HIV Drug Resistance at Mother-to-Child Transmission & Emergence During Breastfeeding

Presented by Ceejay Boyce, PhD Student
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Co-Authors: Tatiana Sils, Daisy Ko, Annie Wong-on-Wing, Sheila Styrchak, Ingrid Beck, Patricia DeMarrais, Camlin Tierney, Lynda Stranix-Chibanda, Taha E Taha, Maxensia Owor, Mary Glenn Fowler, Lisa Frenkel, for the Promoting Maternal and Infant Survival Everywhere (PROMISE) Study Team
Disclosures

• No conflicts of interest to disclose
HIV Mother-to-Child Transmission (MTCT)

- Global effort to eliminate HIV MTCT to reduce the total number of new HIV infections annually
- Without ART, HIV MTCT rates range from 15-45%
- ↑ ART coverage = ↓ in MTCT

New HIV infections among children (0-14 years) and coverage of ART to prevent MTCT

2017 estimates | UNAIDS
HIV Drug Resistance

• ↑ ART coverage = ↑ rates of pre-treatment drug resistance

• Women have higher rates of pre-treatment drug resistance
  • Diagnosed earlier in course of infection due to pregnancy

• Unknown if drug resistance (DR) in mothers increases the risk of MTCT

In several low- and middle-income countries,

1 in 10 adults starting HIV treatment harbour resistant virus

3 in 10 adults restarting first-line ART with prior exposure to antiretroviral drugs harbour resistant virus

Women

starting first-line ART are two times more likely than men to harbour a resistant virus
Study Goals

**Aim 1:** Assess the association of maternal DR with the risk of MTCT

**Aim 2:** Describe DR in HIV-infected infants
Study Population & Case-Control Design

- **Population**: mother-infant pairs from the PROMISE 1077 BF Study
  - Trial across 14 clinical sites in Malawi, South Africa, Zimbabwe, Tanzania, Uganda, Zambia, & India

![Time Line Diagram]

- Pregnancy (14-40 weeks)
- Birth
- 2 Weeks Old
- 104 Weeks
Study Population & Case-Control Design

- **Population**: mother-infant pairs from the PROMISE 1077 BF Study

**Design of case-control study**:
- 1:3 case-control ratio of HIV-infected mothers, matched by delivery date and clinical site
- **Cases** = transmitting mothers and their infants (n = 85)
  - 48 in utero/peripartum infections
  - 37 breastfeeding infections
- **Controls** = non-transmitting mothers (n = 254)

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**Antepartum Randomization**:
- ZDV + sdNVP/TRV tail
  - OR
- Three-drug ART (PI-based)

**Postpartum Randomization**:
- Maternal ART + Infant NVP (6wks)
  - OR
- Infant NVP Prophylaxis ONLY
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**Study Population & Case-Control Design**

- **Pregnancy (14-40 weeks)**
  - Antepartum Randomization:
    - ZDV + sdNVP/TRV tail
    - OR
    - Three-drug ART (PI-based)

- **Birth**
  - Postpartum Randomization:
    - Maternal ART + Infant NVP (6wks)
    - OR
    - Infant NVP Prophylaxis ONLY
Study Design

Aim 1: Assess the association of maternal DR with the risk of MTCT
  - Compare rate of HIV DR in case (MTCT) vs control (no MTCT) mothers; adjusting for HIV RNA viral load and antepartum treatment regimen

Aim 2: Describe DR in HIV-infected infants
  - Compare rate of HIV DR in infants with *in utero* MTCT vs breastfeeding MTCT at HIV diagnosis and over time
Study Methods

• Genotypic HIV drug resistance by consensus sequencing of HIV \textit{pol}

Mother Plasma Collected:

Infant Plasma Collected:

• Mothers and infants categorized as wild-type (\textit{WT}) or drug resistant (\textit{DR}) using major drug resistance mutations defined by Stanford HIV Database
Aim 1: Assess the association of maternal DR with the risk of MTCT

Hypothesis: Presence of DR HIV in maternal plasma will be associated with increased risk of MTCT compared to mothers with WT HIV
Results: DR greater in maternal cases vs controls at infant HIV diagnosis

- Overall, transmitting mothers had a higher probability of DR at infant HIV diagnosis (14.6% vs 6.2%, $p=0.039$)
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Compared using Fisher's Exact test
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Compared using Fisher's Exact test

1 transmitting mother with NRTI resistance
Results: DR greater in maternal cases vs controls at infant HIV diagnosis

- Overall, transmitting mothers had a higher probability of DR at infant HIV diagnosis (14.6% vs 6.2%, p=0.039)

<table>
<thead>
<tr>
<th>Type of Mother-to-Child Transmission</th>
<th>Percentage of Mothers with DR</th>
<th>Cases (MTCT)</th>
<th>Controls (No MTCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero/Peripartum</td>
<td>p = 0.676</td>
<td>n=45</td>
<td>n=123</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>p = 0.002</td>
<td>n=37</td>
<td>n=102</td>
</tr>
<tr>
<td>Overall</td>
<td>p = 0.039</td>
<td>n=82</td>
<td>n=225</td>
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</tbody>
</table>

Compared using Fisher's Exact test

1 transmitting mother with NRTI resistance
11 transmitting mothers with NNRTI resistance, only 2/11 were prescribed NNRTI
Results: DR mutations detected in maternal cases and controls at infant HIV diagnosis

