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

Presented by Ceejay Boyce, PhD Student
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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
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
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
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)

**Timeline**:

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

- **Birth** 2 Weeks Old
  - Postpartum Randomization: Maternal ART + Infant NVP (6wks) OR Infant NVP Prophylaxis ONLY

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

  - **In utero MTCT**
    - Antepartum Randomization: ZDV + sdNVP/TRV tail
    - OR
      - Three-drug ART (PI-based)
    - Postpartum Randomization: Maternal ART + Infant NVP (6wks)
    - OR
      - Infant NVP Prophylaxis ONLY

  - **Breastfeeding MTCT**

• **Design of case-control study:**
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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 pol

Mother Plasma Collected:  

Diagnosis   ART start  Last Study Visit

Infant Plasma Collected:  

- Mothers and infants categorized as wild-type (WT) or drug resistant (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)

Compared using Fisher's Exact test
Results: DR greater in maternal cases vs controls at infant HIV diagnosis

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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)
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></td>
<td></td>
<td>n = 82</td>
<td>n = 225</td>
</tr>
<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></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>NRTI</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>7 (8.5%)</td>
<td>6 (2.7%)</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>
<tr>
<td>Total # of Mothers with ≥1 DR Mutation</td>
<td>12 (14.6%)</td>
<td>14 (6.2%)</td>
<td></td>
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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
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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

<table>
<thead>
<tr>
<th>Covariate</th>
<th>(Reference)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<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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<td>0.042</td>
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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**)

### Mutations Detected

<table>
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<th>Mutations Detected</th>
<th>In utero or Peripartum</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></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><strong>NNRTI</strong></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><strong>NRTI &amp; NNRTI</strong></td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

| Total # of DR infants | 5 (12.5%) | 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): 2.8%
- Discordant (WT Mother, DR Infant): 9.7%

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

Compared using Fisher's Exact test

In utero/Peripartum
- Diagnosis: n=40, p = 0.003
- ART-Start: n=8, p = 0.006
- Last Study Visit: n=24

Breastfeeding
- Diagnosis: n=35
- ART-Start: n=10, p = 0.036
- Last Study Visit: n=23

Type of Mother-to-Child Transmission

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

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  - Diagnosis: n=40, p=0.006
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- Breastfeeding:
  - Diagnosis: n=35
  - ART-Start: n=10, p=0.036
  - Last Study Visit: n=23
  - 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 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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• **Finding:** DR was less prevalent at diagnosis in infants with *in utero* MTCT vs breastfeeding MTCT, but over time DR emerged in both groups

• **Interpretation:** Prolonged exposure to NVP prophylaxis or maternal ART during breastfeeding led to the emergence of DR in infants
Conclusions & Future Directions

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

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- **Interpretation**: Prolonged exposure to NVP prophylaxis or maternal ART during breastfeeding led to the emergence of DR in infants.

- **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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