Data Evaluation and CIPHER Preparation for an HIV Exposed Uninfected Child Cohort Collaboration

5th HIV-Exposed Uninfected Child and Adolescent Workshop
21st July 2019, Mexico City, Mexico

Barbara Burmen
On behalf of the DECIPHER Project Team
• No conflicts of interest
Presentation Outline

• Importance of person-first language
• CIPHER background
• DECIPHER project
  – Background
  – Proposed project definitions
  – Practical applications
  – Next steps
Abbreviations

- Getting to person-first language

Children HIV exposed & uninfected – CHEU
Children HIV unexposed & presumed uninfected – CHU(U)
Collaborative Initiative for Paediatric HIV Education and Research-CIPHER
CIPHER Cohort Collaboration

>100 cohorts
>180,000 children & adolescents with HIV

CCASAnet 2,036

PHACS & IMPAACT 1558

EPPICC 5,816

IeDEA West Africa 5,688

IeDEA Central Africa 1,798

IeDEA SA 58,125

IeDEA East Africa 15,114

BIPAI 18,291

IeDEA Asia Pacific 3,777

Optimal Models 57,568

The epidemiology of adolescents living with perinatally acquired HIV: A cross-region global cohort analysis

Incidence of switching to second-line antiretroviral therapy and associated factors in children with HIV: an international cohort collaboration
The DECIPHER Project

- Is expansion of maternal ART in combination with safer breastfeeding is sufficient to ameliorate CHEU health disparities compared to CHUU?

- Through consensus, to develop standardized exposure and outcome definitions in key domains where disparities have been identified between CHEU and CHUU outcomes.
Postdoctoral Research Fellow
HIV-Exposed Uninfected Child health outcomes

Barbara Burmen

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<td>IeDEA-SA</td>
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DECIPHER Project Aims

1. To appraise and collate definitions and measurements of CHEU exposures and outcomes through a systematic review of literature within 2 to 3 priority domains.

2. To identify and collate from broader child health research, relevant exposure and outcome definitions and measurement tools applicable to CHEU child research.
Key Domains

- **Exposures**
  - HIV and ARV exposure status
  - Infant feeding

- **Outcomes**
  - Birth outcomes
  - Growth
  - Neonatal morbidity and mortality
  - Neurodevelopment & behavioral development
Key Domains

- Exposures
  - HIV and ARV exposure status
    - Infant feeding

- Outcomes
  - Birth outcomes
  - Growth
  - Neonatal morbidity and mortality
  - Neurodevelopment & behavioral development
Brighton Cohort Collaboration

Level 1 (High)
- Highest specificity
- Sensitive for the respective diagnosis

Level 2 (Moderate)
- Intermediate level of specificity
- Sensitive for the respective diagnosis

Level 3 (Low)
- Lower level of specificity
- Highly sensitive for the respective diagnosis

Gold standard diagnostic test

Routine diagnostic test

Signs/symptoms

Specificity

Sensitivity
## Classification Accuracy

<table>
<thead>
<tr>
<th>Component</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>Maternal testing</td>
<td>Assessment of HIV exposure</td>
</tr>
<tr>
<td>Child testing</td>
<td>Assessment of HIV infection</td>
</tr>
<tr>
<td>Child feeding option</td>
<td>Assessment of ongoing HIV acquisition risk</td>
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CHEU definition: focus on excluding HIV *Infection* in the CHEU  
CHU(U) definition: focus on excluding HIV *Exposure* in the CHU(U)
Levels of certainty of infection status of CHEU

- **Low level of certainty of child’s HIV infection status**
  - Child of mother known with HIV AND
    - child NEVER tested negative for HIV
    OR – tested at < 10 weeks of age

- **Moderate level of certainty of child’s HIV infection status**
  - Child of mother known with HIV AND child tested HIV negative at least once ≥ 10 weeks of age, but last test was:
    - If child is breastfeeding, < 6 weeks after breastfeeding cessation
    OR – If child received ARV prophylaxis, < 4 weeks after any child ARV prophylaxis has ended

- **High level of certainty of child’s HIV infection status**
  - Child of mother known with HIV AND child tested HIV negative
    - In the absence of breastfeeding or ARV prophylaxis, at least once ≥ 10 weeks
    OR – If child is breastfeeding beyond 10 weeks of age, ≥ 6 weeks after end of breastfeeding
    OR – If child received ARV prophylaxis beyond 6 weeks of age, ≥ 4 weeks after ARV prophylaxis completion
    OR – If breastfeeding with extended child ARV prophylaxis, ≥ 6 weeks after end of breastfeeding OR >= 4 weeks after ARV completion whichever comes later
    OR – If a negative test is documented after a study outcome of interest
Scenarios 1.0 CHEU

Birth | 4 weeks | 10 weeks | 4 months | 6 months | 24 months
Scenarios 1.0 CHEU

- Birth
- 4 weeks
- 10 weeks
- 4 months
- 6 months
- 24 months

Breastfeeding duration

ARV prophylaxis
Scenario 1.1-Formula-fed infant on ARV prophylaxis

- **Birth**
- **4 weeks**
- **10 weeks**
- **4 months**
- **6 months**
- **24 months**

