HIV-1 Prevention and the Potential for Antiretroviral Resistance

John Mellors, MD
Urvi Parikh, PhD
Outline

• Quick refresher on resistance
  – Principles, types, major vs. minor

• What have we learned in the last year and what do we still need to learn?
  – About resistance from oral or topical PrEP?

• Focus on resistance to NNRTIs
  – General features
  – Dapivirine and dapivirine ring (MTN-020)
Resistance Refresher: Principles

• HIV-1 can develop resistance to any ARV
  – If it’s any good as an inhibitor of replication
• HIV-1 replication + drug = resistance
• No replication (3 drug ART) = no resistance
• Remove drug, resistance decays but…
  – Depends on mutation and drug
  – 184V (3TC/FTC) = fast vs. 103N (NNRTI) = slow
Types of Resistance

• Transmitted Resistance
  – Person is infected with resistant virus
    ▪ Never exposed to ARVs
    ▪ Partner rec’d ART, sdNVP or PrEP
    ▪ Or, partner infected with resistant virus from a
      another partner: a “secondary” transmission

• Selected Resistance (most common)
  – Infected with wildtype virus
  – Resistance selected by sdNVP, ART, or PrEP
Major vs. Minor Resistance

• Major
  – ≥ 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 ASP, SGS, deep sequencing
What Have We Learned in 1 Year?

• No infection on PrEP, no resistance 😊
  – CAPRISA, iPrEX, TDF2, Partners PrEP

• No PrEP exposure, rare resistance but infection 😞
  – iPrEX, TDF2, Partners PrEP, FEM-PrEP
HIV-1 Drug Resistance from PrEP

• Infrequent cases of drug resistance among PrEP study participants who seroconverted while receiving active drug

<table>
<thead>
<tr>
<th>Study</th>
<th>Infections on Study</th>
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<tbody>
<tr>
<td></td>
<td># infected</td>
<td># resistant to FTC or TDF</td>
<td></td>
</tr>
<tr>
<td>iPrEx</td>
<td>131</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>82</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>TDF2</td>
<td>33</td>
<td>1 placebo (K65R &lt;1%)*</td>
<td></td>
</tr>
</tbody>
</table>
| FEM-PrEP       | 68                  | 1 placebo (M184V)*  
                            |          | 4 FTC/TDF (M184V/I)** |

* Transmitted (primary) resistance can occur independent of PrEP, which likely explains resistance in the placebo arm

** 1 probable and 2 possible transmitted resistance; 1 uncertain timing of infection (HIV RNA detectable at first follow-up visit)
Infrequent Drug Resistance

• Why?
  – Risk of infection and drug exposure are inversely related
  – No or low drug exposure, no selection by drug, no resistance, but infection
  – Good exposure → no infection & no resistance

• Resistance is still possible
  – At drug exposures that permit infection but also provide selection of resistant variants
  – Appears to be uncommon
Theoretical Infection-Exposure-Resistance Relationships

- No Drug
- No Resistance
- Infection

Fraction infected or resistant

Drug Exposure

- HIV infection
- Resistant infection

Low    High
Theoretical Infection-Exposure-Resistance Relationships

- No Drug
- No Resistance
- Infection
Theoretical Infection-Exposure-Resistance Relationships

- No Drug
- No Resistance
- No Infection

Drug Exposure

Fraction infected or resistant

- Low
- High

Zone of Resistance Risk

HIV infection

Resistant infection
What Have We Learned in 1 Year?

• Resistance more likely if PrEP given during unrecognized acute infection
  – iPrEX, TDF2, Partners PrEP, FEM-PrEP
**Resistance More Likely if PrEP is Given During Unrecognized Acute Infection**

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline infections</th>
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<tbody>
<tr>
<td></td>
<td># infected</td>
</tr>
<tr>
<td>iPrEx</td>
<td>10</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>14</td>
</tr>
<tr>
<td>TDF2</td>
<td>3</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>2</td>
</tr>
</tbody>
</table>

*Infection + incomplete suppression of replication selects resistance Transmitted (primary) resistance can occur, independent of PrEP, which likely explains resistance in the placebo arm*
What Have We Learned (con’t)

- Topical PrEP (TNV gel), no systemic resistance
  - CAPRISA 004
  - No major or minor resistance
  - Relevant for MTN-020 (dapivirine ring)
What Have We Learned (con’t)

• Resistance from ART is common
  – 15-20% of first-line therapy
  – Evidence of spread: prevalence pretherapy has increased in some countries from <5% to >12%
  – Uganda, Cameroon
Hamers et al., Lancet Infectious Dis 2011
What do we need to Learn?

