dose (300 mg) of TMC278LA did not prevent HIV-1 in one individual in the SSAT 040 trial.

• Frequent cross-resistance to RPV is observed among HIV-1 subtype C viruses from individuals experiencing failure of first-line NNRTI-containing ART.

• The frequency of resistance selection from long-acting PrEP agents should be carefully investigated.
Global Threat of Resistance

Cross-Resistance

ART Failure

>>> Resistance

PrEP Failure

Transmitted Resistance
Overcome Fear of Resistance!

Benefits of PrEP

Risk of Drug Resistance
But Continue Diligence in Monitoring for Resistance from PrEP!

Critically important to monitor ART failures and PrEP failures for standard and low-frequency resistance in trials and during roll-out.
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- Raquel Viana

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- Akil Jackson

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VOICE Protocol Team
MTN Sites
All Study Participants

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- Laura Else

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Questions?