**ARV prophylaxis**

**Testing at 4 weeks**

**CHEU GRADING**  
Low Diagnostic Certainty: based on a HIV negative test at the age of less than 10 weeks
Scenario 1.2-Formula-fed infant on ARV prophylaxis

Birth  4 weeks  10 weeks  4 months  6 months  24 months

ARV prophylaxis

Testing at 10 weeks

Moderate Diagnostic Certainty: based on testing HIV negative at the age of at least 10 weeks but last test was less than 4 weeks after cessation of infant ARV prophylaxis
Scenario 1.3-Formula-fed infant on ARV prophylaxis

Birth 4 weeks 10 weeks 4 months 6 months 24 months

**ARV prophylaxis**

Testing at 10 weeks

**High Diagnostic Certainty:** based on testing HIV negative at the age of at least 10 weeks or older and the last test was at least 4 weeks after the cessation of infant prophylaxis
Scenario 1.4a-Breast-fed infant on ARV prophylaxis

High Diagnostic Certainty: based on testing HIV negative at the age of 10 weeks or older & last test was at least at 6 weeks after cessation of breastfeeding exposure

Birth  | 4 weeks  | 10 weeks  | 4 months  | 6 months  | 24 months

Breastfeeding duration

ARV prophylaxis

Testing at 6 months

CHEU GRADING

www.iasociety.org/cipher
Scenario 1.4b-Breast-fed infant on ARV prophylaxis

Birth | 4 weeks | 10 weeks | 4 months | 6 months | 24 months

**ARV prophylaxis**

**Breastfeeding duration**

**Outcome Assessment**

**Testing at 6 months**

**High Diagnostic Certainty**: based on testing HIV negative at the age of 10 weeks or older and last test was at least at 6 weeks after cessation of breastfeeding exposure.

**CHEU GRADING**
Practical Application of CHEU Definitions

<table>
<thead>
<tr>
<th>Diagnostic Certainty</th>
<th>Birth Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2015 (n=251)</td>
</tr>
<tr>
<td>Low</td>
<td>62 (25)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (3)</td>
</tr>
<tr>
<td>High</td>
<td>182 (72)</td>
</tr>
</tbody>
</table>

Source: PHACS SMARTT
Levels of certainty of exposure status of CHU(U)

- **Low level of certainty of child’s HIV exposure status**
  - Child of mother assumed to not have HIV where mother was tested only once for HIV
    - before the end of pregnancy where breastfeeding is not practiced
    - before the end of breastfeeding where breastfeeding is practiced
    - before the time of child’s study outcome determination if ongoing postnatal (breastfeeding) exposure

- **Moderate level of certainty of child’s HIV exposure status**
  - Child of mother assumed to not have HIV where mother tested more than once for HIV during pregnancy and breastfeeding but the mother’s last test was
    - before the end of pregnancy where breastfeeding is not practiced
    - before the end of breastfeeding where breastfeeding is practiced
    - before the time of child’s study outcome determination if ongoing postnatal (breastfeeding) exposure

- **High level of certainty of child’s HIV exposure status**
  - Child of mother without HIV where mother was confirmed as HIV-uninfected
    - at the end of pregnancy where breastfeeding is not practiced
    - at the end of breastfeeding where breastfeeding is practiced
    - at the time of child’s study outcome determination or later
    - child tests HIV negative
    - OR
    - AND
Scenario 2.0-CHUU

12 months

24 months
Scenario 2.0-CHUU

Breastfeeding duration

12 months

24 months
Scenario 2.1-Breastfed infant

Breastfeeding duration

Testing at 1st trimester

Low Diagnostic Certainty: based on mother testing HIV negative once before the end of the potential HIV exposure period (i.e. the end of breastfeeding)
Scenario 2.2-Breastfed infant

Breastfeeding duration

<table>
<thead>
<tr>
<th>CHUU GRADING</th>
<th>Moderate Diagnostic Certainty: based on mother testing HIV negative twice before the end of the potential HIV exposure period (i.e. the end of breastfeeding)</th>
</tr>
</thead>
</table>

Testing at 1st trimester

Testing at 9 months

12 months

24 months
Scenario 2.3a-Breastfed infant

Breastfeeding duration

High Diagnostic Certainty: based on mother testing HIV negative at the end of breastfeeding and child confirmed HIV negative

CHUU GRADING

Testing at 20 months

12 months

24 months
Scenario 2.3b-Breastfed infant

12 months

Breastfeeding duration

24 months

Testing at 20 months

High Diagnostic Certainty:
based on mother testing HIV negative at the end of breastfeeding and child confirmed HIV negative
## Summary: Research studies

### Certainty of CHEU Exposure Status

<table>
<thead>
<tr>
<th>Certainty of CHUU Infection Status</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>TOTAL CHEU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL CHEU</strong></td>
<td>0</td>
<td>5</td>
<td>11</td>
<td><strong>16</strong></td>
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Next steps

- Apply diagnostic certainty definitions using ongoing CHEU and CHUU research cohorts to compare select outcomes

- Develop standardized ARV exposure definitions

- Create harmonized birth outcome and neonatal morbidity data collection instruments
Acknowledgement

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  - Marissa Vicari
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  - Mary Paul
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