• What level of PrEP exposure, if any, results in infection + resistance?
• What is the significance of minor resistance
  – Thought we knew but…
A5208 Trial 1 (sdNVP): Risk of Failure vs. Mutation Frequency by Allele-Specific PCR

HIV Drug Resistance Program
National Cancer Institute at Frederick

Boltz et al. PNAS 2011
A5208 Trial 2 (no sdNVP): No Increased Risk of Failure vs. Mutation Frequency by Allele-Specific PCR in the NVP Arm

<table>
<thead>
<tr>
<th>Mutant Frequencies</th>
<th>Percent of Patients Failing</th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>no mutation</td>
<td>9/63</td>
<td>31/180</td>
<td></td>
</tr>
<tr>
<td>0.1 to &lt;1%</td>
<td>5/18</td>
<td>6/21</td>
<td></td>
</tr>
<tr>
<td>1% to 10%</td>
<td>8/18</td>
<td>2/13</td>
<td></td>
</tr>
<tr>
<td>&gt;10%</td>
<td>8/15</td>
<td>0/5</td>
<td></td>
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p-values:
- p=1.0
- p=1.0
- p=0.233
Not All Minor Resistance is the Same

• Minor drug resistance after sdNVP is associated with increased risk of failure of NVP-containing ART
• Spontaneous, pre-existing resistance is not
• So, if we detect minor resistance in a person with uncertain prior drug exposure (e.g. PrEP), we don’t know its significance
  – Working on additional ways to distinguish risk
NNRTIs and NNRTI Resistance
General Characteristics of NNRTIs

- Hydrophobic (water fearing) molecules
- Bind to a hydrophobic “grease pit” in HIV-1 RT near the catalytic site called the NNRTI binding pocket
- Inhibit RT function by multiple mechanisms
  - Distort the active site
  - Alter primer binding
  - Freeze RT in the open (non-catalytic) position
Structure of HIV-1 Reverse Transcriptase

- Pol Active Site
- RNase H Active Site
- NNRTI Binding Pocket
FDA-approved NNRTIs

• First generation
  – Delavirdine, Nevirapine, Efavirenz

• Second generation
  – Etravirine (TMC-125), Rilpivirine (TMC-278)
Structures of FDA-approved NNRTI

Nevirapine

Etravirine

Delavirdine

Efavirenz

Rilpivirine
Multiple NNRTI Resistance Mutations

Johnson et al., IAS USA 2011
General Features of NNRTI Resistance

• The “grease pit” is not conserved
• Mutations decrease NNRTI binding
  – Direct loss of hydrophobic interaction (Y181C)
  – Closing of entry to the pit (K103N)
  – Steric hindrance (G190E)
• Some mutations have minimal effect on fitness
  – May persist after drug is withdrawn (K103N)
• Cross-resistance is common among NNRTI
  – Extensive for 1\textsuperscript{st} generation
  – Less between 1\textsuperscript{st} & 2\textsuperscript{nd} generation but still problematic
Dapivirine is an analog of ETV and RIL and binds to the same pocket. Figure shows overlay of the 3 drugs
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure</th>
<th>EC$_{50}$ in µM</th>
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<tbody>
<tr>
<td></td>
<td>Wild-type</td>
<td>K103N</td>
</tr>
<tr>
<td>TMC278</td>
<td>0.0004</td>
<td>0.0003</td>
</tr>
<tr>
<td>TMC125</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>TMC120</td>
<td>0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0.001</td>
<td>0.039</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>0.016</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>0.085</td>
<td>&gt;1</td>
</tr>
</tbody>
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Das et al. PNAS 2008
Dapivirine (TMC-120) Ring

• **Advantages**
  – Very potent inhibitor of HIV-1 ($EC_{50} = 1 \text{ nM}$)
  – Local delivery, so systemic resistance unlikely
  – Very high local concentrations may inhibit resistance development as well as NNRTI-resistant HIV-1 that comes from an infected partner
Dapivirine (TMC-120) Ring

- **Potential limitations**
  - Not active against high-level NNRTI resistant variants from a source partner
    - Uncommon now but could increase
  - Selection of resistance in the GT of INFECTED women
    - Theoretically transmissible
  - Resistance likely to be minor so more difficult to detect
    - MTN Virology Core will be prepared!
Take Home Messages

• Don’t give PrEP (Dapivirine Ring) to HIV+’s
  – Screen carefully for acute infection

• Look hard for minor drug resistance among seroconverters in MTN-020/ASPIRE
  – Comparisons with placebo arm are key

• Monitor prevalence of NNRTI resistance in ART- naïve and -experienced persons in RLS
  – Transmission of NNRTI-resistant virus is likely to increase
  – Potential for dapivirine ring breakthrough exists
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The women in Africa who participated in A5208 and the 10 study sites
Any Questions?