- Most common DR mutation was K103N in both cases and controls

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mutation</th>
<th># Cases (%)</th>
<th># Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>M46I</td>
<td>-</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>M41L</td>
<td>-</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>NRTI</td>
<td>D67N</td>
<td>-</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>K70R</td>
<td>-</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td></td>
<td>K219N</td>
<td>1 (1.2%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>A98G</td>
<td>-</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td></td>
<td>K101E</td>
<td>1 (1.2%)</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td></td>
<td><strong>K103N</strong></td>
<td><strong>7 (8.5%)</strong></td>
<td><strong>6 (2.7%)</strong></td>
</tr>
<tr>
<td>NNRTI</td>
<td>V179D</td>
<td>1 (1.2%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Y181C</td>
<td>1 (1.2%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Y188C</td>
<td>1 (1.2%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>G190A/E</td>
<td>2 (2.4%)</td>
<td>2 (0.9%)</td>
</tr>
</tbody>
</table>

Total # of Mothers with ≥1 DR Mutation: 12 (14.6%) cases, 14 (6.2%) controls
Results: Plasma HIV RNA higher in maternal cases vs controls at infant HIV diagnosis

- Overall, transmitting mothers had higher median HIV RNA levels at infant HIV diagnosis (4.28 vs. 3.86 log10 copies/mL, p<0.0001)

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Plasma Viral Load (Log10 c/mL)

Compared using Mann-Whitney test
Results: Plasma HIV RNA higher in maternal cases vs controls at infant HIV diagnosis

• Overall, transmitting mothers had higher median HIV RNA levels at infant HIV diagnosis (4.28 vs. 3.86 log10 copies/mL, p<0.0001)

Compared using Mann-Whitney test
Results: Maternal DR associated with increased risk of MTCT during breastfeeding and “overall”

- Multivariable analysis adjusted for maternal plasma HIV RNA, genotype, and antepartum treatment regimen

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<thead>
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<th>Covariate</th>
<th>Reference</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>≥4 Log c/mL Plasma Viral Load</td>
<td>(&lt;4 Log c/mL)</td>
<td>2.33 (1.29-4.21)</td>
<td>0.005</td>
</tr>
<tr>
<td>DR Genotype</td>
<td>(WT Genotype)</td>
<td>2.45 (1.03-5.81)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Compared using Conditional Logistic Regression
Results: Maternal DR associated with increased risk of MTCT during breastfeeding and “overall”

- Multivariable analysis adjusted for maternal plasma HIV RNA, genotype, and antepartum treatment regimen
- Adjusting for maternal plasma HIV viral load at infant diagnosis, DR was still significantly associated with increased risk of MTCT

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Compared using Conditional Logistic Regression
Aim 2: Describe DR in HIV-infected infants

Hypotheses:
1. Resistance mutations detected at HIV diagnosis will persist over time
2. Prolonged selective pressure from infant nevirapine (NVP) prophylaxis or maternal and/or infant ART could select DR mutations
Results: HIV DR was less frequent in infants with *in utero* MTCT vs. breastfeeding MTCT

- At HIV diagnosis, prevalence of DR was lower in infants with *in utero/peripartum* MTCT vs breastfeeding MTCT (12.5% vs 54.3%, p<0.001)
Results: HIV DR was less frequent in infants with *in utero* MTCT vs. breastfeeding MTCT

- At HIV diagnosis, prevalence of DR was lower in infants with *in utero*/peripartum MTCT vs breastfeeding MTCT (12.5% vs 54.3%, p<0.001)

<table>
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<th>Mutations Detected</th>
<th>In utero or Peripartum (n=40)</th>
<th>Breastfeeding (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Multiple</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Multiple</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>NRTI &amp; NNRTI</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Total # of DR infants: 5 (12.5%) vs 19 (54.3%)
Results: ~25% of mother-infant pairs had discordant genotypes, 90% were WT moms with DR infants.

Genotype Concordance of Mother-Infant Pairs at Infant Diagnosis

- Concordant WT: 63.9%
- Concordant DR: 23.6%
- Discordant (DR Mother, WT Infant): 9.7%
- Discordant (WT Mother, DR Infant): 2.8%

N = 72
Results: HIV DR emerged in infants over time during breastfeeding.

Compared using Fisher's Exact test.
Results: HIV DR emerged in infants over time during breastfeeding

Compared using Fisher’s Exact test

Type of Mother-to-Child Transmission

- In utero/Peripartum
- Breastfeeding

Percentage of Infants with DR

- Diagnosis
- ART-Start
- Last Study Visit

n=40
n=8
n=24
n=35
n=10
n=23

p = 0.006
p = 0.003
p = 0.036
p = 0.171
Conclusions & Future Directions

- **Finding**: At infant HIV diagnosis, maternal plasma HIV RNA and HIV DR were both independently associated with increased risk of MTCT.

- **Interpretation**: In addition to non-suppression of HIV replication, HIV DR in mothers appears to reduce effectiveness of infant NVP prophylaxis.
  - Maternal NNRTI DR appears transmitted as 9/11 (82%) did not have a history of NNRTI.
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• **Interpretation**: Prolonged exposure to NVP prophylaxis or maternal ART during breastfeeding led to the emergence of DR in infants
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• **Our conclusion**: Replacement of NVP prophylaxis for MTCT with regimens that have a greater barrier to DR and would retain NNRTI susceptibility in infected infants
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